OPEN ACCESS GOVERNMENT

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228 THE RISE AND FUTURE **OF BLOCKCHAIN**

THE FOUNDER AND CO-FOUNDER OF THE BLOCKCHAIN FEDERATION **PROVIDE INSIGHT INTO THE FUTURE** FOR A BLOCKCHAIN-BASED PURPOSE-ECONOMY

IN THIS ISSUE

Vytenis Andriukaitis, European 12 **Commissioner for Health and Food** safety outlines the EU's 'One Health' approach to tackling antimicrobial resistance

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collaboration following Brexit

202

The Balgrist

on the importance of maintaining international

Sir John Holman, President of the

Royal Society of Chemistry reflects

varberg

Julian King, European **Commissioner for Security Union**, underlines the role of the EU and national governments in keeping citizens safe

Featured eBook

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Bright minds, better future



FOREWORD

Günther H. Oettinger European Commissioner in charge of budget and human resources European Commission

The latest statistics show eight million jobs created in the European Union since the current European Commission took office. At the same time, over the past two years the EU's economic growth has surpassed that of the US. I'm convinced that the EU policies and budget have played an important part.

Doing more with less

The budgetary amounts we work with are not negligible while representing just 1% of GNI of the 28-member states. They are strictly defined by a 7-year financial framework. The current one runs until 2020 and for the first time in EU history is smaller than the previous one. When it was adopted in 2013 the European economy was still taking its first steps on the path to recovery, the unemployment rate was at its record high of 11% and we were facing a massive investment gap of about €700 billion per year. It was perfectly clear that if we wanted to live up to the expectations of European citizens, we needed to do more with less.

"Thanks to the European Social Fund and the Youth Employment Initiative 235,000 people were back in employment, 180,000 gained qualification, 100,000 received education or training by the end of 2016."

Shifting the focus towards results

An efficiency-guided approach was therefore of the utmost importance. We concentrated on improving planning and implementation and making sure that every euro spent brings real economic and social benefits. We have taken a variety of measures to associate even better the funds we allocate to the results achieved. We now have an improved performance framework, allowing for continuous monitoring and reviewing of the projects. As about 80% of the EU funds are implemented by national and regional authorities, we have stepped up our collective efforts to ensure that efficiency is paramount all the way: from concept stage to completion. Right now, we are finalising a "spending review", which will give us further insight into what else should be improved and how to better adjust our spending after 2020. This fits into the ongoing reflection process on the future of Europe, where EU finances play an important role.

"When it was adopted in 2013 the European economy was still taking its first steps on the path to recovery, the unemployment rate was at its record high of 11% and we were facing a massive investment gap of about €700 billion per year. It was perfectly clear that if we wanted to live up to the expectations of European citizens, we needed to do more with less."

Seeking to sustain economic growth and job creation

Our funding efforts so far have been concentrated on our political priorities, in particular to stimulate economic growth and job creation. Reinforcing the EU's industrial leadership, catching-up in research and innovation and sharpening our competitive edge are of great importance, along with enhancing education and skills.

In the last three years the Horizon 2020 research and innovation programme has provided support to 340,000 researchers, leading to a number of scientific break-throughs and discoveries. 17 Nobel Prize laureates have been funded by the EU budget before or after their award, and hundreds of innovative projects have been financed, resulting in a number of new patents and trademarks. We expect our Digital Single Market, also supported by the EU budget, to generate hundreds of thousands of new jobs. The resilient Energy Union we are building requires adequate infrastructure and we have already invested €1.7 billion in 96 electricity, smart grid and gas infrastructure projects.

Using the right instruments to multiply limited resources

For the first two years of its existence, the European Fund for Strategic Investment (EFSI), the so-called Juncker Plan, has triggered ≤ 225 billion of investment, supporting 300,000 jobs. This shows that by sharing the risk through a relatively small EU guarantee of ≤ 16 billion, we can mobilise serious private and public capital to work for EU citizens. Thousands of businesses, small and medium sized enterprises and start-ups have managed to acquire momentum, to expand and hire new employees. This means that we have put our money where our mouth is, and this approach is paying off.

EU budget success stories to be proud of

Targeted financing for our traditional polices is also yielding significant measurable results. Thanks to the European Social Fund and the Youth Employment Initiative 235,000 people were back in employment, 180,000 gained qualification, 100,000 received education or training by the end of 2016. 4% additional GDP growth was generated in the 12 countries that joined the EU after 2004, as a result of investment from the Cohesion policy and rural development funds. In 2016 alone, the EU budget supported about 7 million farmers. In the same year EU exports of agricultural and food products reached a new record level of €130 billion.

All this is only a small fraction of the measurable results achieved. And then there are those things we cannot measure: the impact of the EU being the world leader in humanitarian aid, for example, or saving thousands of lives in the Mediterranean. The same goes for funding cancer research or paying for fruit and vegetables for school-children across Europe. The list is a long one. And this is what the EU budget is all about: serving the EU citizens and adding value to their everyday lives.



Jonathan Miles Editor

Digital Editor Ciara Ruane

Production Coordinator Nick Wilde

Designers Andrew Bosworth Ben Green

Sales Natalia Barbah Debbie Cotterill John Hoinville

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INTRODUCTION

elcome to the November edition of Open Access Government. This comprehensive edition highlights a wide range of policy issues, including health, research, Blockchain, security, agriculture, energy and transport.

I am delighted that this edition begins with a foreword by the European Commissioner in charge of budget and human resources, Günther H. Oettinger. We learn that since the current European Commission took office, 8 million jobs have been created in the European Union. Added to this, we find out that, "the EU's economic growth has surpassed that of the US."

Blockchain is a very exciting area that this journal focuses on, as highlighted for example in an excellent article from the founder and co-founder of the Blockchain Federation, who both provide a glimpse into the future for a Blockchain-based purpose-economy. There is also a very compelling glimpse into Bitcoin - in a written contribution by the European Commission's Benoît Abeloos.

On a topical note, we also consider security issues, such as the comment from European Commissioner for the Security Union, Julian King who underlines the role of the EU and national governments in keeping citizens safe. I also spoke to Alix Leboulanger and Samuel O'Toole at Frost & Sullivan, to get their expert perspective on the current state of the military combat vehicles market.

Heading up our in-depth health and social care section is an excellent feature by European Commissioner for Health and Food safety, Vytenis Andriukaitis who outlines the EU's 'One Health' approach to tackling antimicrobial resistance. This section also incorporates a focus on cancer, including a comment from a group of experts at Frost & Sullivan and Cancer Research UK. Some of the other many subjects covered in this section are Parkinson's disease, lung diseases, cardiovascular diseases, rare diseases as well as mental health and infection control to name a few.

Following on from this, our insightful research and innovation section provides a number of interesting comment pieces on chemistry for instance, with compelling comment from the Royal Society of Chemistry, the US National Science Foundation and the Society of Environmental Toxicology and Chemistry.

You will enjoy browsing through the impressive environment section, which is headed up by the European Commissioner for the Environment, Karmenu Vella and no less than 3 ministers. For example, Secretary of State for Environment, Food and Rural Affairs at DEFRA in the UK, The Rt Hon Michael Gove MP outlines his priorities for the environment.

I hope that you find this edition thought-provoking. I would certainly welcome any comments you have on this packed journal, or for any editions in the future.

Jonathan Miles Editor





CONTENTS

OPEN ACCESS GOVERNMENT | NOVEMBER 2017



HEALTH & SOCIAL CARE

12 The EU's 'One Health' on tackling antimicrobial

resistance. European Commissioner for Health and Food safety Vytenis Andriukaitis outlines the EU's 'One Health' approach to tackling antimicrobial resistance

18 Making it happen: Addressing the implementation gap in European health policy and practice. Dr

Usman Khan, Executive Director of the European Health Management Association tells us his thoughts on public health in the European space

20 How is the UK supporting biotech to create innovative

medicines? CEO of the BioIndustry Association (BIA), Steve Bates explores how the UK government is supporting biotech in order to create innovative medicines

22 From biobanking to precision medicine. A group

of experts from ISBER shed light on the science of biobanking and its role in delivering modern and precision medicine

27 Suicide: A major public health concern. Dr. Jane

Pearson from NIMH highlights suicide as a public health concern and addresses how it can be prevented and the contributing factors behind it

38 Early stage diagnosis – spotting early stage cancer

events. Cecilia Van Cauwenberghe, Vandana Iyer and Bhargav Rajan from Frost & Sullivan examine of how nanotechnology helps spot early stage cancer

48 Publishing national chemotherapy data.

Publishing national chemotherapy data has helped NHS hospitals make changes that should improve treatment, as Emma Saxon reveals in this article

54 Living with Leukaemia. Bethany Torr, campaigns and advocacy officer at Leukaemia Care introduces 'Leukaemia' and its different forms and explains how people live with the disease

58 The future of the Danish Ministry of Health.

Jonathan Miles from Open Access Government explored the work the Danish Ministry of Health does to improve health policy across the country

62 The symptoms of Huntington's disease.

Chief Executive of the Huntington's Disease Association, Cath Stanley explores the symptoms, causes, and the vital role of research within the field

66 Membranous nephropathy and how can it be identified

and treated. The National Kidney Foundation analyses the causes of membranous nephropathy and the science available to identify and treat it

70 Treatments and symptoms of Parkinson's. Prof. David Dexter, deputy director of research at Parkinson's UK shares his thoughts on the symptoms of Parkinson's and the chances of finding a cure **74** The dyspnoea crisis. Wendy Preston and Katy Beckford of ARNS tell us about the problem of dysnopeaand how it impacts on morbidity, mortality and healthcare utilisation

78 The impact of stroke in young people. Jukka Putaala from the European Stroke Organisation outlines the effects of stroke in young people compared to stroke in the older generation

82 Heart valve Disease: The heart of the matter. Associate medical director of the British Heart Foundation, Dr Mike Knapton explores the fundamentals of heart valve disease

86 Cardiology: Prevention is better than cure. Joep Perk from the European Society of Cardiology talks about methods of preventing cardiovascular diseases and research into cures

90 Achieving sustainable health in Europe. The World Health Organisation is working towards equitable and sustainable health in Europe, as Open Access Government finds out

94 Dutch health targets for the future. The aims for Dutch health and Netherland's place in Europe from the Ministry of Health, Welfare & Sport are explored here by Open Access Government

96 Modern research into rare project manager at EURORDIS, Virginie Bros-Facer highlights the extent of rare diseases in Europe in this insightful article

100 Health, prevention, and long-term care in Germany. Germany's Federal Ministry of Health (BMG)

is centred around health, prevention, and long-term care, as Open Access Government discovers

104 Tackling the UK's obesity epidemic. Professor Russell Viner from the Royal College of Paediatrics shares his thoughts on the UK Government's strategy to tackle the UK's obesity epidemic

106 The continuous improvement of care.

European Association of Hospital Pharmacists (EAHP) on developing the hospital pharmacy profession and the improvement of care for patients in Europe

108 Fostering and supporting excellence in clinical pharmacy practice. Islam Elkonaissi

and Zahra Laftah from the UKCPA explore the British model of supporting excellence in clinical pharmacy practice

116 Europe can lead curing asthma. Susanna Palkonen of

the European Federation of Allergies and Airways Diseases Patients' Associations underlines research around asthma in Europe today

122 Workplace mental health: Healthy workforce,

healthy society. The European Brain Council (EBC) highlights the challenges around workplace mental health, following World Mental Health Day on 10th October

124 Supporting measures that improve health for all.

The Wellcome Trust backs ideas from all over the world to improve health for everyone, as Open Access Government learns

128 The challenge of mental disorders: European neuroscience answers the call.

Executive Director of the European College of Neuropsychopharmacology (ECNP), Alexander Schubert looks at how science is unravelling the complexity of the human brain

135 Dementia as a progressive condition. Alzheimer's Society in the UK provides a fascinating glimpse into the most common types of dementia, all of which are progressive

140 Malaria kills over 1000 people a day – technology and transparency offer the

solutions. Peter Sherratt, executive chairman of AMF explains how novel ideas are being applied to a well-tested intervention in the battle against malaria

144 Effective prevention and control of infectious

diseases. David Partridge from the British Infection Association provides a comprehensive overview of effective infection prevention and control in the UK today

146 Maintaining high standards of infection prevention and control. Elaine Ross,

board member of the Infection Prevention Society (IPS) details the key issues around infection prevention and control (IPC) in the UK today

151 Living with lung disease in the UK. The British Lung

Foundation's research findings are explored here on lung disease in the UK and their 'battle for breath' campaign



RESEARCH & INNOVATION

156 The role of education and educational research for a sustainable future. The European Educational Research Association stresses the important role of education in helping people to participate in a democratic society

158 Why should we trust science? Carlos Moedas,

Commissioner for Research, Science and Innovation recently unveiled his thoughts in a speech on the whether we trust science itself

168 Denmark in Horizon substance. Niels C. Beier, Deputy Director of the Danish Agency for Science and Higher Education explains Denmark in Horizon 2020 and the framework

in Horizon 2020 and the framework programme

172 The organisation of the German Research Foundation. The inner workings of the

German Research Foundation (DFG) are placed under the spotlight by Open Access Government in this insightful article

178 Challenging the stereotypes in science. Chief Executive of the British Science Association Katherine Mathieson provides a compelling insight into how we can challenge stereotypes in science

180 Dutch government policy and its social impact.

The Netherlands Institute for Social Research (SCP), unveil their fascinating research into the social impact of government policy

184 The outermost frontiers of knowledge and scientific progress. The National Science

Foundation (NSF) is an agency created in 1950 to further scientific progress, as Open Access Government reveals **197 Looking forward to the future of chemistry.** Angela K. Wilson and Carol A. Bessel from the Division of Chemistry (CHE) at the NSF provide a fascinating insight into the future of chemistry

202 Maintaining international collaboration: Chemistry has no nationality. Royal Society of Chemistry President Professor Sir John Holman reflects on the importance of maintaining international collaboration following Brexit

206 Swedish research and ducation is at the forefront of change. The work of Swedish Minister for Research and Education, Helene Hellmark Knutsson, is profiled by Open Access Government in this compelling article

210 Environmental toxicology in the regulation of

chemicals. A group of experts at the Society of Environmental Toxicology and Chemistry-Europe shed light on the environmental risk assessment of chemicals

214 Promoting Science: Stepby-step is a step in the right direction. Gustavo Carvalho and Emanuel Matias from the Youth Science Association's (AJC) discuss the importance of promoting science amongst young people in Portugal

220 Human sperm cells, the overlooked sentinel of our living environment.

Luigi Montano of the Local Health Authority (ASL) Salerno and Alberto Mantovani from Istituto Superiore di Sanità explore the relationships between the environment and sperm cells

222 Supporting world-class research in France.

Open Access Government lifts the lid on the work of the French Minister of Higher Education, Research and Innovation and the National Center for Scientific Research

SPECIAL FOCUS: BLOCKCHAIN, INNOVATION & GROWTH



228 The rise and future of Blockchain. In this article, the founder and co-founder of the Blockchain Federation provide insight into the future for a blockchain-based purpose-economy

232 Blockchain insurance set to change the industry. Open Access Government's Jonathan Miles explores the tremendous potential of Blockchain in the European insurance industry

234 Linking consumption and production. James Lomax from the Economy Division at UN Environment offers his thoughts on the policy priorities for global food systems 240 Blockchain: what is in it for the European economy? Benoît Abeloos, Policy Officer at the European Commission gives a compelling glimpse into how virtual currency could affect the economy

242 The outlook of the Finnish economy. Finland's Ministry of Finance lifts the lid on the current phase of rapid growth of the Finnish economy and their expectations for the same in 2018



250 Cyber security concerns all of us. European Commissioner Dimitris Avramopoulos underlines the responsibility of companies, governments and citizens when it comes to cyber security

256 Changing regulatory rules in financial institutions. Jean Noël Georges at Frost

& Sullivan explains how RegTech providers can aid financial service organisations in meeting changing regulatory rules

262 Welcome to the era of open government. Director, Policy & Community at BCS David Evans provides an expert insight into the world of open government digital services

268 Why the EU Single Market has still not reached its

full potential. Marco Hafner shares his insights into why the EU Single Market has still not yet reached its full potential and where it can go in the future



SECURITY

272 Searching for the silver bullet: towards a more effective Security Union.

European Commissioner for Security Union, Julian King underlines the role of the EU and national governments in keeping citizens safe

276 A vehicle for change: Today's combat vehicles market. We spoke to Alix Leboulanger and Samuel O'Toole at Frost & Sullivan to get their insights into the current state of the combat vehicles market



GOVERNMENT

282 A renewed relationship and Indigenous affairs. In this article, Minister Carolyn Bennett details her key priorities concerning the advancement of Indigenous Affairs in Canada

286 Rationalising the UK government estate through the Government Property Unit. The Government Property Unit aims to streamline the public-sector estate and generate better value for money from its assets, as OAG discovers



ENVIRONMENT

292 Zero Waste Scotland on the government's drinks containers return scheme. Zero

Waste Scotland reveals their thoughts on the Scottish Government's plans for a drinks containers deposit return scheme

294 The future of the natural environment. The UK's Secretary of State for Environment, Food and Rural Affairs Michael Gove sets out his vision for the future of the natural environment

298 How the Scottish Government is taking responsibility for global issues.

In an exclusive interview a spokesperson from the Scottish Government speaks to Open Access Government about how Scotland is fighting climate change

302 The European union explores new approaches to marine health. Karmenu Vella

explains how EU policies will innovate our approach to oceans and help to ensure the marine health of our planet

306 The efficient use of resources from the

environment. Norwegian Minister of Climate and Environment shares his thoughts on the struggle to reduce marine litter **310** Austria's climate change policy reflects its own research. Federal Minister of Agriculture, Forestry, Environment and Water Management Andrä Rupprechter reveals Austria's climate change policy

314 Science and policy in the Arctic States. Ambassador Aleksi Härkönen provides a compelling glimpse of the organisation's efforts on climate change and pollution in the Arctic States

318 Changes in the Arctic and Matarctic under global warming. T. Yamanouchi & H. Enomoto from the National Institute of Polar Research explore the abrupt and potentially worrying changes in the Arctic today

322 Innovative research in Access Government provides an insight into the work of The National Science Foundation's Office of Polar Programmes' research about the Polar Regions

326 Biodiversity loss – political will lacking in Europe. Member of the European Economic and Social Committee (EESC), Lutz Ribbe lifts the lid on biodiversity loss and nature protection issues



THE BUILT ENVIRONMENT

332 The importance of cities as partners in successful governance. Anna Lisa Boni, secretary

general of EUROCITIES, shares her reflections on the growing importance of cities as agenda setters **336 The UK's untold stories.** EPP-coordinator for REGI, MEP Lambert van Nistelrooij sheds light on the importance of engaging citizens and improving communication with the EU



AGRICULTURE

342 The 21st Century belongs to Canadian agriculture.

Canadian agriculture has deep roots and the government is working to build a future for the next generation of farmers, says Minister Lawrence MacAulay

344 Water and Agriculture in Hogan recently shared his thoughts on the role of agriculture in water sustainability, during a speech at European Policy Centre Dialogue

352 The approval process of pesticides and the science behind it. Graeme Taylor, director of public affairs at European Crop Protection Association reveals the impact of technology on the pesticide approval process

354 Food production: The role of the animal health industry in Europe. Secretary General of AnimalhealthEurope Roxane Feller,

of AnimalhealthEurope Roxane Feller, outlines the important role that the animal health industry plays in food production in Europe today

356 USDA's high-tech tools to identify dangerous pests. Greg Rosenthal of the U.S. Department of Agriculture's (USDA) lifts the lid on their work with digital identification tools to identify dangerous pests

366 Leading America towards a better future through

in-house research. The Agricultural Research Service (ARS) is the U.S. Department of Agriculture's scientific in-house research agency, as Open Access Government discovers

370 How communities are strengthening their food systems. Assistant vice president of programmes at American Farmland Trust, Julia Freedgood explains the challenges around the increasing demands to food systems



ENERGY

for the future

372 Energy efficiency a win-win for Canada and industry. The Honourable Jim Carr, Canada's Minister of Natural Resources, looks at the potential of energy efficiency **378** A fusion future. Laban Coblentz, Head of Communication, ITER gives an absorbing insight into all things fusion and the future of fusion energy



ECONOMIC AFFAIRS

382 'inon-statutory' economic development practitioners. The

Institute of Economic Development (IED) puts forward the case for supporting economic development practitioners in local government

386 UK set to improve in funding research and development. Warwick Business

School's Professor Stephen Roper reveals the UK Government's exciting plans for funding research and development in business

388 Backing innovation for commercial success.

Dr David Wilkes, Innovate UK's Deputy Director – Connect Portfolio explores the importance of driving UK productivity and economic growth by supporting businesses to realise the potential of new technologies



IKAN2PUKI

390 Priorities for rail transport in Denmark.

Ove Holm, from the Danish Transport and Logistics Association (DTL) reveals his opinion on the challenges around rail transport in Denmark, including ERTMS

396 Right on track – the future of European rail. Nicolas Furio from Unife explores the latest developments in the all-important European rail industry and what they mean for the future

400 The key role of the aviation sector in the

UK economy. Graham Bolton, Chairman of the British Aviation Group provides an insight into the role of the aviation sector within the UK economy



EDUCATION & YOUNG PEOPLE

404 The Education Policy Institute and education performance in England. Executive Director of the Education Policy Institute, Natalie Perera shares her reflections on education performance in England today

406 Bercow: children's communication skills ten years on. Mary Hartshorne, Head of Evidence at I CAN, the children's communication charity writes about the importance of good language and communication skills





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The EU's 'One Health' on tackling antimicrobial resistance

European Commissioner for Health and Food safety Vytenis Andriukaitis outlines the EU's 'One Health' approach to tackling antimicrobial resistance

Any of us know that misuse of antibiotics in people leads to antimicrobial resistance (AMR) – a growing challenge already responsible for 25,000 deaths in the EU every year. However, practices in veterinary medicine and farming also play a role in increasing bacterial resistance. To address the risks, including the one emanating from our food chain, the EU has championed a 'one health' approach to tackling antimicrobial resistance for nearly two decades, taking concrete actions in human and veterinary medicines simultaneously.

Experts agree that reducing antimicrobial use in foodproducing animals would help decrease the level of AMR we see in Europe and worldwide today. They urge, for example, that critically important antimicrobials for human medicine should only be used in animals as a last resort, and that the use of medicated feed as a preventative measure in food-producing animals, should be stopped.

Taking this advice seriously, the Commission adopted back in 2014 a legislative proposal on veterinary medicinal products and on medicated feed. They include regulatory tools that enable the Commission and EU countries to continue protecting animal health and welfare, whilst reducing the development and spread of AMR resistance in animals and hence in the food chain. I encourage both the Council of Ministers and the European Parliament to adopt these two pieces of legislation with no further delay.

This June, I presented a new EU 'One Health' Action Plan on AMR, taking account of the lessons learned from the previous one which ran from 2011 to 2016. I want us to focus on key areas with the highest added value for EU countries and make sure that human, animal and food-related actions are prominent in all three of its pillars. Examples include:

Pillar 1: Making the EU a best practice region

- Reviewing EU implementing legislation on monitoring AMR in farm animals and food;
- Providing evidence-based data on possible links between consumption of antimicrobial agents and the occurrence of antimicrobial resistance in humans and food producing animals and;
- Continuing to promote animal husbandry systems and feeding regimes which support good animal health, while reducing antimicrobial consumption.

Pillar 2: Boosting research and innovation

- Supporting research to better understand the epidemiology of AMR, in particular the pathways of transmission between animals and humans, and their impact;
- Increasing the knowledge-base on barriers to the wider use of vaccination in medical and veterinary practice and;
- Encouraging the uptake of diagnostics in medical and veterinary practice.

Pillar 3: Shaping the global agenda

- Working towards continued high-level political attention and commitment to one health AMR action, including in the United Nations forums, the G7 and G20;
- Advocating the EU one health standards and measures for tackling AMR in trade agreements and;
- Helping develop AMR strategies in the areas of food safety and animal health in developing countries, through regional training workshops.

Only a few months on from the action plan's adoption,



I am pleased with the progress we are making on its veterinary medicine and food safety aspects:

The EU One Health Network, bringing together chief veterinary officers and chief public health officers from all EU countries has already met to discuss objectives and working methods. In July, three EU-level scientific agencies added to scientific evidence on the 'one health' aspect of AMR with the JIACRA II report which confirms the positive association between antimicrobial consumption and resistance in both humans and food-producing animals.

On 29 September, the Commission and the Food and Agriculture Organisation on the United Nations (FAO) committed to intensify cooperation on tackling the spread of AMR on farms and in food systems. Before the end of October, our scientific agencies will adopt a list of indicators for the surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals.

As cooperation and coordination are essential to make all aspects of the action plan a success, I am pleased with the welcome and the offers of cooperation and support I have received from national health and agriculture ministers. I also welcome the support and commitment of international bodies such as the WHO, OIE and FAO. I am confident that together we can make progress in tackling AMR with a one planet, one voice and one health approach.

The European Food Safety Agency (EFSA), The European Centre for Disease Prevention and Control (ECDC) and The European Medicines Agency (EMA).

Vytenis Andriukaitis EU Commissioner for Health and Food Safety European Commission cab-andriukaitis-webpage@ec.europa.eu https://ec.europa.eu/commission/commissioners/2014-2019/ andriukaitis en #teamJunckerEU www.twitter.com/V_Andriukaitis

What is the future for clinical and health research in Europe?

Experts discuss the FEAM-BioMed Alliance paper, which outlines how the next EU Framework Programme can further support biomedical research in Europe

he ultimate goal of clinical and health research is improving people's health and wellbeing, by addressing medical needs which are still unmet. Such an effort requires collaboration going beyond national borders. For this reason, the European Union has been supporting research collaborations at a European scale from the foundation of the European Economic Community in 1957 until today's Horizon 2020, the European Union Framework Programme for Research and Innovation. As this Programme will end in 2020, debates have already started on its successor, the so called FP9.

How to strengthen the environment for clinical and health research in Europe? What are the gaps to be addressed to overcome current fragmentation in funding?

The Federation of European Academies of Medicine (FEAM) and the Alliance for Biomedical Research in Europe (BioMed Alliance) have joined forces to address these issues. In a recently published position <u>paper</u> on Strengthening biomedical research for the benefit of European citizens, the two organisations put forward recommendations to help improve clinical and health research in Europe. These tackle the following 5 areas:

Collaborative multidisciplinary translational research

To improve patients' lives, new approaches are needed in the translation of basic research into real clinical benefit. The European Union and its Member States need to jointly address the current fragmentation in funding for clinical and health-related research and establish collaborative multidisciplinary networks to support novel research and/or explore newly emerging research topics.

Paradoxically, successful collaborative projects would need also mechanisms of selection for individual participants, beyond their need for funding and their willingness to join a particular network. This means that the EU must have a mechanism whereby one individual researcher is funded for one focused precise scientific and biomedical question. If successful, such an individual research group/investigator would qualify to join the networks of translational teams. For this model to function, the networks that provided major advances should be maintained, as we suggest in the next section.

Continuity of funding for excellent projects

EU grants for research and innovation have helped making important contributions to science. But what occurs after the end of the financial support? Many promising collaborations are often disbanded once the grant has expired and current conditions make it difficult to achieve sustainability.

FP9 should address this issue and introduce mechanisms which allow to extend funding for projects which have accomplished unique results, widely used by the scientific and biomedical communities and which need to be continued to maximise the potential of real successes and innovation. Such stable networks would then be joined by new groups, their selection based on merit being essential. As stated above, a first step should be advances made on specific problems supported by early individual grants. This system would combine the advantages of USA system, with the tradition of collaboration and building schools in Europe.

The importance of precision medicine in designing clinical trials

The development of precision medicine is leading to new patient-focused clinical outcome measures, novel approaches to clinical trial design and the establishment of new systems and infrastructures to enable the collection of healthcare data. However, lack of sufficient funding and focus prevents the European Union from making the most out of the new inter-



ventions under development and from ensuring compliance with regulatory guidelines, ultimately preventing patients to access the best available treatments. This issue is also complicated by the unclear and unequal reimbursement policies with respect to molecular/genomics analyses for patients.

Training programmes for the next generation

Education and training play a key role in in preparing the next generation of research-oriented clinicians and clinically-oriented researchers, thus making sure that clinical researchers are knowledgeable in basic research, while basic researchers understand clinical challenges. Major investment will be needed to achieve this and to make sure the current divergence of training requirements across Europe is overcome. Given the increasingly international nature of research and clinical practice, this represents a bottleneck to be urgently solved.

A vision for a European Council for Health Research

FEAM and BioMed Alliance paper supports the European Commission's Scientific Panel for Health's idea¹ to further investigate the concept of a science-driven European Council for Health Research. Such a council can act as catalyst for reform, as proper funding mechanism and as a scientific advice platform. Acting as a unique hub for health research innovation, the objectives of the European Council for Health Research would be to implement long-term sustainable research programs and to exploit in full the benefits of cooperation and coordination across Europe.

As a conclusion, the European Union provided great support to clinical and health research. However, certain challenges emerged and they need to be tackled in order to improve the life of patients and for the benefit of the society as a whole. Solutions can come only through integrated efforts from a broad community of stakeholders including researchers but also policymakers, healthcare professionals, industry, and patients. That is why, to continue debate around this important issue, the FEAM European Biomedical Policy Forum (a new initiative of FEAM which provides a platform for discussion on key policy issues for the biomedical community) will organise in early 2018, its first annual lecture on the future of biomedical and health research in Europe. This will provide an excellent opportunity for interaction and cross-sectorial discussions among European biomedical stakeholders.

1 This idea is expressed in the Scientific Panel for Health, vision on '<u>Better Research for Better Health</u>', May 2016.





Stefan N. Constantinescu, MD, PhD Professor, Université Catholique de Louvain, de Duve Institute stefan.constantinescu@uclouvain.be

Silvia Bottaro

FEAM Forum Policy Officer silvia.bottaro@feam.eu.com Federation of European Academies of Medicine (FEAM)

Laurence Legros Executive Director

laurence.legros@feam.eu.com Federation of European Academies of Medicine (FEAM)

Avenue Hippocrate 74, UCL 75-4 Brussels 1200 Tel: +322 764 7540 Fax: +322 764 65655 https://www.deduveinstitute.be http://www.ludwigcancerresearch.org

European health information project BRIDGE Health looks to the future

Petronille Bogaert and Herman Van Oyen at BRIDGE Health provide a fascinating overview of the European health information project today

BRIDGE Health was a European health project under the third European Union (EU) Health Programme. The acronym stands for Bridging Information and Data Generation for Evidence-based Health Policy and Research. The project was launched in May 2015 and ran until October 2017. It was coordinated by the Scientific Institute of Public Health in Belgium and included 31 partners in 16 countries.

It also assured a knowledge transfer from past health and research frameworks in domains of population health and health system monitoring, indicator development, health examination surveys, environment and health, population-based injury and disease registries, maternal and child health, clinical and administrative health data collection systems and methods of health system performance assessment.

One of the major tasks of BRIDGE Health was to prepare a comprehensive, integrated and sustainable EU Health Information System, which incorporates know-how and technical tools to coordinate and harmonise research and surveillance for member states in key EU health policy areas.

The Concept Paper: how to improve the EU health information system?

The Concept Paper presents the

BRIDGE Health analysis of the current situation and the possibilities for creating an organisational entity that could take up some of the support tasks that come with the need for strengthening the EU health information system. Using multi-criteria analysis, the advantages, disadvantages and short-term feasibility were investigated for strengthening or extending existing structures (ECDC, DG SANTE, the JRC, Eurostat, WHO or OECD) or by creating a new structure (a new agency, an ERIC, a Joint Action, or a supra-European structure).

This analysis concludes that a European Research Infrastructure Consortium on Health Information for Research and Evidence-based Policy (HIREP-ERIC) is now the most feasible option. This may set important steps in the right direction and fulfil some of the most important criteria for an effective organisation around the scientific underpinning of health policy by new and better evidence from more and better comparable data.

What is the HIREP-ERIC?

A European Research Infrastructure Consortium or ERIC, is a legal structure recognised under European Union law that brings together scientists and researchers across Europe. The ERIC consortium provides a network of relations between scientists from various countries, and between scientists and policy-makers. In this way an ERIC facilitates interaction of existing institutions and ensures a more permanent and sustainable collaboration.

The HIREP-ERIC strives to this for the field of health information. It can facilitate the governance of health information activities in the EU by bringing together existing networks in health information and support the development of new ones both within and between Member States. In practice, the HIREP-ERIC provides central governance for regular availability and easy access to high quality and comparable data from EU countries for research and policy purposes at national, EU and international level in fields of population health monitoring and health system performance assessment.

The activities of the HIREP-ERIC

The HIREP-ERIC will focus its activities around generating, hosting, exchanging and translating health information.

Generating health data and indicators

The HIREP-ERIC will provide technical and expert support for the development of comparable, standardised and accessible data and indicators for health status and health determinants, health services and health systems. This includes updating and developing new indicators, where needed, and improving and evaluating existing indicator sets.



Hosting health information

The HIREP-ERIC will facilitate and support the development and hosting of virtual and interoperable repository platforms. It will provide central coordination for EU countries to provide data and exploit economies of scale by facilitating the extension of existing data repositories.

Exchange health information

The HIREP-ERIC will enhance best practice exchange between countries and support mutual learning by focused capacity building. This can be done through dedicated training programs set-up and supported by the HIREP-ERIC.

Translate health information

The evidence and knowledge produced by research are not always readily available and may need further analyses, syntheses and translations to inform policy making. The HIREP-ERIC will support researchers and institution in charge of health monitoring to optimise their output to better inform policymakers and citizens.

The HIREP-ERIC structure

The HIREP-ERIC will host two types of networks of scientists.

- The national network. These are in EU countries national counterparts that are member of the HIREP-ERIC. The national network brings together the key players in health information in a country and ensures there is interaction between those players at national level. Additionally, the national network will be a national health information provider and interact with the HIREP-ERIC. The national networks work on crosscutting issues.
- The domain specific networks. These are network coordinators in health information domains. They are content specific and respond to current priorities and projects. The domain specific networks carry out deep analysis in area for which capacity does not always lie at national level. They can liaise with national networks providing guidance on how to collect and analyse data at national level, and through this, harmonise activities.

What after BRIDGE Health?

Every end is a new beginning. A new Joint Action on Health Information entitled InfAct will start and continue the work described here. Among other tasks, InfAct will focus on the development of the business case and roadmap for implementation of the HIREP-ERIC, including the set-up of national networks and domainspecific networks.



Petronille Bogaert Project Researcher

Herman Van Oyen Director

Scientific Institute of Public Health Belgium Tel: +32 2 642 57 48 bridge.coordination@wiv-isp.be www.bridge-health.eu www.twitter.com/bridge_health

Making it happen: Addressing the implementation gap in European health policy and practice

Dr Usman Khan, Executive Director of the European Health Management Association tells us his thoughts on public health in the European space

n a post-truth age, there still appears to be a degree of consensus that undertaking comparative research is a good thing to do. It is certainly the case that a significant amount of health research is undertaken at European level through established streams of work, such as the European Commission's Horizon 2020 programme.

As a long-established partner in providing expertise in stakeholder engagement and knowledge dissemination for such projects, the European Health Management Association (EHMA) has seen this particular aspect of the European policy process at first hand. Yet whilst as a membership led Brussels based NGO, EHMA is fully committed to supporting the development of effective health care solutions.

I used a recent keynote presentation at an international public health conference in Sofia to reassess the ultimate value of such work. The question I sought to answer was to assess if there is a gap between the 'what' of European health policy and the 'how' of practice on the ground at a national level and if so, whether such a gap can be bridged?

The question can most usefully be broken down into the following five sub-questions:

- 1. Do European and national health policies align?
- 2. Is there a common understanding of what works?
- 3. Do we know how to transfer knowledge on what works?
- 4. Do we know the value of European collaboration in supporting improvement?
- 5. Do we know how to bring this all together?

That first question, raising as it does the notion of health system convergence, would appear to provide for a broadly affirmative response. European nations are increasing finding themselves facing aligned demand drivers, characterised by a general levelling or fall in injuries and communicable diseases, set against marked increases in non-communicable disease such as diabetes and cardiovascular disease. This is feeding itself into a degree of policy alignment, which is manifested at a global level through initiatives such as the WHO's Sustainable Development Goals and at a European level, with programmes such as the European Innovation Partnership (EIP) on Active & Healthy Ageing.

But agreeing on 'what?' does not necessarily imply that there is common agreement as to 'what works?' And in this regard the connection between policy development, evaluation and evidenced based healthcare requires further scrutiny. From experience, EHMA has often found that whilst what one may term the long game - programme evaluation and impact assessment are well developed at the European level, it could be contended that this does not always translate into programmes of fully assessed and road tested programmes ready to implement at a national level. That said, I have also seen increasing evidence of a more flexible and dynamic approach emerging in some research programmes, incorporating more immediately accessible methodologies such as the Plan, Do, Study, Act approach.

Taking the discussion one step further, it is also evident that spinning a golden thread that connects policy to practice, not only requires a clear and evidenced assessment of what works, but it also requires that stakeholders know how to transfer this knowledge from a supranational to a national, local and institutional level.



Like the childhood game of 'broken phone', the risk of the essence of an improvement initiative being lost as it is repeatedly represented in different settings, is a significant one, but at EHMA our experience is that the policy process is responding to this challenge by finding new and innovative ways to facilitate effective knowledge transfer. Many of these connect to the fourth question I have posed, of assessing the particular added value of European collaboration, where the quite unique combination of a common political mandate can provide a particularly empowering space for a mutually beneficial knowledge exchange.

So, one comes full circle to consider the overall effectiveness of the European knowledge transfer and improvement project, where the school report is likely to say, 'good progress, but could do better'. The key to such improvement will involve further evolution of the relationship between European agencies and their academic and NGO partners and national agencies and service delivery organisations. Improved two-way communication, the ability to creatively interject within the research process and a greater focus on developing the toolkit for knowledge transfer – will all help to ensure that the greatest value is reaped from this significant part of the European improvement project.

Usman Khan Executive Director

European Health Management Association Tel: +32 (0)2 502 6525 Usman.Khan@ehma.org http://ehma.org/ www.twitter.com/EHMAinfo

How is the UK supporting biotech to create innovative medicines?

CEO of the BioIndustry Association (BIA), Steve Bates explores how the UK government is supporting biotech in order to create innovative medicines

The UK has some of the world's most exciting science, a supportive business environment, and strong companies led by experienced management teams. It also has a unique ecosystem that is wider than just industry, with world leading universities (the top 2 universities in the world), charity sector and institutes. In terms of financing, UK practices of supporting biotech attracts the most venture capital financing in Europe and the third most in the world.

As the nation looks towards Brexit in 2019, the government has taken steps to help ensure the future of the sector. The recent release of the Life Sciences Industrial Strategy and new proposals for sector funding in the Patient Capital Review are important steps forward in ensuring that the industry can continue to thrive and provide cutting edge treatments for patients.

The BIA has long called for a revived industrial strategy to maintain and build investment into the UK and grow and scale the UK's innovative bioscience companies. The strategy provides a wide-ranging view on many of the issues that underpin the life sciences ecosystem, including discovery and translational science, NHS collaboration, manufacturing and skills.

It also challenges the sector to engage further with the opportunities in healthcare presented by new technology through the proposed Health Advanced Research Programme (HARP). Industry will continue to engage with government, to ensure that this strategy can pave the way for an impactful sector deal that can help deliver the BIA's vision to establish the UK as the third global cluster for life sciences.

Alongside the publication of the strategy, the government also announced a new £13 million funding competition for a medicines manufacturing centre, a £66



Steve Bates, CEO of the Biolndustry Association (BIA)

million investment in a vaccines development and manufacturing centre, a £30 million investment in cell and gene therapy treatment centres, a £12 million cell and gene therapy investment in Stevenage and £25 million to support SMEs and boost innovation.

Collaboration

These new investments and funding competitions bring to life the calls the BIA has made, both individually and through collaborations such as the Medicines Manufacturing Industry Partnership, to grow our industry's future. It is great to see SMEs front and centre of the government's vision for the UK life sciences sector.

For the sector to achieve its potential and ambition, a sea change in the levels of scale-up capital and fiscal support is required. It is great to see many of the necessary actions the BIA has called for in this strategy, from reform of Entrepreneurs Relief to making R&D tax credits work better for SMEs. These recommendations, alongside the focus of the forthcoming Patient Capital Review, provide a great foundation to take the UK's life sciences sector to the next level.



The aim of the Patient Capital Review is to strengthen the UK further as a place for growing innovative firms to obtain the long-term 'patient' finance that they need to scale up, building on current best practices and the BIA recently made its own submission to the review.

The UK has the world-leading science and commercial skills to truly change and improve the world in the 21st century. Exciting breakthroughs are happening almost every day in cell and gene therapy, genomics and engineering biology. UK bioscience companies have global ambitions but have long-lacked the domestic financial support they need to scale and take on their US and Asian rivals.

It's great to see the government taking this issue seriously and willing to work with industry to address it through the Patient Capital Review. Critically, we need to open up opportunities for pension funds and other large investors to support the growth of innovative UK businesses. The proposed National Innovation Fund is an exciting and promising action that the government should take forward. This will secure greater economic activity and support the creation of high value sustainable jobs across the UK, whilst helping to address the deficits that many of our pension funds are facing. The BIA submission sets out a series of practical measures that alongside the forthcoming sector deal for life sciences will enable the UK to become the leading place in the world to discover and develop new therapies and technologies for patients, and scale businesses to a global level to capture their full economic potential.

For more information on all the latest UK biotech policy developments go to the BIA's website www.bioindustry.org

Steve Bates CEO

Biolndustry Association (BIA) Tel: +44 (0)20 7630 2180 www.bioindustry.org www.twitter.com/BIA_UK



A group of experts from ISBER shed light on the science of biobanking and its role in delivering modern and precision medicine

wenty years ago, an internet search for the word "biobank" would have returned almost nothing; today, there are millions of results. The term biobank commonly refers to a large collection of tissue samples (with associated biological and medical data), such as surgical biopsies (fresh frozen or in paraffin sections), blood and serum samples, different cell types, DNA, RNA; all carefully collected for research purposes.¹ The science of biobanking is very broad and covers collections of plant, animal, or human specimens. For the purposes of this discussion, we will focus on human biobanks.

Two decades is a very short period of time, for a concept that has become vital to delivering modern, precision medicine – both in terms of research and the clinic itself. One of the first biobanking initiatives came from the Organization for Economic Cooperation and Development (OECD), which advocated the importance of biobanks, but also insisted on the need to have an accreditation system.²

In the years following this OECD proposal, various countries began establishing biobanks as research infrastructure. Thus, many national biobanks and biobank networks were created in Canada, the UK, USA, China, Estonia, South Korea, Finland, Denmark, Sweden, France and many other countries. In our opinion, biobanks crucially underpin and facilitate the national and international medical research efforts, by providing high-quality, research-ready samples. In addition, biobanks are linked to clinical data for investigators, according to a set of best practices and standards.

In 1999, the International Society of Biological and Environmental Repositories (ISBER) was formed



(<u>www.isber.org</u>). Since then, academics, biobankers, NIH Institute representatives, patient advocates, industry representatives, lawyers and others with an interest in biobanking meet annually at the ISBER Annual General Meeting, to share their expert knowledge in the field.

In 2005, ISBER developed and published the Best Practices for Repositories, which was revised at regular intervals and translated into many languages. We are currently anticipating the fourth edition should be published late in 2017.³

This is the premier 'handbook' for biobankers to achieve quality products in their laboratories. Topics such as cost recovery, facilities, equipment, safety, quality assurance and quality control, ethical issues, specimen collection, processing, and retrieval, training, specimen culling, and many more are discussed. ISBER's journal, Biopreservation and Biobanking, is a well-established, international peer-reviewed journal, that highlights vital research in the field.⁴

The road to precision medicine

Medical research in the era of precision medicine is based on the analysis of samples with clinical data – and, because the associations are often weak, we need these samples in large quantities. The implication is clear: if more, well-characterised, high-quality samples are available through biobanks, the faster research will advance and impact upon the faster delivery of healthcare today. However, to fulfil the aim of precision medicine, challenges remain on the road ahead.

"New or more flexible operating and funding models are needed to support the growth of biobanking in the medium and long-term."

Standards and harmonisation

The most important aspects of a biobank are consistency and quality. The validity of the data generated by biobanked samples, depend on their quality, which is in turn dependent on the use of stringent standards in collecting the biospecimens and delineating patient characteristics. Variations associated with collecting, processing and storing different samples and the accompanying clinical data, make it extremely difficult to extrapolate or to merge data from different studies. Without that information, it's easy to introduce invisible bias into the work, leading to irreproducible work! Therefore, the standardisation and harmonisation of biobanking practices are of paramount importance.

Data and ethics

As medical researchers "think bigger" than ever before, their need for data grows ever stronger. It demands the gathering and administration of large collections of samples and related data, often from multiple sources. This is not an endeavour for individuals, single projects, or small research groups, because of the high costs in time, sample access, technological resources and the funding involved.

Hence, 'virtual biobanks' started forming with institutional collaboration and geographically distributed forms of endeavour. One such major collaborative

Clinical and hospital-based biobanking for next generation patient care

Professor Berthold Huppertz from Biobank Graz, highlights the importance of maintaining high sample quality in biobanking

he emerging new ISO standards for pre-analytical handling of samples in biobanking give hope that sample quality can be much better maintained and documented. This of course should lead to improvement of patient care. However, where do you find the link between improving the pre-analytical pathway of sample handling in biobanks and improved patient care?

Overview on the pre-analytical pathway

For any analysis of a human sample, independent of whether this analysis is performed in a research setting or in a clinical routine setting, the sample needs to be taken from the body, transported, processed, maybe stored and used for analysis.

Let's take a blood sample as example. Blood drawing normally takes place in a clinical setting using standard equipment resulting in the receipt of some millilitres of blood in a primary blood tube. In a clinical setting, this primary blood tube is then standing in the clinical ward for a while, transported to a (central) laboratory where processing and analysis takes place.

In a research and biobanking setting, this primary blood will again be taken in a clinical setting, standing in the ward and then is transported to a lab or biobank. Here, the blood is processed, then divided into smaller aliquots, stored (short-term, mid-term or long-



term) and subsequently distributed to be used for a research analysis.

This seems to be an easy path and the question is why there is the need to develop ISO standards for this. To give an answer here, we need to go into detail into this pathway.

The pre-analytical pathway in detail

1. Blood drawing procedure

The person performing the venepuncture needs to have a specialisation and respective training not to harm the donor. Hence, it needs to be documented who has performed the venepuncture and what instruments have been used.

2. Labelling of primary blood tube Not only the person performing the venepuncture, also the donor needs to be identified. Of course, there is no need to have names and direct person-related data. Codes and identification numbers are sufficient. Therefore, the primary blood tube containing blood of the donor must be specifically and uniquely labelled to provide a clear link between donor, primary blood tube and blood sample.

3. Time of blood drawing

As soon as the blood sample has left the body of the donor, the sample is present in a different environment: There is no longer flow of blood, temperature has changed, light is present and the surrounding changed from living cells communicating with the blood cells to a plastic tube. Hence, it is important to document the time of blood drawing to know when the change of environment started.

4. Duration and conditions of sample transport

After blood drawing, the sample is normally placed in a rack together with other samples and waits to be transported to the laboratory. At that time, the sample is still alive and will adapt to the changes of its environment (temperature, light etc.). To give an example: The cells sense lower temperature and stop of blood flow and will react with increasing their level of stress proteins as in the body both conditions are extremely harmful. The longer the samples are staying in the rack the more changes within the sample will occur. This is true for the time the sample is staying in the clinical ward as well as for the time the sample is transported to the laboratory. Hence, documentation of times and temperatures are essential.

5. Biobank

Documentation of the arrival time at the biobank is needed to calculate the duration of sample transport. The sample will be processed according to the protocols of the biobank and divided into smaller aliquots. These aliquots will be taken from a single sample and thus allow multiple different analyses of the same sample without freeze-thawing the sample multiple time. The aliquots are then frozen and stored at minus 80°C or lower until use. Documentation of each step during processing and storage is mandatory for a biobank.

6. Analysis

Finally, the primary blood sample will be distributed and send to a laboratory, where the analysis will take place. Within the laboratory, the sample will be further processed depending on the needs of the analysis, the analysis will be performed and the respective results will be used to increase knowledge.

The pre-analytical pathway today

Today, there is quite some variability between biobanks and hospitals in the documentation details of the pathway described above. In some hospitals all or nearly all the steps are documented as described, while in other hospitals only some or few of the steps are documented. Hence, depending on the hospital setting, sometimes only little data on the pre-analytical pathway can be retrieved for subsequent analysis.

This discrepancy has a major negative impact on research results - and hence on patient care. If biobanked samples are used for analysis, they should be comparable in terms of handling, timing, temperatures, processing etc. If some samples are used with 30 minutes while others are used only the day after blood drawing standing in a room or in the sun in summer or in the cold in winter, this will of course dramatically influence the content of the samples. Hence, there is massive variability in the analytical test results that is simply due to differences in pre-analytical handling of the samples rather than due to differences between healthy and diseased donors.

The pre-analytical pathway tomorrow

The emerging ISO standards for biobanking will set the stage for improved documentation of the pre-analytical pathway. Hence, any variation not linked to the health status of the donor can be linked to variations in pre-analytical handling of the samples.

This, of course, is not enough! What is needed is a much better understanding of the major impact, handling of samples has on the quality of results obtained with these samples. Hence, it is not only documentation that makes the difference, but rather proper handling of the sample at each step of the pathway to optimally maintain its quality.

Only then, results from the clinical setting in combination with the results from the research setting can – without doubt – be directly linked to the health status of the donor.

This will have a direct and major positive impact on:

- Patient care in the clinical setting: no longer false positive or false negative results!
- Research on e.g. identification of new biomarkers for prediction: no longer massive variations in a cohort due to differences in sample handling!
- Development of new treatments and medication: no longer very time consuming pre-clinical testing due to missing comparability of samples!



Professor Berthold Huppertz, PhD Director and CEO, Biobank Graz Head, Organisational Unit of Research Infrastructure Medical University of Graz Neue Stiftingtalstraße 2B/II 8010 Graz, Austria Tel: +43 316 385-72716 (secretary) biobank@medunigraz.at

Continued from page 23

effort, is the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-ERIC).⁵ The pan-European BBMRI vision emerged from the recognition that keeping up with policies and developments elsewhere, most notably in the USA, necessitates integrated European research.

These "big data" approaches in precision medicine require access to personal and often identifiable information and are coupled with ethical challenges. For example, the 'big data' complexity may impact informed consent; or the need/ability to return the outcomes of test to the patients who originally donated their samples. Considered together, a constructive and transparent inclusion of ethical questioning in this rapidly evolving field is necessary to support the societal acceptance and responsible development of the technological advancement.

Costs and sustainability

The aspect of biobank sustainability is critical for precision medicine research. Recent advances in health research (including social and public health research, and advances in technology) have increased demands on the types of samples and processing provided by biobanks.

Specifically, researchers require increasing sample numbers and associated clinical data, biobanks increasingly implement standardised processes to attain higher quality standards, while funders seek performance metrics and assurances for their investments. Research funding agencies, institutions and philanthropic organisations, often assume that beyond the initial start-up operational and infrastructure costs that biobanks at some point should be become "self-sustaining."

This is rarely achievable in the context of planning a large national infrastructure with a 15- to 20-year life cycle even with governmental or institutional funding, and it does not represent most biobanks attached to integrated academic/health institutions or disease focused biobanks, such as those assisting with rare genetic conditions research.⁶ Thus, new or more flexible operating and funding models are needed to support the growth of biobanking in the medium and long-term.

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Zisis Kozlakidis Division of Infection and Immunity University College London, United Kingdom



David Lewandowski Brooks Life Science Systems Chelmsford, United States



Brent Schacter CancerCare Manitoba University of Manitoba Winnipeg, Canada

International Society for Biological and Environmental Repositories (ISBER) Tel: +1 604 484 5693 info@isber.org www.isber.org www.twitter.com/ISBER_ORG

Suicide: A major public health concern

Dr. Jane Pearson from NIMH highlights suicide as a public health concern and addresses how it can be prevented and the contributing factors behind it

Suicide is a major public health concern. Over 40,000 people die by suicide each year in the United States (US); it is the 10th leading cause of death overall. Suicide is complicated and tragic, but it is often preventable. Knowing the warning signs for suicide and how to get help can help save lives.

In the field of public health, it is a type of death that is considered preventable, indeed things can be done in terms of the environment or ways to affect behaviour. Dr. Pearson says that in addition to suicide deaths (mortality), prevention approaches consider suicide attempts as morbidity to prevent, improving ways that people are functioning, feeling, thinking. So, we talk about both prevention of deaths and attempts, in terms of suicide.

"For suicide, it is difficult, because we don't have a blood pressure check or test that tells us much about an individual's suicide risk, so we rely on their ability to describe their internal state. That is not always easy for everyone, so that makes it a challenge now."

Dr. Pearson then tells us more about prevention and what is known about risk factors. Those who consider suicide typically have been on a trajectory which has been shaped by several things piling up, such as a mental illness, hardship, embarrassment and shame. There could also be a family history of mental illness and suicide, in terms of getting a background picture. Dr. Pearson describes why a history of attempting suicide increases risk for suicide death.

"There are many risk factors, which in them- selves are not specific, but people who have attempted suicide are at increased risk. We think that is because they have done it once before, and as such, they are not afraid to repeat those behaviours, and previous thoughts return that focus on suicide as the only solution. Because of the need to avoid psychological pain, these 'familiar' self-destructive tendencies may cancel out more 'life preserving' thoughts.

"So, the pattern is a complicated one, indeed researchers have asked people about their suicide thought patterns. Suicide thoughts can ebb and flow during the course of a day, weeks or even months. We are only just beginning to get an understanding of how this affects people daily. Sometimes however, there are precipitating events and we do have research in the US about the economic recession, such as losing their home which can be a precipitating event."

Signs and symptoms

Dr. Pearson explains the signs and symptoms of suicide – that is when people are thinking about it and their state of mind – from a public health perspective.

"If there is a means of suicide that is readily available when someone is contemplating suicide, then we know that is not a good combination. We want to put time between the person who is thinking about suicide, and how they are considering it.

"In the US, half of our suicides are by firearms. We know that if somebody is in a house with a firearm in it, then the risk is much higher for suicide. There is much international research, which reveals that if you have less access to lethal means, such as reducing access to guns or pesticides and the more time you can buy, then the less suicides they are.

"Another issue is having somebody else who can be there with you, in terms of having a social connection. We try to think though some ways that are acceptable to people and feasible for communities – and there



have been many interesting approaches to that when you think of the individual person's context.

"So, if it concerns an older adult – then they may be becoming increasingly isolated for several reasons – how would they make connections? If it was a youth in school, who feels they are not doing well and have no support or friends, we are trying to figure out ways to ensure they get help that is effective.

"While we have several studies from the community perspective, we also are thinking about how healthcare systems should know how to address people who are suicidal, especially when it comes to behavioural health. Unfortunately, training in mental health does not always include suicide prevention, but those requirements are beginning to change."

Ongoing research

In order to know who is most at risk and to prevent

suicide, scientists need to understand the role of longterm factors (such as adverse childhood experiences) as well as more immediate factors like mental health and recent life events. Researchers also are looking at how genes can either increase risk or make someone more resilient to loss and hardships, Dr. Pearson goes on to say.

There are a few institutes at NIH that recognise the behavioural side of suicide prevention. For suicide, there are no specific genes, but we might have some inkling of what might put somebody at risk (e.g., excessive drinking and other risk-taking behaviour), which is true for many other disorders where there is no specific gene.

"We also endeavour to access as many areas of health care now, in terms of larger data sets, by letting the computers pull out what might be considered as risk. If we have data from people who are followed over time, including whether they have died by suicide or not, we can figure out what the risk trajectories are.

Then the next step is to determine the best ways to talk to patients about their risk, as well as advising clinicians on what do with the information.

"For suicide, it is difficult, because we don't have a blood pressure check or test that tells us much about an individual's suicide risk, so we rely on their ability to describe their internal state. That is not always easy for everyone, so that makes it a challenge now."

Treatments and therapies

Research has shown that there are multiple risk factors for suicide and that these factors may vary with age, gender, physical and mental well-being, and with individual experiences. Dr. Pearson then underscores that there are treatments and preventative methods that are out there – to help prevent someone from taking their own life.

"If there is a means of suicide that is readily available when someone is contemplating suicide, then we know that is not a good combination. We want to put time between the person who is thinking about suicide, and how they are considering it."

She also tells us that there aren't many types of medication available now – which has been something of an issue in the US – because most pharmaceutical companies in the psychiatry area have not focused on preventing suicide death.

"They want medication to look safe, so there hasn't been much incentive to test medicine for suicidal people. There is one medication that reduces suicide risk for those with schizophrenia – and there is a lot of descriptive data on the value of lithium for people with bipolar disorder – to prevent relapse. While it's protective, it's very difficult to do long-term studies for proving that it specifically prevents suicide.

"As we are depending on people's thoughts and actions, which is true for mood and anxiety disorders generally, some of most effective treatments are therapies that help people to identify feelings, how not to act on them and what opposite actions could be taken. Cognitive therapy has been shown to be very effective for preventing suicide attempts. So, we must think about the specific thoughts and behaviours around suicide."

Concluding thoughts

In closing, Dr. Pearson stresses that when addressing suicide, it is vitally important to have an open and honest conversation concerning the subject. She also highlights the toll-free National Suicide Prevention Lifeline (NSPL) that is available.

"It's also important to keep a distance between themselves and the means they are think of, such as keeping them away from tall buildings and to be supportive and be there for them.

"The US has a national hotline, manned by some highly-trained counsellors. They work very hard to ensure people stay safe and get connected to health. It's also worth noting this is a tough haul – people don't reach a suicidal state overnight – the are many contributing factors."

Further information: You can call the toll-free National Suicide Prevention Lifeline (NSPL) at +1 800 273 TALK (8255), 24 hours a day, 7 days a week. The service is available to everyone. The deaf and hard of hearing can contact the Lifeline via TTY at +1 800 799 4889. All calls are confidential. The National Institute of Mental Health also encourages children to put the crisis number in their mobile phone contacts.

Dr. Jane Pearson Chair, NIMH Suicide Research Consortium at National Institute of Mental Health National Institute of Mental Health

Tel: +1 301 496 4000 NIHinfo@od.nih.gov www.nih.gov www.twitter.com/NIH

Genetic studies of suicide risk and research into mental illness

The Department of Psychiatry; University of Utah School of Medicine lifts the lid on their research into mental illness and suicide

early 800,000 people die by suicide every year, and suicide is the leading cause of death for people aged 15-29. While the environment has had an undeniable impact, evidence suggests that genetic factors play a major role in completed suicide.

Furthermore, while mental illness and suicide are often intertwined, most people who struggle with mental illness do not die by suicide, which implicates unique suicide genetic risk factors. Our team are focused on searching for these genetic risks. We believe that by increasing our understanding of underlying biological mechanisms, we can help to understand why some individuals are more vulnerable than others, and ultimately learn how to design both effective treatments and interventions.

Recent growth in the number of studies investigating suicide genetics has resulted in promising findings from studies of specific genes selected by research teams (candidate gene studies), and from broader studies of the entire genome (genome-wide association studies, or GWAS).

However, replicated findings have been rare, perhaps not a surprising result, given the likelihood of hundreds of different genetic risk factors. Replication has also been hampered by sample differences across studies, including differences in demographics



and/or in the primary diagnoses of cases.

For example, a study identifying genetic risks within older veteran suicides who had major psychiatric diagnoses, may not replicate results from a study of youth suicide cases with drug abuse. Studies also focus on a range of outcomes, from suicidal thoughts and behaviours to completed suicide. Previous studies suggest that genetic risk for suicidal thoughts and behaviours may be different from risks of actual completed suicide, so results across studies focusing on these different outcomes would not necessarily overlap.

Finally, designing genetic studies of suicide risk poses basic challenges for researchers. Candidate gene studies assume that the research team has made the correct choice among thousands of potential candidate genes. Genome-wide association (GWAS) studies avoid the need to choose genes to analyse, but the fact that there are likely so many different genetic risk factors makes separating true genetic signals from the noise caused by this heterogeneity quite daunting. Successful GWAS studies of similarly heterogeneous conditions, such as schizophrenia, have required genetic information from tens of thousands of cases and matched control samples before significant results became apparent.

In our studies, we have focused on the genetic piece of the suicide risk puzzle, because of several unique resources in Utah that circumvent many of these research difficulties. The foundation of our research study



is access to over 4500 DNA samples from individuals from the state of Utah, who died by suicide. These samples have been linked to genealogical records dating back 10 generations, that are housed within the Utah Population Database (UPDB; <u>https://healthcare.utah.edu/huntsmancancerinstitut</u> <u>e/research/updb</u>). This is a computerised database also including death certificates, demographic data, and current medical information on over 8 million individuals.

"Our team are focused on searching for these genetic risks. We believe that by increasing our understanding of underlying biological mechanisms, we can help to understand why some individuals are more vulnerable than others, and ultimately learn how to design both effective treatments and interventions."

After death certificates from suicide cases were linked within this database, our research team received only completely de-identified information, to protect the privacy of families. The anonymised information that we have received includes demographics, family structure, and the presence of co-occurring conditions.

We have focused our initial studies on a subset of suicide cases related to each other, in large extended high-risk families. These families have anywhere from twice the population risk, to over 10 times the population risk of suicide. They encompass from 7 to 9 generations and have anywhere from three to 13 suicide cases with DNA, for study. Investigating the patterns in the DNA that are shared among the suicide cases in these families allows us to discover genetic changes that may lead to increased suicide risk. The high-risk family design has three major advantages.

Design advantages

Firstly, studying these distantly related familial cases minimises the effects of a shared environment in the home or neighbourhood that could lead to suicide, and allows us to focus more clearly on just the genetic risk. Secondly, cases within families are more likely to share a smaller number of genetic risks from their common ancestors, reducing the heterogeneity problem. Thirdly, many of the families we study are very informative, in the sense that we can get a significant statistical result of genetic risk within a single family; the shared familial genetic risk is magnified through its repetition in the related suicide cases. Even if that risk is rare and only occurs in one extended family, the results can shed light on biological mechanisms that may occur more broadly.

We are now wrapping up preliminary work on 43 of our largest high-risk families. The regions of the genome, that are significantly shared among the suicide cases in these families, contained seven genes with corroborating evidence of association with suicide from previous studies, a finding suggesting that our methods are on the right track. While specific evidence of genetic risk factors for suicide are growing, the numbers of reported genes are still small, and we would have expected at most only one gene with previous suicide evidence in our findings just by chance.

The shared regions in our high-risk families also contain many genes, with known psychiatric associations. Perhaps more surprising, we also discovered genes with links to other processes, such as inflammation, immune response, and metabolic conditions, suggesting possible new ways to study suicide risk. The 249 genes identified by this first study gives us many places to start, with additional work in our own data resource.

In closing, I would like to say that our results will stimulate further analysis in other studies of suicide risk, in the worldwide scientific community. As more genetic changes leading to risk are discovered through our efforts and those of our colleagues, our understanding of suicide risk will lead to more targeted, effective prevention.



Dr Hilary Coon Professor Department of Psychiatry University of Utah School of Medicine Tel: +1 801 585 3068 hilary.coon@hsc.utah.edu https://faculty.utah.edu/u0035633-HI-LARY_COON/research/index.hml www.twitter.com/UofUDepMedicine

Personalising antibody directed therapy in Acute Myeloid Leukaemia (AML)

Professor Jatinder Lamba from the Department of Pharmacotherapy and Translational Research explores the current progress in Acute Myeloid Leukaemia (AML)

cute Myeloid Leukaemia (AML) is the most common leukaemia in adults and second most common leukaemia in children. AML is very heterogeneous disease characterised by several genomic alterations and cytogenetic abnormalities that are utilised for risk group stratification. Advances in recent years have also identified several mutations of significant prognostic value that are currently being evaluated.

However, in spite of all the efforts to establish the molecular and genetic landscape of AML, improvement in outcome has been dismal. Although initial response to induction therapy is observed in many AML patients' refractory disease and occurrence of relapse is a major challenge in successful treatment of AML. The overall 5 year survival for AML ranges from 60% in children to <25% in elderly AML patients with conventional chemotherapy and hematopoietic stem cell transplants, thus warranting the need for newer therapies or redesigning the treatment regimens guided by patient's genome.

Immunotherapy in AML: An emerging approach to treat AML involves use of monoclonal antibodies or antibody drug conjugates. The cell surface antigen currently most exploited is CD33, as it is expressed on AML blasts of majority of patients as well as on leukemic stem cells making it an attractive therapeutic target. The



recognition that antibodies were internalised after binding to CD33 led to the development of an immunoconjugate between an anti-CD33 antibody and a toxic calicheamicin-y derivative termed Gemtuzumab Ozagamicin (GO Mylotarg[™]). GO is the first cancer immuno-conjugate to be approved for treatment of CD33 positive AML. GO received an accelerated approval in 2000 for treatment of relapsed AML in older patients⁽¹⁾ but was withdrawn from the market, due to lack of benefit and increased mortality in the FDA-mandated confirmatory trial⁽²⁾.

However, several follow-up randomised

studies demonstrated GO improved outcomes in adult AML when GO was added to initial intensive chemotherapy⁽²⁻⁷⁾; these findings were most pronounced in patients with favourable-risk cytogenetics^(8, 9). Within paediatric AML, Children's Oncology Group trials COG AAML03P1 and COG AAML0531 demonstrated that GO was tolerable(10) and improved event-free survival (EFS), by reducing relapse risk⁽¹¹⁾.

The data from these trials also suggest that although we see improvement in outcome, the response is very variable suggesting an unmet need for biomarkers predictive of response.



Patients with reference allele

In some of the clinical trials, wide inter-patient variation in CD33 cell surface expression has been reported and benefit from adding GO is observed for those patients with higher CD33 expression⁽¹²⁾.

Biomarker predicting GO response

While a lot of emphasis is being given in characterisation of tumour (in this case Leukaemia cell), genome, germline genetic variation (pharmaogenomics) can have significant impact on drug response. Dr. Lamba's lab focuses on identification, characterisation and functional validation of genomic/ epigenomic/pharmacogenomics features predictive of treatment response in AML. Integration of these genomic features with tumour genome can enhance our selection of right agents and prediction of treatment response.

In her quest to identify biomarkers that could presumably predict clinical response to this new and re-emerging drug in AML, her lab investigated whether genetic variation in CD33 gene itself exists in the population and if so whether it impacts clinical efficacy to GO.

Interestingly Dr. Lamba's group identified several coding single nucleotide polymorphisms (SNPs) in CD33 that were promising^(13, 14). Most significant and impressive results so far is the discovery of a splicing and coding SNP in CD33 rs12459419 (C>T; Ala14Val), which is present in exon-2 and alters splicing, resulting in loss of exon-2. Exon-2 codes for IgV-domain and IgVdomain is recognised by both GO and hP67.6-CD33 antibody, which is used for diagnostic immunophenotyping (figure 1).

Thus, loss of this domain can not only interfere with the detection of total CD33, but can also compromise therapeutic efficacy of GO by influencing the binding or internalisation of CD33-GO complex. Recent report from Dr. Lamba's group from the largest-randomised paediatric AML trial ever-AAML0531, demonstrates exactly this point: CD33 splicing SNP is a strong predictor of leukemic cell surface CD33 levels as well as clinical response to GO. Patients with the variant T-allele (CT and TT genotypes) that results in skipping of exon 2, show no difference in outcome between patients treated with or without addition of GO.

Whereas for patients homozygous for reference allele (CC-genotype) that codes for full length CD33, dramatic reduction in relapse risk (from 49% to 26% in NO-GO vs. GO arms) and significant improvement in disease free survival when given GO (Journal of Clinical Oncology; Lamba et al, 2017) ⁽¹⁵⁾.

This is an incredible finding and presence of this variant defines a genotypic driven prediction of response to GO, at much greater level as compared any of the factors known so far including measurement of CD33 expression levels. Given the recent news from USFDA reapproving GO for treatment of CD33 + AML, once validated, preemptive genotype testing of CD33 variant will set a stage to personalise GO therapy to achieve maximum therapeutic benefit.

Based on the results of the genotype testing, patients likely to benefit from anti-CD33 therapy, such as GO could be selected and at the same time for patients with variant genotype who are less likely to response to GObased chemotherapy alternate treatment strategies could be developed (Figure 2). These results could also serve as significant biomarker to be tested in AML patients for selection of other CD33-based chemotherapy.

These results also bring forward a significant role of pharmacogenomics especially indicating not to ignore host genetic features in our quest to



Lamba Lab group (left to right): Biswadeep Dhar, Salma Bargal, Dr. Jatinder Lamba, Dr. Roya Rafiee and Dr. Bradley Stockhard. Not included in picture : Abdel Rehman Elsayed, Mohammed Gbadamosi, Dr. Lata Chauhan and Dr. Miyoung Shin.

leverage tumour genetics, as variation in host genetics can have significant impact on response.

This also sets a precedent of probably digging deeper to identify predictive biomarkers in this new era where immunotherapy is being actively pursued in treatment of cancer.

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Professor Jatinder Lamba Department of Pharmacotherapy and Translational Research Tel: +1 352 273 6425 jlamba@cop.ufl.edu



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In the midst of life: the importance of community-based services

Director of the Pfalzklinikum facility "Care-Foster-Live", Birgit Fuchs, underlines the vital community-based services of the company and how they improve tolerance and acceptance

he requirements and services in community psychiatry are as individual as their users – however, they all have the same goal: to accept impaired people in the community, to organise their daily lives and to promote tolerance and understanding over and over again. For almost 20 years, Pfalzklinikum has worked towards turning patients into residents. An important step in this respect is the decentralisation of the services offered in many communities in the Palatinate.

Out of the long-time care sector of clinics into the communities: with this goal in mind the community-based services with the name "Care-Foster-Live" was founded at the end of the 1990's. The work of the facility is based on a resource-oriented attitude. This means that the focus is not on the clients' deficiencies, but on their strengths and abilities and how to use and foster them. Trying to distinguish itself from the clinical departments, the facility developed new structures and services in the communities - a first step towards decentralisation. Initially, two living groups were built up in Palatinate communities during this period.

At home in the Palatinate

In 2007, a process started which was intensely characterised by moving services into the communities and by enhancing the portfolio: in the meantime, Care-Foster-Live has become an integral part in eleven communities in the Palatinate, partially offering several services. The product range comprises outpatient outreach care services (in four larger areas), miscellaneous residential offers (in eight communities), day centres for persons with mental impairments (in one community) and for the elderly (in three communities), a contact point as well as services for integration into the world of work (in two communities).

The concepts of the diverse services mainly focus on the basic idea of centering on persons and on the requirements in various care areas. The wide range of offers often produces creative solutions for the benefit of clients. An example is the participation Centre in Bellheim: On the one hand, this service ensures that the residents get the intense support they need. On the other hand, they have the opportunity to largely organise their daily life independently since they live in their own apartments or shared flats.

Challenges of decentralised services

The areas have a mainly rural structure and show great differences in their infrastructure and prosperity, the financial resources of the communal funding organization's and in demographic development.

Therefore, they have diverse requirements concerning the organisation of the services. For example, the organisation of outpatient services with long travel times is a major challenge which is not reflected in the financing logic of the systems existing in the various communities.

"Through the years, Care-Foster-Live has specialised in persons with challenging behaviour patterns, thanks to the proximity of the acute psychiatric services offered by Pfalzklinikum."

Additionally, most regions neither have a wide range of service providers nor community mental health groups. Selfhelp for persons with mental diseases or impairments as an important cooperation partner does virtually not exist. Therefore, the work in networks is impeded, especially regarding creative solutions. Consequently, important quarrelling partners for the development of concepts and cooperation partners for the tailoring of regional solutions are missing. So, one possibility of counteracting is to work together with the Regional Association of (Ex-) Users of Mental Health Services.

In a close cooperation the training course "Experience Involved" (ExIn) is offered, enabling (ex-) users of mental health services to be trained as "recovery companions" and participate actively in the services of the facility as members of staff. With their personal experience, they function as mediators between persons treating and persons affected. Moreover, such cooperation strengthens the regional self-help.
Participation in (social) life

Outreach and outpatient services

Promote acceptance

At a glance:

Community-Based Services of Pfalzklinikum

Promote resources and independence

Self-determined organisation of work and leisure

Being accepted in

the community

Maintain social contacts

Reduce fears and stigmas No separate worlds in clinics

Individual services for individual people

Through the years, Care-Foster-Live has specialised in persons with challenging behaviour patterns, thanks to the proximity to the acute psychiatric services offered by Pfalzklinikum. After their clinical treatment, many of these persons do not find a service provider that develops possible solutions with them. With a view to the Federal Act of Participation the staff members of the facility develop, on the one hand, decentralised, lasting solutions in the miscellaneous regions. On the other hand, in cooperation with clinical services, they establish specialised services where the length of the clients' stay is limited.

Care-Foster-Live plans, for instance, the care service for young adults (BJE). With their challenging behaviour practices, some young adults switching from youth welfare services to integration aid reach their limits when they are confronted with the existing services. For this reason, Care-FosterLive has developed a concept for intense out-patient care in Speyer. This service offers the right balance between care and retreat possibilities and thus, makes it easier for young adults to switch to integration aid. Such specialised time-limited intermediate solutions between treatment and assistance in the community should be the starting point for creative solutions, as well as enabling a self-determined life.

All these developments could be launched thanks to the facilities of employees and executives who, for a long time, reflected, discussed and questioned their attitudes, underwent training and enhanced their perspectives by participating in country-wide events. In particular, the intense dialogue with the persons concerned led to a change in professional selfunderstanding. An integral part of this process is to adopt an attitude of trust in other people. By a close conceptual and organisational linking to the clinical services, a provider of a complex array of psycho-social care services has been established which is distinguished not by exclusion, but by cooperation and the willingness to dare creative social innovations outside the regulations of the German Social Act.





Birgit Fuchs Director of Care-Foster-Live Pfalzklinikum AdöR birgit.fuchs@pfalzklinikum.de https://www.pfalzklinikum.de/home/

Early stage diagnosis – spotting early stage cancer events

Cecilia Van Cauwenberghe, Vandana Iyer and Bhargav Rajan from Frost & Sullivan examine of how nanotechnology helps spot early stage cancer

arly stage cancer diagnosis has always been a crucial step for timely cancer management. While conventional diagnostic methods have relied on tissue biopsy methods for cancer diagnosis, there is a growing focus towards the use of bio-fluid samples for cancer profiling applications as it offers a minimally invasive or non-invasive screening method. Tissue biopsy methods only provide a snapshot of cancer heterogeneity and are often limited by sampling bias.

However, liquid biopsy techniques use easily accessible samples, such as blood or urine and provide deep molecular insights across tumour heterogeneity. These tests also aid several clinical applications such as early cancer screening, treatment monitoring, drug resistance evaluation and residual disease quantitation.

As more immunotherapies are emerging for enhanced cancer management, liquid biopsy tests will also play a significant role in predicting the efficacy of such targeted therapies in the future. Hence, such liquid biopsy tests are likely to have an increasing role for a wide range of cancer management applications.

Additionally, rapid advances in nanotechnology have also fuelled enhanced cancer imaging applications and are increasingly facilitating early tumour detection. Researchers are looking to develop nanoscale devices that can be conjugated with functional molecules, such as tumour-specific ligands and antibodies for nanoscale imaging applications across personalised cancer therapy.

As nanoprobes tend to be 100 to 1,000-fold smaller than cancer cells, they can be easily transported through blood to interact with tumour-antigens on or inside cancer cells. Therefore, nanoscale contrast agents are being developed for diverse imaging applications that use positron-emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) technologies.

Technologies empowering cancer diagnosis

Although CTCs are released spontaneously into the peripheral blood either from a primary lesion at early stage of cancer development or a metastatic lesion generated into distant metastases, circulating tumour cells (CTCs) have demonstrated to appear in the bloodstream suddenly early. Indeed, a number of well renowned studies have corroborated the hypothesis that appoints CTCs as relevant markers in predicting disease progression and survival. Liang and Fu, 2017, have published an exhaustive review of them, clearly depicting how circulating tumour DNA (ctDNA) can encode tumour specific sequences and reveal specific genotype information of the tumour to be used as liquid biopsy, potentially replacing tumour biopsy.

On that note, ctDNA are expected to promptly monitor tumour progression and therapeutic responses of various types of solid cancers. In addition, single-cell technology can provide new ways for cancer diagnosis and treatment by detecting other types of rare tumour cells, such as cancer stem cells (CSCs). These cells may be indicative of early tumour dissemination.

Furthermore, single-cell technology enables to differentiate intratumour heterogeneity (ITH) in solid tumours by examining genotypes via single-cell sequencing (SCS) on patient-derived xenograft cells.

Epigenetics in cancer research has gained significant attention during the past decade. Epigenetic alterations such as DNA methylation, histone modification, chromatin remodeling and non-coding RNA regulation are known to encompass the process and evolution of



tumourigenesis. As a result, such epigenetic alterations can work as biomarkers for early diagnosis and may also become new targets for cancer prevention and treatment. Single-cell technology remarkably helps during this process by facilitating the definition of epigenetic states within a population of tumour cells even in conditions of important cell heterogeneity and stability.

Stelzer et al., 2015, have reported a series of case studies in which genomic methylation allowed the investigation of dynamic DNA methylation changes during early stage disease development at single-cell resolution.

It is important to highlight that ITH still remains as the major obstacle to develop effective early stage, personalised, diagnostic tools and anticancer therapeutics. In addressing this concern, single-cell technology has significantly optimised treatment strategy through singlecell RNA sequencing, while single-cell pharmacokinetic imaging has come into sight as a formidable tool in revealing the principal mechanisms of drug resistance in tumours. Van Cauwenberghe and Iyer, 2017, have unveiled targeted and personalised therapeutics are likely to transform the existing precision medicine landscape in a research report recently published by Frost & Sullivan.

From an imaging standpoint, nanotechnological advances have often been limited by inconsistencies in nanoparticle transport to cancer tissues, which leads to errors in cancer assessment. Additionally, differences in the tumour microenvironment across primary and metastatic sites lead to significant differences in nanoparticle distribution. Therefore, there is a growing need to develop bespoke targeted nanoparticle imaging agents that are ideally suited for the relevant tumour microenvironment.

Innovations accelerating the pace of cancer detection

Liquid biopsy tests enable the quantitation of a wide range of biomarkers such as cell free DNA (cfDNA), circulating tumour DNA (ctDNA), cell free RNA (cfRNA), circulating tumour cells (CTCs), extra-cellular vesicles (such as exosomes and microvesicles), platelets, white blood cells (WBCs), and red blood cells (RBCs).

However, the most commonly used markers for cancer liquid biopsy assays include ctDNA, CTCs and exosomes. ctDNA is often the preferred liquid biopsy marker as it very closely matches the corresponding tumour DNA and can be used to identify clinically relevant mutations within those tumours.

Rangesa, 2017, performed a review study exhibiting a comprehensive analysis of minimally-invasive and non-invasive biopsy platforms that enable enhanced tumour profiling, treatment monitoring and precision oncology applications in a research report recently published by Frost & Sullivan.

Currently, several PCR-based technology platforms are commercially available for ctDNA analysis. Some of the prevalent technologies include Bio-Rad's droplet digital (dd) PCR and MDxHealth's methylation-specific (MS) PCR technologies. Bio-Rad is also looking to combine NGS with ddPCR platforms, which may fuel a paradigm shift in the enhancing the sensitivity of liquid biopsy technologies.

Rapid technological advancements and plummeting sequencing costs have also fuelled the increasing use of next-generation sequencing (NGS) methods for ctDNA assessment. There are several companies, such as Guardant Health, cancer Genetics Inc., MDxHealth, Roche, and Qiagen, which offer NGS platforms as part of the company's product or service solution for analysing ctDNA mutations.

Certain emerging companies also offer a laboratory developed platform for analysing ctDNA mutations across multi-gene panels, using NGS platforms licensed from larger biotech establishments. New techniques for ctDNA assessment, such as microarray-based CGH (array-CGH), whole genome sequencing (WGS), whole exome sequencing (WES), and targeted NGS are also likely to garner increased focus for cancer management applications.

CTCs comprise cells that have metastasised from the tumour origin into the circulatory system. Technologies that assess CTCs typically comprise the evaluation of cancer-specific biomarkers present in the CTCs derived from blood samples. Several companies, such as Cytolumina Technologies Corp and Janssen Diagnostics, are currently using imaging, cytometry and immunoassay methods to detect cellular and proteomic markers in CTCs. However, there are emerging platforms that also use NGS and microfluidic technologies for CTCs assessment

EVs, another emerging biomarker for liquid biopsy test, primarily consist of several vesicular bodies such as apoptotic vesicles, ectosomes, microvesicles, microparticles, oncosomes and exosomes secreted by living cells into the extracellular space. Several upcoming technologies, such as that offered by Exosome Sciences and Exosome Diagnostics, are looking to leverage exosome evaluation for cancer profiling and treatment monitoring applications. As EVs contain genomic, transcriptomic, proteomic and metabolomic biomarkers, there are several methods that can be used to quantitate EVs or its components for disease profiling and monitoring purposes.

"Researchers are looking to develop nanoscale devices that can be conjugated with functional molecules, such as tumour-specific ligands and antibodies for nanoscale imaging applications across personalised cancer therapy."

Checkpoint-inhibitor therapy is a new and rapidly emerging area of cancer treatment. However, it is often limited by patient responsiveness. Hence, there is a need to develop tools that will help predict treatment response for immunotherapy approaches. Interestingly, recent research at University of California San Diego School of Medicine has revealed that a liquid biopsy test can predict the efficacy of cancer checkpoint-inhibitor therapy. The research revealed that tumours with most mutations are most likely to respond well to checkpoint immunotherapy. This finding could help select cancer patients for immunotherapies.

Hence, liquid biopsy assays will not only play a significant role in cancer screening applications, but will also help drive several clinical decisions soon. Liquid biopsy markers are suitably poised to usher in a new era of personalised treatment by enabling improved patient selection and personalised treatment strategies.

Post the development of novel nano therapies, there is a growing focus toward the development of nan-scale imaging modalities. Scientists are looking to develop nanotechnology-based imaging agents for MRI, X-ray/CT,

optical and US imaging applications. Nanoparticles are also being developed as bi-modal imaging agents for hybrid imaging platforms such as MR/CT and MR/OI.

Advances in microscopic resolution from 100s of nanometers to 10s of nanometers have enabled high quality imaging and can be leveraged for several biomedical applications, including early cancer diagnostics. For instance, 3D Light MicrOscopical nanosizing microscopy (LIMON) can be very useful for precision oncology applications.

A spin-off from Oxford University, Oxford Nanoimaging, focuses on the development of super-resolution microscope that provides a resolution of 20 nanometers. This unique platform can be leveraged for live cell imaging and sub-cellular interaction studies and may provide useful molecular insights across cancer pathogenesis and progress.

Final remarks

According to Frost & Sullivan investigations, the global market for cancer diagnostics in 2016 reached \$2.6 billion. The global cancer diagnostics market is expected to rise to nearly \$4.8 billion by 2021, growing at a compound annual growth rate (CAGR) of 13.4% from 2016 to 2021.

Frost & Sullivan's analyses reflect the advent of singlecell technology and the impact generated by such developments in the cancer diagnostics market. Singlecell technology has provided during the past five years a powerful tool in resolving ITH into distinct morphological and phenotypic profiles at early stages.

Rare cancer cells including CTCs and CSCs, can be detected by using single-cell technology. Moreover, ITH unveiling the mechanism of tumour metastasis as well as epigenetic alterations, can be investigated with the aim to improve understanding of the biological characteristics that exhibit the occurrence of cancer events.

While diverting technology focus toward nanoscale cancer imaging platforms, it is important to note that market adoption of nano-enabled biomedical imaging is sustained by a steady move from imaging at the micro- to nano-level. A growing global demand for highend microscopes, rising innovations in image sensors and image processing tools are enabling enhanced image quality for driving informed clinical decisions, especially across cancer settings.

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Cecilia Van Cauwenberghe, PhD, MSc, BA, Associate fellow and senior industry analyst, TechVision Group cecilia.vancauwenberghe@frost.com

Vandana lyer

Senior research analyst, TechVision Group vandanai@frost.com

Bhargav Rajan Industry analyst, TechVision Group Frost & Sullivan Tel: +91 (0)22 6160 6666 saenquiries@frost.com https://ww2.frost.com/ www.twitter.com/Frost_Sullivan

Characterising operating catalysts with electrons and x-rays

Christian Danvad Damsgaard at DTU Cen provides an insight into *in situ* investigation of operating catalysts by combining x-ray based characterisation with electron microscopy

undamental insight into structure-functionality relationships is key to understand the function of catalysts and improve catalytic properties. As catalysts may change their structure with respect to the environment, it is essential to investigate the catalysts under reaction conditions. Furthermore, structural and compositional information have to be acquired on different length scales¹ and such *in situ* studies require dedicated complementary techniques.

In situ x-ray diffraction (XRD) and x-ray absorption spectroscopy (XAS) are eminent to follow the catalyst's average structural and electronic changes during synthesis and reaction conditions². In order to follow the dynamics (stability, topography, etc.) of the surface and interfaces, imaging is often the solution³. Nanoscale imaging and spectroscopy of catalysts in a gaseous environment is usually performed in an environmental transmission electron microscope (ETEM) (Figure 1). TEM gives insight in the structural changes at the atomic scale during reaction, however it is restricted to relatively low pressure (<~1 kPa) and a thin sample (<~100 nm)⁴. Recent developments provide special sample holders with nano-reactor in which the sample can be exposed to conditions around 100kPa.

Spatially resolved information on the meso scale (50 nm – 1 μ m) can be obtained by x-ray microscopy, which enables *in situ* studies at both ambient and elevated pressure⁶. Furthermore,

due to the much higher penetration depth of x-rays compared to electrons, x-ray based characterisation techniques are more suited for realistic sample environment and geometry. By use of a special designed *in situ* cell, catalytic systems can be studied with hard x-ray microscopy (x-ray ptychography)⁷ during reaction (Figure 2). The *in situ* cell is based on a MEMS-based TEM heater chip , which enables *ex situ* electron microscopy imaging before and after reaction⁶.

Figure 1 and 2 illustrate the complementary nature of *in situ* hard x-ray ptychography and electron microscopy applied on a Cu/ZnO@zeolite coreshell catalyst for direct production of dimethyl ether. The combination of ETEM results, obtained at low pressure



as-prepared



reduced



reoxidized

Figure 1: Environmental scanning transmission electron microscopy of a 100 nm slice of a Cu/ZnO@zeolite core-shell catalyst for direct production of dimethyl ether. The micrographs shows the interface between the core of Cu/ZnO/Al₂O₃ and the zeolite-shell: (a) as-prepared catalyst studied at RT in H_2 , (b) catalyst under reducing conditions at 250°C in 1.1 mbar of H_2 , (c) catalyst under oxidising conditions at 250°C in 3.2 mbar of O_2^7



Figure 2: In situ ptychograms (phase contrast) at 10^{5} Pa of a 300-400nm slice of a Cu/ZnO@zeolite core-shell catalyst at room temperature in He (a), 250°C in H₂ (b), 250°C in O₂ (c), 350°C in H₂ (e), and 350°C in O₂ (f), respectively. (d) inverted backscattered electron (BSE)-scanning electron microscopy (SEM) image showing material with a high atomic number as darker areas. The BSE-SEM images were recorded ex situ before the in situ x-ray ptychography treatment of the sample⁷

of a thin ~100nm slice, with ptycography results, obtained at high pressure of a thicker 300-400 nm slice, enables bridging of both material gap (thin vs. thicker) as well as pressure gap. The study reveals a stable core-shell interface at 250°C, although reduction of the Cu containing core material led to a shrinkage of the particles on the nanometer scale. At further heating to 350°C, changes on the µm scale were observed. The catalytic performance of the catalysts was not characterised in the above study as the reactor volume to sample volume is too large in the current in situ cell and the ETEM.

The results underline the need for complementary techniques and highlight the potential of these for application in catalysis. Future developments should be focused on closing the material gap, as well as the pressure gap and make it possible to study catalysts with complimentary methods under directly comparable conditions such as pressure, temperature and gas flow. Furthermore, actions should be taken towards measuring the activity of the catalyst, such as for example, mass spectrometry to clearly and without any doubt be able to state that the measurements were performed on a working catalyst.

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DTU Cen Center for Electron Nanoscopy

Christian Danvad Damsgaard Associate Professor

Center for Electron Nanoscopy DTU Cen, Technical University of Denmark Tel: +45 4525 6487 christian.damsgaard@cen.dtu.dk www.cen.dtu.dk www.danchip.dtu.dk www.twitter.com/dtu_danchip_cen

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University of California scientists target glioblastoma with stem cell research

Targeted stem cell research at the University of California, Irvine could one day eradicate glioblastoma brain tumours, explains John Lowengrub

G lioblastoma (World Health Organization Grade IV Astrocytoma, GBM) is the most aggressive and dangerous brain tumour. More than 10 thousand GBM patients die each year in the United States, while the median patient survival for GBM is less than 12 months¹. It remains a challenge to eradicate glioblastoma due to its high heterogeneity, intense vascularization and innate treatment resistance.

Over the past decades, various therapies have been studied and tested clinically. The standard of care treatment for newly-diagnosed GBM patients consists of surgical resection of the tumour, followed by combined radiation and chemotherapy². Unfortunately, almost all the patients progress during or shortly after the treatment, and tumour recurrence is frequently observed. The FDA-approved antiangiogenic therapy for recurrent glioblastoma patients also fails to improve the survival rate³. This prompts a thorough understanding of the heterogeneity in glioblastoma, and the development of new, personalised and more effective cancer therapies.

In glioblastoma, the glioma stem cell (GSC) hierarchy has been found to play a crucial role in tumour development⁴. Tumours with high GSC population are more aggressive, and GSCs are



Fig. 1. (A) Image of vascularised GBM and model schematic. Green: GBM cells (U-87, GFP-transduced); red: endothelial cells (EC, m-Cherry transduced). (B) GBM infiltrates the normal brain. GSCs are positioned at the edge of the invading zone. Patient tumours, IHC staining with GSC marker, TRIM 11 [14]. (C) Spatial distribution of tumour cells (blue: tumour boundary; red: GSC; green: GCP; yellow: GEC) and vasculature (red dots: vessel initiation points; grey: vessel sprouts; blue: functional vessels; green dots: anastomosis points). Adapted from [8].



Fig. 2. Modelling cancer therapies. AA: anti-angiogenic therapy; Diff: anti-GSC (differentiation) therapy; AM: anti-mitotic (chemo- or radiotherapy); AEC: anti-trans differentiation therapy. AA significantly increases tumour invasion, while AA combined with Diff removes GSC clusters from tumour boundary and reduces invasion. However, the tumour cannot be eradicated, even with AM, since GECs are distributed near tumour boundary and support GSC proliferation and self-renewal. Therefore, combinatorial therapies that include AEC can effectively reduce tumour size and invasiveness, and eventually kill the tumour. Adapted from [8].

believed to be responsible for tumour resistance to radiotherapy and chemotherapy⁵. Primary human endothelial cells (ECs) are found to help to maintain the GSC pool and increase the size of tumour spheres, suggesting positive feedback from ECs to stem cells⁶. Furthermore, GSCs have been found to transdifferentiate into bona-fide vascular endothelial cells (GEC), which inherit mutations present in GSC, support GSC proliferation and self-renewal, and are resistant to traditional anti-angiogenic therapies⁷.

In recent work, Yan et al.⁸ have developed a 3D hybrid continuum-discrete model of GBM that accounts for GBM cancer stem cells and their progeny, feedback among the different cell types, and tumour-induced neovascularisation (Fig. 1A). Their model, which builds upon earlier work by Cristini and Lowengrub⁹, shows that GSCs self-organise and GSC clusters emerge at tumour boundary (Fig. 1C). These GSC clusters generate invasive fingers with GSCs staying at finger tips and differentiated cells trailing behind, which has been observed clinically (Fig. 1B). Vessel sprouts form near the tumour boundary, then grow and anastomose into functional vessels that are connected to host vasculature and supply nutrients to the tumour. GECs form a network within the hypoxic core, consistent with experimental findings. In the tumour interior, the vessel density and the level of EC-GSC crosstalk is highest, resulting in multiple new GSC clusters. Consequently, cell proliferation is enhanced and the tumour volume grows rapidly. Since the EC-GSC crosstalk has fuelled the tumour growth, it should be targeted in anti-tumour therapies.

Growth reduction

Yan et al. first targeted the crosstalk using an extreme scenario in which the vasculature is removed completely from the tumour and the microenvironment, and new vessels are not allowed to form. When this anti-angiogenic therapy (AA) is applied continuously, the overall volume growth is reduced. The growth is driven by the GSC clusters at the finger tips, which are less affected by the removal of the vessels. Consequently, the fingers continue elongating and penetrating the host. Thus, AA considerably increases tumour invasiveness (Fig. 2, top), consistent with experimental and clinical findings¹⁰.

Since GSC clusters near the tumour boundary plays an important role in tumour invasion driving invasive fingering, Yan et al. target these GSCs by modelling an anti-GSC therapy where the background vasculature continuously releases GSC differentiation promoters. Combining this differentiation therapy (Diff) with anti-angiogenic therapy, which has been shown to slow down tumour growth, also reduces invasiveness (Fig. 2, AA+Diff). However, the tumour cannot be eradicated since GECs are distributed at the tumour boundary and protect GSC

from differentiation (Fig. 2, yellow). When the tumour is treated additionally by an anti-mitotic therapy (e.g. chemo- and radiotherapy), the GECs still cover the tumour boundary and support GSCs (Fig. 2, AA+Diff+AM). Thus, Yan et al. turn to a combinatorial therapy that incorporates anti-GEC, anti-GSC (differentiation), anti-angiogenic, and anti-mitotic (e.g. chemotherapy) treatments. This combinatorial therapy is shown to be able to eradicate the tumour (Fig. 2, bottom), without recurrence even after the treatment is stopped, allowing the patient to enjoy true, long-lasting remission.

In these modelling studies, Yan et al. have shown that targeting the EC-GSC crosstalk may hold promise as a novel anticancer therapy. In addition, using combinatorial therapies to target transdifferentiated vascular endothelial cells present in glioblastomas could eradicate these deadly brain tumours without recurrence. One candidate agent is potentially an EGFR blocker. EGFR is involved in proliferation, differentiation, migration and angiogenesis regulation in many glioma tumours¹¹ and the EGFR mutation is also present in the GECs12. Therefore, blocking EGFR could effectively target GECs, among other targets. The latest generation of EGFR inhibitors, such as irreversible tyrosine kinase inhibitors (dacomitinib) effectively reduce the tumour volume in animal models by decreasing the GSC population by enhancing differentiation¹³. Therefore, Yan et al. suggest that a brain-penetrant EGFR inhibitor potentially matches the need for a differentiation promoter, anti-GSC and anti-GEC agent, which could be combined in future clinical trials with both anti-angiogenic therapy and chemotherapy.

Contributors:

Huaming Yan^{1,7}, Mónica Romero-López², Lesly I. Benitez⁴, Kaijun Di^{4,9}, Hermann B. Frieboes^{5,6}, Christopher C. W. Hughes^{2,4,7,8}, Daniela A. Bota^{8,9,10}, Vittorio Cristini¹¹, John Lowengrub^{1,2,7,8}

- 1 Dept. of Mathematics, University of California, Irvine, CA 92697
- 2 Dept. of Biomedical Engineering, University of California, Irvine, CA 92697. Current address: Orthopedic Surgery, Stanford University, Redwood City, CA 94063
- 3 Dept. of Developmental and Cell Biology, University of California, Irvine, CA 92697
- 4 Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92697
- 5 Department of Bioengineering, University of Louisville, Louisville, KY 40292
- 6 James Graham Brown Cancer Center, University of Louisville, Louisville, KY 40292
- 7 Center for Complex Biological Systems, University of California, Irvine, CA 92697
- 8 Chao Comprehensive Cancer Center, University of California, Irvine, CA 92697
- 9 Department of Neurology, University of California, Irvine, CA 92697
- 10 Department of Neurological Surgery, University of California, Irvine, CA 92697
- 11 Center for Precision Biomedicine, Brown Foundation Institute of Molecular Medicine, University of Texas Health Science Center at Houston (UTHealth) McGovern Medical School, Houston, TX 77030, USA

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John Lowengrub

Chancellor's Professor of Mathematics, Biomedical Engineering, Chemical Engineering & Materials Science

Director, Interdisciplinary Graduate Program in Mathematical, Computational and Systems Biology 540H Rowland Hall University of California, Irvine Mobile: 949-751-9700 Tel: 949-824-8456 Fax: 949-824-7993

Publishing national chemotherapy data

Publishing national chemotherapy data has helped NHS hospitals make changes that should improve treatment, as Emma Saxon reveals in this article

t's often research into new drugs that makes headlines. But examining routine chemotherapy data can also help doctors continually improve how they use treatments already available. To do that the NHS needs to look at how these treatments are being used and how different patients fare following treatment.

Last year, we worked with Public Health England to do exactly that. Our world-first study of patients treated for breast and lung cancer in 2014 gave us a national picture of what happened to patients following treatment with chemotherapy, 'targeted' drugs and immunotherapy. The study was made possible by routine data collected by Public Health England as part of the treatment of all patients across the English NHS.

And for the first time each English NHS hospital trust could see how well their breast and lung cancer patients fared in the first 30 days after receiving these treatments compared with other trusts.

This measure, called '30-day mortality', is really useful. If a patient dies in that short window of time, it's unlikely they benefitted from the treatment and they might still have experienced its side effects, even if it didn't directly lead to their death.

For those patients, other types of treatment and support might have led to a better outcome. But the only way to know this is by giving treatment teams data to help them spot where they could make improvements.

So how did the doctors who make decisions about these treatments feel about their trust's 30-day mortality levels? Especially where they were higher than they might have hoped. A year on, we spoke to doctors at Addenbrooke's hospital in Cambridge, and the Royal Free hospital in London, to find out. **Improving the outlook for cancer patients** For Cambridge University Hospitals NHS Foundation trust, 30-day mortality for breast cancer patients receiving palliative treatment seemed to be higher than average in 2014.

According to Dr Hugo Ford, the director of cancer services at Addenbrooke's hospital in Cambridge, the new national chemotherapy data set was like a canary in a coal mine. It flagged a problem, but it was up to his team to solve it.

"Ultimately, the decision about whether or not to accept chemotherapy lies with the patient, with advice from their doctor. And this can be a really difficult decision to make."

"You obviously worry that increased 30-day mortality is due to the treatment," says Ford. But when he looked more closely at the patients who had died, what he found reassured him that wasn't the case. "Very few people died because of complications of chemotherapy – it was nearly always their breast cancer," he explains.

"So, the question then became: 'Are we giving those patients chemotherapy for too long?' rather than: 'Are we giving them the wrong treatment?"' Knowing the right question to ask led Ford and his team to an answer they could use in their hospital.

Following a breast cancer diagnosis, long-term survival is high: almost 8 in 10 breast cancer patients (78%) survive for at least 10 years. That means many patients will get to know the treatment teams managing the chemotherapy they're given.

So, if chemotherapy stops working, making the transition to palliative care teams – who help patients to



manage pain and other symptoms – can be particularly difficult and upsetting for patients. "We want to bring palliative care teams into the clinics, so that they can be involved with patients from an earlier stage," explains Ford.

"They can also help to give advice and support to the doctors involved in their care." He told us that having these new data about patients helped the team put these plans into action sooner.

"It's given us more of an argument for the resources we need to actually change the support we give patients in their transition to palliative care," he says.

In January this year the team changed how they approach discussions with patients so that they're introduced to palliative care teams earlier. Ford says they're "really interested to see what impact that has on our patients' outcomes in the next year or two".

And he believes that being able to share these results with other trusts will be the key to improving patient outcomes nationally.

"Following a breast cancer diagnosis, long-term survival is high: almost 8 in 10 breast cancer patients (78%) survive for at least 10 years. That means many patients will get to know the treatment teams managing the chemotherapy they're given."

"I don't for a minute pretend that the changes we've got planned will be perfect – but other people will have these same experiences. Public Health England will be able to look at what some trusts have done that has improved patients' experiences and outcomes, and say



that these are the sorts of things that other trusts should think about doing."

Digging deeper into patient data

But it's not just about solving problems. For trusts whose overall 30-day mortality wasn't significantly higher than average, there may also be opportunities to improve patient care.

"Until now, almost all the information on how well treatments work for patients came from clinical trials. These remain the gold standard of evidence, but they tend to involve patients who are younger and with few other medical problems."

Dr Roopinder Gillmore, chemotherapy lead for the Royal Free London NHS foundation trust, explains that the study made her team change how it reviews cases where individual patients die shortly after starting treatment.

"We used to hold meetings every 3 months where we discussed cancer patients who had died within 30 days

of receiving chemotherapy," she says. We now do them in real time at monthly meetings for anybody who dies unexpectedly, or shortly after being given chemotherapy with the intent of curing their cancer. We need to learn from those cases."

The 30-day mortality study found that there were some patients – such as those who are generally less well, or who haven't had any chemotherapy previously – who had a higher risk of dying in the 30 days following treatment.

So now, she says, they're exploring whether the patients they discuss in their meetings have anything in common, to help them understand when they might need to take extra care when deciding on treatment.

"We're looking at patients who begin chemotherapy during their stay in hospital – since they may be frailer – or those who are generally less well. If those patients crop up more in mortality meetings we need to make sure we discuss those patients properly, so that we can make well-informed decisions with them."

Ultimately, the decision about whether or not to accept chemotherapy lies with the patient, with advice from their doctor. And this can be a really difficult decision to make. But Gillmore feels optimistic that looking at national data on these treatments will help doctors and their patients make the right choices for them.

"For patients who might not benefit from chemotherapy, but who still want it, we need to help them understand why a different treatment strategy might give them a better outcome.

"I don't for a minute pretend that the changes we've got planned will be perfect – but other people will have these same experiences. Public Health England will be able to look at what some trusts have done that has improved patients' experiences and outcomes, and say that these are the sorts of things that other trusts should think about doing."

"Now I'll be able to say that we look at the effect of all our treatments at a national level, to make sure that we are acting in their best interests at every stage of their journey."

What else could we learn from these data?

The new information has already changed how some hospitals manage and review chemotherapy treatment. But this is just the beginning. Public Health England is now exploring other ways of using data to help improve patient outcomes. One way will be to expand the data collection to include more cancer types in future, and to track these data over time.

"My speciality is pancreatic cancer, so I'd love to know how many pancreatic cancer patients get treated, and what sort of treatments they're given," says Gillmore. I don't really have a feel for what's happening day-to-day across the country."

Until now, almost all the information on how well treatments work for patients came from clinical trials. These remain the gold standard of evidence, but they tend to involve patients who are younger and with few other medical problems. But doctors in the NHS have to care for a wide range of patients. Public Health England's data includes all cancer patients receiving these treatments across England – that's around 489,000 patients so far. And it can be used to help doctors ensure patients receive the treatments that are most likely to be right for them, something doctors like Ford are keen to find out.

"If we don't know how well treatments work in the normal population, how are we supposed to advise patients properly on what sort of treatment they ought to be having?" he says.

These answers will only come if trusts put high quality data into the system. Public Health England is working closely with trusts to make sure all their data are present and correct, for every patient, which is no mean feat. But the reward will be steady improvements in patient care, for all cancer patients in the NHS, for years to come. And that's worth it.

Emma Saxon

Cancer intelligence officer and co-lead author on the SACT study

Cancer Research UK Tel: +44 (0)300 123 1022 supporter.services@cancer.org.uk www.cancerresearchuk.org www.twitter.com/CR_UK

Drug development for cancer and inflammatory disease

Sumith A Kularatne, Vice President of Research and Development at On Target Laboratories shares the research strides he has made in drug development

en are haunted by the vastness of eternity. And so we ask ourselves: will our actions echo across the centuries? Will strangers hear our names long after we are gone and wonder who we were, how bravely we fought, how fiercely we loved?" – Odysseus (Troy).

Sumith A. Kularatne, Ph.D., is the Vice President of Research & Development at, On Target Laboratories, LLC (OTL), West Lafayette, IN (March 2012 – present). Dr. Kularatne is a world-class researcher and problem solver within the field of drug design and development for cancer and inflammatory disease. In fact, his distinctive and unparalleled approach to solve the problems associated with the diagnosis and treatment of cancer has been nothing short of unique and groundbreaking.

Dr. Kularatne says that "health holds a very important role in one's life, as President Thomas Jefferson said. Liberty is to the collective body, what health is to every individual body... Without health no pleasure can be tasted by man... without liberty, no happiness can be enjoyed by society".

Therefore, Dr. Kularatne uses his diverse set of skills, ranging from medicinal chemistry, organic chemistry, cancer biology, biochemistry, molecular biology, protein and antibody engineering, and animal model development for drug testing that



enables him to solve problems from a multidisciplinary approach and to discover better therapies with higher efficacy. Throughout his research career, Dr. Kularatne has been dedicated to developing targeted-imaging agents, diagnostic methods, and – therapeutic agents for cancers such as prostate, ovarian, lung, breast, and leukaemia and their metastatic disease and inflammatory diseases, such as rheumatoid arthritis and heart disease.

Research strides

Under his guidance, OTL has developed a strong pipeline for several types of cancer and inflammatory diseases. OTL38, a folate receptor (FR)-targeted near infrared (NIR) dye, has been proven safe in a phase I trial and effective in a completed phase II clinical trial for ovarian cancer. A phase II trial for lung cancer and a phase III trial for ovarian cancer began in summer 2017. The same NIR dye has been conjugated to additional ligands targeting receptors on prostate (OTL78: PSMA-targeted NIR agent), colon (OTL338: CA-IX-targeted NIR agent), and pancreatic (OTL81: CCK2R-Targeted NIR agent) cancers. These ligands can also be conjugated to a photodynamic therapeutic (PDT) agent, giving surgeons the option to visualize and 'burn' targeted lesions using the same light source and camera. A lead folate- PDT compound (OTL228) has been identified with others to follow.

He pursued his postdoctoral studies in molecular biology and biomedicines with Peter G. Schultz, CEO and Professor of Chemistry at The Scripps

Research Institute (TSRI), San Diego, CA (Dec 2009-Feb 2012). Dr. Schultz was the founder and former director of GNF, and is the founding director of the California Institute for Biomedical Research (Calibr) La Jolla, CA. Dr. Kularatne's projects at TSRI focused on selective diminishing of primary tumor masses, metastatic cancers, and cancer stem cells using antibody drug conjugates (ADCs) or using bispecific antibodies (antibody-dependent cellmediated cytotoxicity or ADCC).

"Innovation is a process that starts from coming up with a new idea to launching a new product in the market." Dr Sumith A Kularatne.

Dr. Kularatne earned his Ph.D. in organic/medicinal chemistry from Purdue University, West Lafayette, IN (Dec 2005-Dec 2009), conducting research under the guidance of Philip S. Low, the Ralph C. Corley Distinguished Professor of Chemistry and Director of the Purdue Center for Drug Discovery at Purdue University. Dr. Low is also the co-founder and CSO of both Endocyte and On Target Laboratories. Dr. Kularatne's research at Purdue University concentrated on small molecule-targeted drugs for cancers and inflammatory diseases.

His scientific efforts have resulted in 6 drug candidate in human clinical trials with multiple companies, over 50 US and foreign issued/pending patents and over 30 peer-reviewed publications. He has given multiple invited seminars/lectures in prestigious conferences such as "Gordon Research Conference" on "Drug Carriers in Medicine & Biology", as well as in national and international conferences, universities, and industries. Dr. Kularatne's scientific involvements have also led to several international

and national awards including, "SBIR Phase II Grant Award for Non-Small Cell Lung Cancer Research (2017)", "Distinguished Partners in Hope Award for OTL for fueling innovation, and providing hope to lung cancer patients (2016), "Innovation Corps at NIH program for SBIR Award for Drug Development for Non-Small Cell Lung Cancer (2016)", "SBIR Phase I Grant Award for Non-Small Cell Lung Cancer Research (2014)", "AAPS Postdoctoral Fellow Award sponsored by Merck (2012) for CXCR4-targeted antibody drug conjugates for metastatic cancers", "the Skaggs Postdoctoral Fellow Award (2010)", "AAPS Graduate Student Award in Biotechnology, sponsored by Pfizer (2009) for PSMAtargeted drugs for prostate cancer, AAPS Graduate Student Symposium sponsored by Eli Lilly (2009) for PSMA-targeted drugs for prostate cancer, Delano Maggard, Jr. graduate research award (2005)", ACS recognition Chemist of the year (2004), E. A. Talaty fellowship (2003) and the B. L. Paker Endowed fellowship (2002). He is an invited member of multiple honorary societies including Phi Kappa Phi (NSF), National Society of Collegiate Scholars, and Beta Phi Upsilon. He is also an invited peer reviewer for multiple scientific journals including Journal of Organic Chemistry, Molecular Pharmaceutics, Journal of Medical Case Reports, Nature Publishing group, and Drug Delivery.

Looking back on his 11 year career, Dr. Kularatne said that "I am fortunate and blessed to develop drugs that can possibly make a tremendous impact on human life, especially those who are suffering from cancer and their loved one". He believes what Michael Jordan said "talent wins games, but teamwork and intelligence wins championships". Dr. Kularatne stated that "I want to



emphasis that all the accomplishments I have been involved with were a team effort. I have always been around a great group of people committed to work in cohesion with one another. I have been guided by great leaders and mentors. I have great parents, family and friends who support me unconditionally. So, I feel I was prepared by mentors and family to accomplish great things as mentioned by Sun Tzu, The Art of War, 400 B.C. "Every battle is won before it is fought".



Sumith A Kularatne PhD VP of R&D

On Target Laboratories, LLC 1281 Win Hentschel Blvd West Lafayette IN 47906 Tel: +1 765 588 4547 skularatne@ontargetlabs.com www.researchgate.net/profile/ Sumith_Kularatne http://bit.ly/1Q4Ji8V https://twitter.com/SumithKularatne http://bit.ly/GooglePlusSumith http://bit.ly/FacebookSumith

Living with Leukaemia

Bethany Torr, campaigns and advocacy officer at Leukaemia Care introduces 'Leukaemia' and its different forms and explains how people live with the disease

eukaemia' is an umbrella term for cancers of the white blood cells – 'leuk' means white and 'aemia' refers to a condition of the blood. 26 people are diagnosed with a leukaemia every day in the UK and there is currently no known cause.

White blood cells fight infection but leukaemia cells lose this ability. Some of the common signs and symptoms of leukaemia are a consequence of this. Others are due to leukaemia cells taking over space within the blood, leaving less room for healthy blood cells. Commonly experienced symptoms are: fatigue, shortness of breath, fever or night sweats, bruising or bleeding, joint or bone pain and sleeping problems.

Leukaemia is a term that many people have heard of, but very few have an understanding that there are four different types of leukaemia, plus additional rarer types. The main types are distinguished by the blood stem cell affected (myeloid or lymphoid) and the progression of the cancer, either acute (quickly progressing) or chronic (slowly progressing).

Big differences are seen in the experience of acute leukaemia patients compared to chronic leukaemia patients, from diagnosis through to treatment and beyond¹.

Acute leukaemia requires quick intervention. Unfortunately, over half of patients are diagnosed by an emergency route. This is a consequence of both patients delaying in seeking medical attention – many do not suspect their symptoms are signs of cancer prior to diagnosis – and a delay at primary health, with 1 in 5 acute patients being treated for something else by their GP prior to diagnosis. Acute leukaemia can be cured, but late, emergency diagnosis significantly impacts outcomes.



1 in 5 acute patients are being treated for something else by their GP prior to diagnosis

Acute lymphoblastic leukaemia (ALL)

ALL is one of the only cancers that is more common in children than adults, with the average age of diagnosis being between 2 and 4 years old. Current treatment for ALL is an intense course of chemotherapy. Fortunately, with most patients being young and fit they can tolerate the treatments, and long-term survival rates in children reach almost 90%.

New treatments in development are less intensive, causing fewer side-effects. Most recently, the American FDA approved the use of CAR T-Cell immunotherapy in the treatment of paediatric ALL. This therapy involves collecting the patient's immune cells and using genome-editing tools to enable them to target leukaemia cells.

Acute Myeloid Leukaemia (AML)

Most AML patients are over the age of 65 years old, but AML is still the most common leukaemia diagnosis in 25-49-year olds and accounts for 25% of childhood leukaemias. Survival rates for AML are as low as 30%, as many patients are not fit enough to tolerate the intense chemotherapy treatments.

AML can be split into subtypes defined by the genetic changes driving the cancer. Each subtype can be a predictor of response to treatment and prognosis. If tailored treatments can be developed to subtypes it is







AML accounts for 25% of childhood leukaemias

likely that they will be less intensive and therefore more tolerable by patients.

Chronic leukaemia on the other hand is currently understood to be treatable, but not typically curable. This means that a patient will have leukaemia for life but in many cases, it can be well managed, leading to a normal life-span.

Chronic lymphocytic leukaemia (CLL)

CLL is the most common of all leukaemia types affecting around 3,500 patients each year in the UK, around 60% of which are over 70 years old. One third of patients will require treatment straight away and others will be on 'watch and wait'.

Watch and wait' is a process where the progression of CLL is monitored over time and only treated when necessary. For many patients, adjusting to this process can be difficult and a time of significant worry. Unfortunately, many patients are not given access to appropriate support during this time. For example, more than 3 in 5 patients did not have access to a clinical nurse specialist (CNS).

Chronic Myeloid Leukaemia (CML)

Around 700 people are diagnosed with CML each year in the UK, with the average age being ~60 years old. Over 95% of CML cases are Philadelphia positive,



One third of CLL patients will require treatment straight away



Over 95% of CLL cases are Philadelphia positive

meaning the cancer is driven by a tyrosine kinase; the product of the BCR-ABL gene created by the joining of chromosomes 9 and 22.

A decade ago, tyrosine kinase inhibitor (TKI) drugs began to be used in the treatment of CML. Labelled wonder drugs; one pill each day sees the majority of CML patients living a normal life-span with few side effects despite having a supposedly incurable condition. Clinical trials are now assessing whether longterm remission will be maintained with removal of the treatment (TFR).

1 Leukaemia CARE (2017) 'Living with Leukaemia' report. Available online: http://www.leukaemiacare.org.uk/resources/living-with-leukaemia-report



Bethany Torr Campaigns and advocacy officer Leukaemia Care Tel: +44 (0)1905 755 977 Bethany.Torr@leukaemiacare.org.uk www.leukaemiacare.org.uk www.twitter.com/LeukaemiaCareUK

Tumour-host interactions, paediatric sarcomas, and cancer progression

Ivan Stamenkovic, professor of experimental pathology at the University of Lausanne underlines research taking place around cancer progression

ancer progression, meaning the evolution of localised tumour growth to invasion of adjacent tissue and dissemination to distant organs is a complex process that is intimately related to interactions between tumour cells and the host tissue stroma, which includes the extracellular matrix (ECM) and a broad panel of cell types.

Cancer growth invariably triggers an inflammatory response intermingled with tissue remodelling and regeneration, all of which mimic wound healing – leading to the notion coined by Harold Dvorak in 1986 that cancer is "a wound that never heals". In adult epithelial malignancies, or carcinomas, tumour-host interactions are an intensely investigated field and it is well established that the stromal, "wound healing" response to cancer progression conditions both local growth, helping sustain cancer cell survival, as well as dissemination.

In sarcomas, the nature and effects of the interactions with the host tissue stroma are largely unexplored. Given that sarcomas are, in a sense, a malignant stroma, the obvious question is to what extent the normal stroma contributes to sarcoma growth, invasion and dissemination. Histological analysis shows that, like carcinomas, paediatric sarcomas display variable degrees of infiltration by a variety of leukocyte subtypes. However, the mutual influence between sarcoma cells and the infiltrating leukocytes remains obscure and requires elucidation. Carcinoma cells induce the host tissue stroma to secrete factors that are directly or indirectly beneficial to the tumour cells. Thus, the tumour cells alone may not secrete a broad repertoire of cytokines and proteolytic enzymes that may provide them with optimal growth conditions and break down physical barriers that limit their migration.

However, they can recruit and activate host tissue cells, including a variety of leukocyte subsets, mesenchymal stem cells and fibroblasts, which can produce a plethora of cytokines and enzymes. Many of the cytokines promote tumour cell survival and growth and help maintain tumour cell plasticity. The proteolytic enzymes may remodel the surrounding host tissue, liberating growth factors that are normally sequestered within the ECM and creating a path for tumour cells to migrate along. Sarcoma cells are naturally motile and produce a variety of proteolytic enzymes themselves.

It is therefore unclear whether and to what extent they require intervention of the host tissue stroma to divide and disseminate. What is also unknown is the relationship of sarcoma cells and the immune system. A great deal of effort has been committed toward understanding how the immune system responds to cancer growth and how cancer cells defend themselves from immune aggression. The hope is that by boosting the immune response in a variety of ways, cancer progression and growth may be blunted or even reversed.

Although spectacular results have been obtained in some cancer types, the immune response to paediatric sarcomas and their mechanisms of defence remain to be fully explored. Tumour-host interactions in paediatric sarcomas are therefore a promising and important field of study.

Metastasis is responsible for 90% of cancer-related death. Sarcomas typically display high metastatic proclivity, which renders their prognosis particularly poor, as metastases are for the most part unresponsive to conventional chemotherapy, even if the primary tumour displays sensitivity. Most of our understanding of the multistep process, which constitutes metastasis, comes from studies on carcinomas.

Interestingly, carcinomas mimic the sarcoma phenotype to metastasize. Most disseminating carcinoma cells undergo epithelial-to-mesenchymal transition (EMT), a reversible process by which they transiently adopt a variable mesenchymal phenotype. EMT appears to be critical for carcinoma



cell motility, as epithelial cells are typically non-motile, invasion, and possibly other steps leading up to secondary colony formation.

Once they have reached their final destination, disseminated carcinoma cells revert to their epithelial phenotype to grow and form metastatic tumours. Being of mesenchymal origin, sarcoma cells are naturally motile and probably possess all the properties necessary for dissemination. They therefore do not need to undergo any particular phenotypic changes and provide ideal cells to study metastasis and determine how the metastatic lesions may differ from the primary tumours.

An age-old issue that remains unresolved is that whereas carcinomas typically disseminate by the lymphatics first and later by blood vessels, sarcomas tend to disseminate by the blood and relatively seldom by the lymphatic vessels. The reasons for this difference in dissemination route is unclear but it points to basic biological differences between carcinoma and sarcoma cells that have therapeutic relevance.

A major focus of metastasis research in recent years has been the isolation and characterisation of circulating tumour cells (CTCs). Once again, circulating carcinoma cells have attracted the greatest attention and it has been demonstrated that CTCs display variable EMT and that EMT generally correlates with resistance to therapy.

Very little work has been done on paediatric sarcoma CTCs, but it will

be of interest to determine whether sarcoma CTCs differ from bulk tumour cells, whether they require particular adaptation to sheer stress and whether sarcoma CTCs are enriched in cancer stem cells.

Key additional questions to address include the intrinsic properties of paediatric sarcoma metastatic cells, particularly epigenetic modifications that provide them with the ability to disseminate and form secondary colonies; and the effect that disseminated cancer cell growth may have on it host tissue, which may differ from that exerted by the primary tumour on its microenvironment. It is possible, and in fact likely, that metastatic tumour resistance to therapy is due to a combination of tumour cell-intrinsic properties and elements within the host tissue response. As metastases herald resistance to therapy and, in the vast majority of cases, incurable disease, these issues need to be given high priority in paediatric cancer research.



Ivan Stamenkovic Professor of pathology, director experimental pathology service Centre Hospitalier Universitaire Vaudois (CHUV) University of Lausanne Tel: +41 21 314 7136 Ivan.Stamenkovic@chuv.ch

The future of the Danish Ministry of Health

Jonathan Miles from Open Access Government explored the work the Danish Ministry of Health does to improve health policy across the country

he Danish Ministry of Health was officially established in June 2015 and is responsible for all healthcare policies in Denmark. Once an independent ministry when first in launched in 1926, it has since then been heavily developed, at times merging with other sectors (such as the Ministry of the Interior) and being re-established under different names, before recently becoming a separate ministry once more, in November 2016.

The Ministry is responsible for defining the overall framework in which the national healthcare system successfully thrives, while also considering healthrelated social services for the elderly. Organisation and financing of the health care system are just some the ministry's primary responsibilities along with the approval of pharmaceuticals and the pharmacy sector.

"In Denmark, the five-year cancer survival rate has increased since the year 2000. In 2012-14 the survival rate was 61%, an increase of 13% compared to 2000-2002. In the last couple of years, the cancer mortality rate has declined, but Nørby doesn't plan on stopping there."

The Ministry is composed of five regions in Denmark, with each region being governed by regional councils composed of forty-one members. These members are elected in regional elections every four years, allowing greater flexibility for the citizens of Denmark. The regions organise health services for their citizens according to their regional needs, tailoring and adjusting the national framework to specific demands of the public.

Heading the Ministry is Danish politician Ellen Trane Nørby, who has been her countries Minister of Health since November 28th 2016. Nørby is driving the Health Sector forward, with a recent bid to host the next European Medicines Agency (EMA) in Copenhagen, once the UK leaves the European Union. On February 8th 2017, Nørby released a statement highlighting why Copenhagen would be an excellent environment for the EMA, providing a number of benefits and optimal conditions.

"It is important that we ensure optimal conditions for the EMA to fulfil its tasks, as patients in the EU need to have confidence in the medicinal products on the market. That is why the EMA should be located where there are strong traditions for focusing on patients with regard to safety, patient rights, and transparency".

On top of this, the Ministry of Health released a list of "Top 5 Reasons to Place EMA In Copenhagen. The list included the following:

World-class research environment

Denmark is the leading country in the EU in terms of number of clinical drug trials per capita.

Innovative and vibrant life science cluster

Danish and international companies will provide a highly professional work environment for the European Medicines Agency. Close collaboration between companies, universities and the public health sector provides an ideal ecosystem for innovation.

Efficient infrastructure

Copenhagen is easily accessible with efficient infrastructure and direct flights to all capitals and major commercial cities of the EU Member States from Copenhagen Airport.

High liveability

Copenhagen has well-functioning institutions, a high level of public services, a large number of international schools, and the Danes have strong language skills.



Ellen Trane Nørby

These conditions make it highly attractive for the employees of the European Medicines Agency and their families to live and work in Denmark.

Strong focus on patient safety

This commitment of the Danish Healthcare System creates an ideal setting for the activities of the European Medicines Agency, ensuring that all medicines available on the EU market are safe, effective and of high quality.

This commitment and strong focus on patient's safety is reflected in the constant improvement and restructuring of the Denmark Cancer Plan. Last summer, Cancer Plan IV was presented, aiming to build upon previous plans I, II, and III. It is vital to have a strong national programme for rehabilitation and palliative care based on evidence based clinical guidelines. The safety of the patients is of course a priority for the Ministry of Health.

In Denmark, the five-year cancer survival rate has increased since the year 2000. In 2012-14 the survival rate was 61%, an increase of 13% compared to 2000-2002. In the last couple of years, the cancer mortality rate has declined, but Nørby doesn't plan on stopping

there. She highlighted the new national targets for the plan on International Cancer Day, stating, "the goals are ambitious, but so are the government." The initiatives that will be taken, such as personal cancer plans, and the implementation of a lead physician in charge of treatment of the individual patient will without a doubt strengthen a flourishing Cancer Strategy.

"It is important that we ensure optimal conditions for the EMA to fulfil its tasks, as patients in the EU need to have confidence in the medicinal products on the market. That is why the EMA should be located where there are strong traditions for focusing on patients with regard to safety, patient rights, and transparency".

This area alone demonstrates that the Ministry of Health has come a long way to reach where it is today, and to successfully achieve management of healthcare. Denmark has a population of 5.7 million people, and while it is important to cater to citizens' individual needs, the Ministry must also pursue tasks within the international sphere. As a member of the European Union, Denmark can further its knowledge, technology, and efficiency by working alongside and collaborating with many other countries. Healthcare in Denmark is universal and is based on the principles of free and equal access to healthcare for all citizens. The healthcare system offers high quality services, and will continue to do so if it continues to progress.

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Acute leukemia – driving toward precision and targeted medicine

Eigil Kjeldsen from Aarhus University Hospital gives an expert perspective on the drive towards precision and targeted medicine for acute leukaemia

cute leukemia results in bone marrow failure, and comprise the two major hematological disease groups, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Normal bone marrow function is responsible for the maturation of stem cells (hematopoiesis) that give rise to all cellular components of the blood, including cells from myeloid progenitors. Examples of this include red blood cells (carrying oxygen), platelets (prevent bleeding and aid in clotting of blood), white blood cells such as granulocytes and macrophages (fight infections, removal of dead cells), and cells from lymphoid progenitors such as B- and T-lymphocytes (production of antibodies and killing of invading cells).

The failure of the bone marrow due to acute leukemia often results in anemia, high fever (night sweat) and prolonged infections that cannot be cured by antibiotics. This is caused by an abnormal expansion of immature leukemic cells, commonly known as blasts that may be of either lymphoid or myeloid origin, which ultimately replaces normal hematopoiesis. Individuals with acute leukemia that are left untreated usually die within 3 months.

Acute leukemia is a heterogeneous group of malignant disorders that are not particular common. Approximately, 250 new cases of AML and 25-35 new cases of ALL are diagnosed annually in Denmark. However, acute leukemias are set to becoming an increasing health problem as the population ages, mainly because AML is predominantly diagnosed in patients greater than 60-year of age and may also be secondary to previous chemotherapeutic treatment of e.g. breast cancer.

Furthermore, acute leukemias are challenging to diagnose and expensive to treat. Contemporary therapies of acute leukemias include chemotherapeutics, targeted drugs and hematopoietic stem cell transplantation.

Major advances in diagnostics and classification of acute leukemias

The last three decades have witnessed major advances in diagnosis and biological understanding of this disease group. Until the 1980s, the diagnosis of acute leukemias relied largely on morphological assessment and cytochemistry while immunophenotyping (IP) and chromosome analysis were in their infancy. Continued development of IP, chromosome analysis, including cytogenetics and molecular cytogenetics, and molecular genetics, including sequencing as well as targeted mutation analysis, have greatly improved our understanding of the molecular pathogenesis of acute leukemias following the pioneering work of Nowell and Hungerford¹ and later that of Janet Rowley, who established that acute leukemia is a genetic disease².

Two leukemia patients where their leukemic cells appear identical morphologically and by IP the leukemic cells from each of the two patients may harbor different chromosomal or molecular genetic profiles, that would cause an important variation in response to prescribed contemporary therapies exemplify this.

The most recent high-through put molecular genetic analyses, such as oligo-based aCGH microarray analysis³ and next generation sequencing⁴, have further enhanced our pathogenetic understanding of acute leukemias. Several hundred-specific chromosomal and genetic mutations have been identified until now and we are still counting.

The adoption of WHO classification of hematopoietic neoplasms in 2001, and the subsequent revisions in 2008 and 2016⁵, where diagnosis and classification of subtypes relies on chromosomal and genetic information has had a major impact on diagnostic practice and greatly enhanced treatment outcome.

Impact of chromosomal and/or genetic lesions in leukemic cells

Leukemogenesis requires accumulation of aberrant genomic alterations in the leukemic blasts. Nonrandom (recurrent) chromosomal or genomic abnormalities can be detected in many of the patients with acute leukemias and are usually acquired early in leukeumogenesis. They are often termed driver mutations in which genetic alterations contribute to the pathophysiology of the leukemic cells



Figure 1. Schematic diagram illustrating the function of integrated hematological diagnostics for optimised treatment options and disease monitoring

conferring their survival advantage, by affecting important cellular pathways, which may include dysfunction of genes encoding transcription factors and signaling molecules that delay or block normal hematopoiesis. There are also passenger mutations that are secondary events during leukemogenesis or disease progression. Together these genetic alterations form the basis of prognostic and predictive markers in disease prognostication, as well as emerging targeted therapies.

Modern diagnostics and precision medicine

Targeted agents denote drugs aimed at discrete genetic or phenotypic lesions specific to the leukemia blasts compared with normal cells. It is known from several clinical trials that targeted therapy is both more effective and less toxic than conventional cytotoxic chemotherapy, which adopts to the "one size fits all" – principle.

Targeted therapy is, however, often more expensive than chemotherapy, because development of targeted drugs requires a great amount of knowledge about e.g. the cellular pathways (i.e. molecular pathogenesis), in which the genetic lesions have an impact.

To detect the critical genetic and phenotypic lesions in a timely manner, it is of great importance that modern hematological diagnostics can provide excellence in morphology and immunocytochemistry, IP, cytogenetic as well as molecular genetic analyses (figure 1). Morphology and immunophenotyping are very important for diagnosis, whereas genetic changes are the single most important factor for disease group classification, treatment decision as well as prognosis.

Conclusion

The extensive genetic heterogeneity in acute leukemias provides a wealth of biomarkers in precision and targeted medicine, but only few of these known genetic lesions can currently be targeted by precision medicine. This is because it is one thing is to identify novel genetic aberrations and another, to understand their cellular impact and subsequently how this information can be used to development of a targeted drug.

Thus, many questions remain on the clinical utility of these emerging genetic abnormalities and their implication as prognostic markers for disease outcome or predictive markers, for targeted therapies in different treatment settings.

The era of precision medicine in acute leukemias has just begun, and new diagnostic and therapeutic strategies are yet to be developed and tested.

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Eigil Kjeldsen, MD, DMSCi Professor of Cancer Cytogenetics Senior Consultant Medical Geneticist Head of CancerCytogenetics Section HemoDiagnostic Laboratory Department of Hematology Aarhus University Hospital Tage-Hansens Gade 2, Ent. 4A DK-8000 Aarhus C Denmark Tel: +45 7846 7799 Fax: +45 7846 7399 Eigil.Kjeldsen@clin.au.dk

The symptoms of Huntington's disease

Chief Executive of the Huntington's Disease Association, Cath Stanley explores the symptoms, causes, and the vital role of research within the field

untington's disease is a rare genetic illness caused by a faulty gene on chromosome 4. If a person has Huntington's disease, it means they have inherited a faulty version of the Huntington's gene. The faulty gene that causes Huntington's repeats a particular coding sequence known as CAG (cytosineadenine-guanine) too many times – a bit like adding too much of one ingredient in a recipe. This means the protein it makes damages nerve cells in the brain. If a person has 40 or more CAG repeats, it is certain that they will develop Huntington's at some point.

Huntington's is what's known as an "autosomal dominant disorder" this means that you can inherit the gene, and therefore the disease, from only one parent. One of your parents is likely to have Huntington's too. Every child conceived naturally to a parent who has the faulty Huntington's gene has a 50% chance of inheriting it and the disease. If both parents have the faulty gene, there is a 75% the child will also have the gene. A person can find out if they carry the faulty gene by taking a blood test known as a predictive test. You usually need to be 18 years old to take the test.

Symptoms

The symptoms of Huntington's disease vary widely between people. Even people in the same family may be affected differently. However, changes usually affect three main areas: movement (chorea movements, dystonia, and rigidity), cognitive (difficulties with planning and thinking) and behaviour (changes in behaviour and personality). Symptoms usually develop between the ages of 30-50 years, although they can start at any time. Sometimes, symptoms are present for a long time before a diagnosis of Huntington's disease is made.

Professionals and families can mistake Huntington's for a different illness such as Parkinson's disease or



Cath Stanley, Chief Executive

Alzheimer's disease. This is especially true when people are not aware that the faulty gene is in their family and that they are at risk.

If a person develops symptoms before the age of 20, this is known as Juvenile Huntington's disease. The symptoms may at first appear as stiffness and clumsiness in the arms and legs. Parents may notice a change of performance at school, behavioural changes and disturbances in speech. The disease is progressive, meaning that symptoms worsen over time.

Movement disorder

The movement disorder is usually the most obvious first symptom. This can include physical symptoms such as involuntary and voluntary movements being impaired but also speech and swallowing difficulties. The cognitive disorder is usually the symptom people find affects them most in daily life. This may be less obvious, particularly earlier on in the illness but causes great disruption into a person's ability to function. The behavioural disorder is usually the one that gives patients and carers the most concern. This can present as mood and behavioural changes, impulsivity, frustration, apathy and depression and the inability to wait, all of which can compound social isolation.



Research

It is a really important time in Huntington's research. There are many different avenues of research being carried out. Perhaps one of the most significant is the ISIS-HTTrx. This is a trial involving a drug called ISIS-HTTrx and is the first therapy designed to address the genetic causes of Huntington's directly. It targets the protein huntingtin's RNA and reduces the production of the huntingtin protein. Research in models of Huntington's has shown by lowering huntingtin RNA and protein levels with the drug slowed down the progression of the disease, increased survival and improved symptoms.

The aim of the current study is to determine the drug's safety and dosage levels and is expected to continue throughout 2017.

The Huntingtons Disease Association is a charity that supports people affected by Huntington's. We offer support and advice through our website, literature and from our Specialist Huntington's Disease Advisory service. All our specialist advisers are experienced and compassionate care management professionals. We understand that whole families may need our support.

We have a specialist adviser dedicated to helping young people with Juvenile Huntington's disease and a specialist youth worker.

Our specialist advisers support anyone who needs their help at any stage of the Huntington's journey. They can help people living with the disease, people at risk of inheriting the disease, family members and carers, and children/ young people. They can also advise friends, neighbours, employers and medical teams.

Cath Stanley Chief Executive

Huntington's Disease Association Tel: +44 (0)151 331 5444 info@hda.org.uk www.hda.org.uk www.twitter.com/HDA_tweeting

What's in an aggregate? Therapeutic intervention in Huntington's

Naoko Tanese from New York University School of Medicine outlines their work around Huntington's disease (HD) and effective new targets for therapeutic intervention

untington's disease (HD) is a rare hereditary neurodegenerative disease that strikes patients in mid-life. American physician George Huntington first described the disease in 1872 after seeing affected residents in East Hampton, New York. Patients generally experience a progressive decline in cognitive, psychiatric, and motor functions. The disease is fatal. In 1993 an international team of scientists discovered the gene that causes the disease. Despite years of intense research, no cures or treatments to delay the onset or prevent the progression of the disease are available.

HD is caused by an inherited dominant mutation in the Huntingtin gene, HTT. This means an offspring of a parent who carries a mutant HTT gene has a 50% chance of inheriting the mutant gene. The mutation results in an increased number of repeats (greater than 40) of the amino acid glutamine in the encoded Huntingtin protein (HTT).

A normal HTT protein has between 7 and 35 glutamines. Increased number of glutamine repeats changes the property of the protein and renders it toxic to cells. The HTT protein is present throughout the body and throughout life. However, mutant HTT is toxic to select cells. Postmortem examination of the brains of affected individuals shows massive cell loss in certain parts of the brain, leaving



other cells and tissues intact. This indicates that some neurons are particularly sensitive to the toxic effects of mutant HTT.

The normal HTT protein has been implicated in many cellular functions. However, we have an incomplete understanding of how mutant HTT causes the disease. A better understanding of the functions of the normal and mutant HTT protein is paramount, if effective therapies or cures are to be developed.

Proteins made in cells maintain certain structures dictated by their biochemical and biophysical properties. This is referred to as protein folding. When proteins misfold, they often lose their normal functions. Cells have developed elaborate mechanisms to remove such aberrant, misfolded proteins. This protects the cells from potential harmful effects of misfolded proteins.

However, misfolded proteins can accumulate over time and form irreversible aggregates that impair cellular homeostasis. These aggregates are a hallmark of many neurodegenerative diseases. They are found in postmortem brain tissues of affected individuals. Age-associated diseases such as Alzheimer's disease, are linked to protein misfolding. HD is

also considered a protein misfolding disease although many other mechanisms are thought to play a role in the disease pathogenesis.

Decades of research have uncovered intriguing properties of different types of protein aggregates, some of which are RNA-protein granules found in normal cells. Each granule appears to have distinct properties and its formation is driven by specific sets of proteins and RNA. Some granules are formed in response to stress. This mechanism serves to halt energy-consuming cellular activities, by sequestering proteins involved in key biochemical processes. Upon removal of the stress, granules disassemble and the released proteins resume their normal functions.

Interestingly, mutant proteins linked to several neurodegenerative diseases have been located within these types of granules. They include mutant RNA binding proteins associated with amyotrophic lateral sclerosis, spinal muscular atrophy, and fragile X syndrome. These RNA binding proteins normally play a role in RNA transport, translation of RNA to make proteins, and formation of RNA-protein complexes.

Mutant RNA binding proteins, however, show altered biophysical properties. They have increased propensity to interact with one another and affect the formation and function of granules. There is increasing evidence that over time mutant RNA binding proteins in these granules steadily accumulate and become converted to irreversible aggregates that are toxic to cells. Neurons are vulnerable to aberrant proteins that accumulate because neurons do not divide. Ultimately the machinery in the cell fails to remove toxic proteins, causing cell death. Since the functions of normal HTT and the mechanisms by which its mutant counterpart contributes to HD remain unclear, my lab began investigating the role of HTT in RNA metabolism. New imaging techniques have helped us determine the location of the normal HTT protein inside neurons.

Strikingly, we discovered that HTT could be found near neuronal RNA granules. RNA granules are large RNA-protein assemblies responsible for transporting RNA to specific locations in the neuron. To determine whether HTT influences RNA localisation, we reduced the level of normal HTT in neurons grown in a culture dish and examined its effect on transport of RNA. We found that the reduction of HTT in cells disrupts RNA localisation. The result points to HTT contributing to the integrity of RNA granules during RNA transport.

New experiments in HTT

To further investigate cellular processes that HTT is involved in and how they might differ in mutant HTT, we designed experiments to purify normal and mutant HTT proteins from cells and tissues. We next identified proteins that interacted with each form of HTT. By identifying the functions of the proteins that co-purified with HTT, we uncovered new functions for HTT. Analysis of the binding partners of HTT proteins revealed that both normal and mutant HTT interact with proteins involved in RNA metabolism and protein synthesis.

We have thus uncovered new roles for normal and mutant HTT in RNA metabolism. The findings have several implications for the development of HD. We have located mutant HTT in neuronal granules, similar to those associated with aforementioned RNA binding proteins linked to neurodegenerative diseases. Our results suggest HTT has a role in the formation of RNA-protein granules.

Unlike normal HTT, mutant HTT has a propensity to interact with one another through the increased repeat sequence. At high concentrations, mutant HTT alters biophysical properties of RNA-protein assemblies and shifts the equilibrium in favour of forming aggregates.

Furthermore, a recent study reported stable formation of RNA aggregates containing repeat sequences. Collectively, the findings suggest that mutant HTT together with repeat sequence-containing RNA forms granules that become converted to irreversible toxic aggregates over time. The development of chemical agents that prevent aggregation or disrupt aggregates may serve to reverse the toxicity associated with the mutant protein and RNA. Through understanding of how HTT supports neurons with these functions, we hope to reveal effective new targets for therapeutic intervention.



Naoko Tanese, PhD Associate Dean for Biomedical Sciences, Director, Sackler Institute of Graduate Biomedical Sciences New York University School of Medicine Tel: +1 212 263 8945 tanesn01@med.nyu.edu https://med.nyu.edu/faculty/naoko-tanese www.twitter.com/nyuschoolofmed http://sackler.med.nyu.edu

Membranous nephropathy and how can it be identified and treated

The National Kidney Foundation analyses the causes of membranous nephropathy and the science available to identify and treat it

Any diseases can affect your kidney function by attacking and damaging the glomeruli, the tiny filtering units inside your kidney where blood is cleaned. Glomerular diseases include many conditions with many different genetic and environmental causes. Membranous nephropathy (MN) is a type of glomerular disease and is an autoimmune disease. An autoimmune disease is caused when your body's defence system turns against you and harms your body when it should be protecting you.

Your defence system is known as your immune system, which is "turned on" by glomerular disease. MN is one of the most common causes of nephrotic syndrome. When your immune system attacks the glomeruli in membranous nephropathy, it causes changes to the filters that lead you to lose large amount of protein into the urine. If this continues at high levels, it can eventually lead to kidney failure.

What causes membranous nephropathy?

There are two kinds of MN: idiopathic (or primary) MN and is more common than secondary MN, which is caused by another disease or drug. Although there has been progress in learning about the autoimmune cause of primary MN, a lot more research is needed to find the reason the immune system is triggered. The most common causes of secondary MN are:

- Hepatitis B virus;
- Non-steroidal anti-inflammatory drugs (NSAIDs);
- Systemic lupus erythematosus (lupus for short);
- Cancer and;
- Other diseases and infections.



What are the signs and symptoms of membranous nephropathy?

Membranous nephropathy happens slowly over time, so you may not notice anything is wrong. You may only see some signs on your own, while others may be found by your healthcare provider.

Signs and symptoms of membranous nephropathy include:

- Swelling in body parts like your legs, ankles and around your eyes (called edema);
- Weight gain;
- Fatigue;
- Foaming of the urine caused by high protein levels in the urine (called proteinuria);
- High fat levels in the blood (high cholesterol) and;
- Low levels of protein in the blood.

Which tests are done to find out if I have MN?

- Urine test: A urine test will help find protein and blood in your urine;
- Blood test: A blood test will help find levels of protein, cholesterol, and wastes in your blood;
- Glomerular filtration rate (GFR): A blood test will be done to know how well your kidneys are filtering the wastes from your body;
- Kidney biopsy: In this test, a tiny piece of your kidney is removed with a special needle, and looked at under a microscope. The kidney biopsy may show if you have a certain type of a protein that helps your body fight infection, called an antibody. Your body usually makes this antibody when you have MN.

What are the treatments for MN?

After your healthcare provider finds that you have MN, your doctor will follow up with you very closely without treatment. This waiting period allows time to see if you go into remission (the disease stops being active and causes no symptoms) without having to use strong drugs. During this waiting time, you will be given supportive care (treatments that have little or no risk).

Supportive care includes:

- ACE inhibitor or an ARB: These drugs help to reduce high blood pressure and proteinuria;
- Diuretics: Pills that cause you to urinate more and;
- Low-salt diet: Lowering salt may help to reduce edema (swelling in your body parts like your legs, and around your eyes).

If your symptoms do not go away after supportive care, you may be given treatments that affect your immune system. The goal of your treatment is to manage your symptoms. If you have nephrotic syndrome, your healthcare provider may give you pills to reduce the water in your body (diuretics). It is very important to discuss the side effects of your treatments with your healthcare provider. If you are a woman, and are considering having children, be sure to speak with your doctor about how your treatments may affect this process.

What are the treatments for MN in children?

It is very rare for a child to have MN, so it is important to check for anything that might be causing the disease, especially lupus. If your child needs treatment for MN, the treatment is usually the same as it is for adults. It is important to know that some people with MN go into spontaneous remission, which means it suddenly goes away without any treatments.

"An autoimmune disease is caused when your body's defence system turns against you and harms your body when it should be protecting you."

Will I have kidney failure because of MN?

You should talk with your doctor about your condition, because the progression of the disease depends on many factors. Treatment can slow the process of kidney disease. Everyone is different in how they respond to treatment.

Over time, some patients with MN gradually get worse until they reach kidney failure. If this occurs, they will need a kidney transplant or dialysis to stay alive. Some people respond well to treatment and may live with the disease for many years while being monitored for any signs of change.

National Kidney Foundation (NKF) Tel: +1 212 889 2210 info@kidney.org www.kidney.org www.twitter.com/nkf

Is precision medicine for membranous nephropathy a dream?

Professor Pierre Ronco and Dr Hanna Debiec discuss the viability of precision medicine in treating patients with the rare disease membranous nephropathy

embranous nephropathy (MN) is a rare disease that affects the kidney filter (glomerulus) and induces a massive loss of proteins in the urine. Considerable progress has occurred in the diagnosis and management of patients since the identification of the major antigens, recognised in the glomerulus by toxic antibodies circulating in the blood. Because the antigens are normally present in the glomerulus, one can conclude that MN is auto-immune in nature, and thanks to the recent advances in the disease pathogenesis, it can serve as a model for most organspecific auto-immune diseases. The most prevalent antigen identified in 2009, the receptor of the phospholipase A2 (PLA2R1), is localised on the podocyte, a major cell of the glomerular filter where it serves as target for circulating antibodies.

Diagnosis of membranous nephropathy: Now possible with a simple serological test

Until recently, the diagnosis of MN required a kidney biopsy, an invasive diagnostic procedure with the risk of bleeding observed in less than 5% of patients. The development of assays of circulating anti-PLA2R1 antibodies and their transfer to clinical practice has been amazingly fast. The first immunofluorescence (IF) test used biochips coated with cells expressing the antigen, incubated with the patients' sera. The ELISA using the extracellular domain of human PLA2R1

coated to plastic wells enables a more guantitative and faster determination of anti-PLA2R antibodies, but it is a little bit less sensitive than IF. Detection of PLA2R1 antigen in immune deposits in biopsy specimens is also possible with the use of commercial antibody after a retrieval step to unmask PLA2R1 epitopes (domains of the antigen PLA2R that are recognised by the antibodies). These tests have ushered in a new era of precision medicine. Seventy to 80% of patients with MN have mounted an immune response against PLA2R1, which serves as a diagnostic signature since PLA2R1 antibodies are specific for this disease.

Monitoring patients with membranous nephropathy: Beyond proteinuria

For a long time, proteinuria was the only variable to follow disease activity. Now that specific antibodies have been identified, it has been shown that levels of these antibodies also predict outcome. High titers are correlated with a lower chance of spontaneous or treatment-induced remission, and a higher risk of the emergence of a nephrotic syndrome in non-nephrotic patients, and of renal function deterioration.

Furthermore, anti-PLA2R1 antibodies appear to be sensitive markers of treatment efficacy. Partial or complete depletion of anti-PLA2R antibodies precedes clinical remission, which is disappearance of proteinuria, by several weeks or months, while re-emergence or an increase of these antibodies precedes by several weeks a renal relapse. The time lag of several months from immunological remission (depletion of antibodies) to renal remission is most likely accounted for by resorption of immune deposits and repair of the glomerulus. Even more, anti-PLA2R1 antibody titers at the end of therapy are predictive of later outcomes.

"Because the rate of remission (including partial remissions) does not exceed 70% with current immunosuppressive treatments, we hope that in future trials, close monitoring of anti-PLA2R1 antibody titer and epitope specificity as well as regulatory T-cells will allow a more personalised adaptation of treatment leading to increased rate of complete remission."

Toward a serology-based approach to treatment

Treatment of MN is controversial because of a high rate of spontaneous remission (up to 40%) and toxicity of immunosuppressive drugs that are used to treat patients with persisting nephrotic syndrome. Patients should not be overexposed to toxic medication if they don't need it. This is the reason why treatment is often delayed by 6 months to give the patients a chance to undergo spontaneous remission. We think that the international guidelines should be revised to include anti-PLA2R1 antibody in the



This picture shows the results of immunofluorescence test for the detection of anti-PLA2R1 antibodies (upper left) and those of a meta-anlysis of >2,000 patients showing that anti-PLA2R1 antibodies are highly specific for MN and their sensitivity is close to 80% (upper right).

The scheme at the bottom shows that anti-PLA2R1 (in red) disappear before proteinuria (in green) and reappear before clinical relapse.

decision algorithm for patients with idiopathic MN. Measurement of anti-PLA2R1 antibodies may indeed obviate the need for a "wait and see" period of 6 months, and allow for more rapid treatment decisions. We recommend that antibodies are assessed every month in patients with a high level, and every two months in patients with low levels before starting immunosuppressive therapy to avoid unnecessary treatment in patients entering immunological remission (substantial decrease or disappearance of antibodies). This recommendation does not apply to patients with rapidly declining renal function, in whom a prompt initiation of immunosuppression is warranted.

If immunosuppression has been started, we recommend that antibodies be assessed every month during the first 6 months. Although the rate of antibody reduction varies among studies, the general picture is that antibodies dramatically decrease during the first 3 months, and disappear over 6 to 9 months followed by remission of proteinuria over 12 to 24 months. Patients with a prompt and robust immunologic response may receive shorter than usual courses of immuosuppressive agents, whereas a conversion to an alternative therapy or a reinfusion of rituximab (for patients started on this drug which targets the B-lymphocytes involved in antibody production) should be considered in those who do not show a significant reduction in antibody titer at 6 months.

Toward more precision medicine: Lessons from molecular and cellular studies

There is more to come. Very recent studies by our group and a collaborating group in Nice suggest that diffusion of the immune response to several domains of the PLA2R1 antigen (a phenomenon called epitope spreading) was associated with a lower rate of remission after 6 months in patients treated with rituximab. We also showed that a population of T-lymphocytes, the regulatory T-cells, involved in the control of auto-immunity, was decreased in patients with severe MN and that those who responded to rituximab had a lower percentage of regulatory T-lymphocytes at onset of treatment and an increased percentage of those cells as early as 8 days after starting treatment.

Because the rate of remission (including partial remissions) does not exceed 70% with current immunosuppressive treatments, we hope that in future trials, close monitoring of anti-PLA2R1 antibody titer and epitope specificity as well as regulatory T-cells will allow a more personalised adaptation of treatment leading to increased rate of complete remission.

Inserm

Pierre Ronco Professor Sorbonne Universités (UPMC)

Hanna Debiec

Doctor Institut National de la Sante et de la Recherche Medicale Tel: +33 1 560 16639 pierre.ronco@aphp.fr http://cordis.europa.eu/project/rcn/10484 5_en.html

Treatments and symptoms of Parkinson's

Prof. David Dexter, deputy director of research at Parkinson's UK shares his thoughts on the symptoms of Parkinson's and the chances of finding a cure

arkinson's is a progressive neurological condition caused by the loss of brain cells. The main symptoms of Parkinson's are stiffness, slowness of movement, shaking of the limbs, which, combined with muscle atrophy markedly impact on the ability to move.

However, the disorder can also affect memory, mood and behaviour. While Parkinson's is generally associated with old age, affecting 2-3% of the population over 65 years, 3-5% of those diagnosed are under 40. In total, this costs the UK economy £3.3 billion per year in treatment and other associated costs.

There are treatments for Parkinson's, but they simply replace a chemical messenger called dopamine, which the brain stops producing in Parkinson's. These drugs only treat the symptoms and do not actually stop the brain cells dying, meaning the underlying condition continues to get worse over time. The main drug used to treat Parkinson's was developed more than 50 years ago and it's simply not good enough: we must develop a cure quickly.

While it's more than 200 years since James Parkinson first described the disorder, we still don't know what causes Parkinson's. However, over the last 30 years medical research has played a vital role in enhancing our understanding of the condition. A number of mechanisms which cause the brain cells to die in Parkinson's have been discovered, but we don't know the full story.

In the laboratory, new drugs have been developed to block these pathways, thus preventing brain cell death in cell and animal models of Parkinson's, however there are a number of road blocks preventing their translation to effective drugs for humans. What are these roadblocks?



Image: © Parkinson's Uk James Labous

Prof. David Dexter, Deputy director of research at Parkinson's UK

Lack of Funding

Although the UK invests less in research compared to the USA and some EU partners, UK scientists are some of the most productive in making new discoveries. We are failing to capitalise on this, however¹.

Government and charity funding can facilitate the academic development of novel drugs at the research and development (R&D) and pre-clinical phase of the drug development pipeline (see figure 1), but eventually a large investment of funds is required to translate the drug into clinical use. This funding, normally from pharmaceutical companies, is becoming very difficult to obtain.

Drug development for brain disorders like Parkinson's is very complex, costly and time consuming, particularly since clinical trials need to run for a long time. Consequently, novel drugs can stall at any point along the drug discovery pipeline. Coupled with a high failure rate in drug development in this area, you can appreciate why pharmaceutical companies are increasingly reluctant to invest in new drugs for Parkinson's.

To overcome this roadblock, we need to develop innovative ways of funding further development of novel



drugs that takes them to a stage when they are more attractive and less risky for pharmaceutical companies to take on. The government's Lifesciences Industry Strategy Document¹, released early this year, acknowledges this as a major road block in drug development and proposes some new funding mechanisms to address this. Parkinson's UK is taking a lead on this through its Virtual Biotech funding stream², which provides vital additional funds to cover the further development of novel drugs to a stage when they can partner with pharmaceutical companies.

modeling

No good models of Parkinson's

To develop effective drugs, you need cellular and animal models which closely replicate the disorder. Parkinson's only affects humans and the current animal models only replicate certain aspects of the human condition. The lack of good models has resulted in the development of drugs that protect the brain cells from dying in animal models but fail in human trials.

Clinical trial design and patient recruitment

Testing of drugs in clinical trials is essential to test effectiveness against Parkinson's and safety. Currently, poor trial design, poor patient selection and clinical assessment are roadblocks. Parkinson's can affect people differently, with highly varied progression rates. Hence, the cross the board recruitment of people into clinical trials induces large data variability, making it difficult to assess a drug's effectiveness. This is further hampered by a significant misdiagnosis rate for Parkinson's.

Additionally, the testing of participants is carried out as a short snapshot in hospital environments, failing to capture whether the drug has improved mobility in the real world. The Critical Path for Parkinson's (CPP) project³, funded by Parkinson's UK and other charities, as well as nine pharmaceutical partners, is collecting brain imaging and clinical data from around 7,500 people with Parkinson's, leading to the development of a brain novel drugs from laboratory bench to clinical use

imaging tool for the better selection of patients and a computer clinical trials simulation platform.

CPP will also facilitate the testing of subsets of patients based on their presenting clinical symptoms, thus allowing more effective selection for trials. To address assessment issues, CPP is facilitating the development of wearable devices, like smart-phone apps, which capture clinical symptoms across the whole day, thus enhancing the testing the drug effectiveness. Since trials are the final vital research step in getting a drug approval, health and social care professionals can play a vital role by engaging with patients about their potential involvement in research, thus driving up recruitment.

In conclusion, we have a golden opportunity to cure Parkinson's, but we need researchers, health and social care professionals and research funders to work with us to develop imaginative solutions to these roadblocks if we are going to consign Parkinson's to the medical history books.

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Prof. David Dexter Deputy director of research at Parkinson's UK Parkinson's UK Tel: +44 (0)20 7931 8080 hello@parkinsons.org.uk www.parkinsons.org.uk www.twitter.com/ParkinsonsUK

Therapies for weak muscles

Research into personalised interventions is helping pave the way for a new generation of therapies for weak muscles at the Balgrist Campus

t is estimated that 10% of the cost of healthcare in Switzerland (or the equivalent of €500 billion per annum in the EU) being associated with lost work is related to injury or dysfunction of the musculoskeletal system (Fig. 1). Surgical and subsequent rehabilitative interventions are important part of the therapy that reestablishes musculoskeletal function.

The Laboratory for Muscle Plasticity at Balgrist University Hospital aims to shed light on the underlying mechanisms in skeletal muscle with the goal of translating the findings into more effective clinical applications.

Skeletal muscle plays a major part in control of movement and posture and affects whole body metabolism through its effects on energy expenditure. Affections ranging from simple overuse injury to rupture of tendons and bones, or disease, lead to deconditioning of skeletal muscle as a result of inactivity and damage signals. The consequent loss in muscle strength and fatigue resistance exerts a distinct negative impact on the quality of life and may render the affected individual dependent. In these situations a surgical intervention and rehabilitation may be indicated, yet may come too late as irreversible changes may have resulted.

Focus on muscle plasticity

The Laboratory for Muscle Plasticity investigates the mechanisms that



underlie the conditioning of skeletal muscle structure and function during recovery from surgical interventions and rehabilitation. As shown through research on sport performance, this process is driven by mechanical and metabolic stimuli. It is mediated through a gene response that instructs adjustments in muscle composition with the repeated impact of exercise during training. In consequence, force production and fatigue resistance of muscle may be improved or maintained.

By contrast, a muscle's functional capacity is reduced in the absence of a physiological stimulus by a reduction in the size of muscle fibres and their content in mitochondria (Fig. 2).

In fact, while the safety and effectiveness of physical factors for muscle conditioning are well established, the dose-effect relationship between exercise and muscle adaptation is often not fully respected in clinical practice. An example of this biological regulation is the important role of muscle contraction and loading in preserving muscle mass of the bedridden musculoskeletal patient after surgery, who would otherwise lose muscle mass at a pronounced rate. Genetic factors (so called gene polymorphisms) significantly affect this adaptation. This indicates that gene polymorphisms contribute to the inter-individual variability of the response to surgical interventions and rehabilitation.

Research projects

The emphasis of the research team lead by Prof Martin Flück at Balgrist is on major musculoskeletal affections that arise in the context of the orthopaedic clinics at Balgrist Hospital. A special focus is put on resolving the contribution of gene polymorphisms


Patient-led research

The laboratory is situated in state-ofthe-art research facilities at the Balgrist Campus. A key ingredient of this research facility is an open-space landscape where research and development into musculoskeletal medicine is integrated under one roof between clinicians, biologist, engineers, and industry. The facility situates in the vicinity of the orthopaedic hospital at Balgrist; thus providing a pipeline for a reality-driven approach that re-integrates questions from bedside to bench and returns to the patient. The Laboratory for Muscle Plasticity is looking for potential partners that may want to exploit the research options presented in the future campus in the frame of collaboration.



to inter-individual differences in the healing of muscle with re-attachment of the ruptured rotator cuff tendon, and the strengthening of skeletal muscle with rehabilitative exercise in patients.

The aim is to develop personalised forms of intervention that maximise muscle adaptation (Fig. 3). The latter approach is based on previous investigations pointing out the important exercise-intensity and exercise-type related influence of gene polymorphisms on <u>muscle response to</u> <u>leisure-type sports activities</u>. This opens a venue to tailor the therapeutically effective exercise intervention for patients which otherwise would demonstrate little plasticity to a generic exercise stimulus and for which pharmaceuticals alone do not work due to the importance of activity-induced muscle metabolism for muscle adaptations. In this regard, the clinical investigation ACE-REHAB into <u>personalised rehabilitation of</u> <u>cardiac patients</u> has been initiated.

The Balgrist

Professor Dr Martin Fluck

Laboratory for Muscle Plasticity Balgrist Campus AG Tel: +41 44 510 7350 martin.flueck@balgrist.ch http://balgrist.ch/en/Home/Research-and-Education/Orthopaedics/Muskelplastizitaet.aspx

The dyspnoea crisis

Wendy Preston and Katy Beckford of ARNS tell us about the problem of dysnopea and how it impacts on morbidity, mortality and healthcare utilisation

yspnoea is a common and often progressively debilitating symptom in advanced chronic disease that is associated with fear, anxiety, activity limitations, and profound suffering.

Episodes of breathlessness can occur as symptoms of a worsening chronic problem, such as respiratory or cardiac disease but can also present as a new problem, which can be easily missed. It can be a strong prognostic indicator for hospitalisation and for premature death.

Many people delay seeking medical attention for episodic breathlessness and see it as a sign of ageing or because of the side effects of their aspects of daily living, for example smoking, lack of excercise or being overweight or obese.

In the UK, 10% of the adult population have chronic breathlessness but less than half have this problem recorded. It is important to use tools, such as MRC breathlessness score and make this part of the patients annual health check so that it is detected earlier. It is sensitive for non-COPD causes too.

Causes

Hyperventilation and other breathing pattern abnormalities can co-exist with other causes of breathlessness, as well as be a problem in their own right. If a person is not responding to treatment, reconsidering causes is beneficial and a multidisciplinary approach that might include physiotherapy, occupational therapist and/or psychologist. The non-pharmaceutical elements of a treatment plan are often more important than medication prescribed.

Using a breathlessness assessment algorithm¹ helps the clinician accurately diagnose and can increase confidence in dealing with any issues that are being identified. Not all episodes of breathlessness are due to respiratory conditions and can also be linked to cardiac disease, obesity or diabetes.

Treatments

Non-pharmacological interventions can be beneficial and Booth (2013)² recommends firstly those that effect breathing, for example fan therapy, breathing exercises and neuromuscular electrical stimulation. Secondly, those that effect thinking, that is targeting central perception of breathlessness, for example education, relaxation techniques, cognitive behavioural therapy and active listening. And thirdly, interventions that effect functioning, for example exercise programmes, mobility aids and pacing skills. It would seem that given the complexity of dyspnoea incorporation of one or several of these approaches to management is essential.

There are various pharmaceutical options that can be beneficial however where prescribed they are often used in conjunction to non-pharmaceutical strategies. Opioids, primarily morphine, work by lowering perception of dyspnoea and may decrease respiratory drive and a decrease in anxiety. Yet despite reassurance from limited evidence regarding the safety of using opioids, fear of overdosing and development of respiratory depression persists and limits current prescribing practices. Reassurance of both healthcare professionals and patients is often necessary.

Anxiolytics (such as benzodiazepines) however are prescribed more frequently and are not recommended, due to a lack of evidence regarding the benefit. Oxygen is another drug that is not always recommended unless the cause of the dysponea is hypoxaemia. However, when a patient's blood oxygen level remains normal and they remain breathless this can lead to contention and



Wendy Preston, Chair, Association of Respiratory Nurse Specialists

confusion in practice on whether to prescribe oxygen therapy. Evidence suggests that there is no therapeutic benefit of short burst oxygen therapy for dyspnoea and only limited evidence of reducing dyspnoea, during activity with ambulatory oxygen.

The distressed patient however may perceive that oxygen is "doing something". Other explanations of perceived benefit of oxygen include a cool air sensation on the face; initial studies have found that simple fan-therapy has similar effects in reducing the sensation of dyspnoea.

"In the UK 10% of the adult population have chronic breathlessness but less than half have this problem recorded. It is important to use tools, such as MRC breathlessness score and make this part of the patients' annual health check so that it is detected earlier."

Supporting sufferers

Caregivers often report a feeling of helplessness while watching their nearest ones suffer and health professionals experience similar feelings due to the lack of effective interventions. Having a written action plan is useful that identifies any diagnosis, triggers and treatment plan that includes non-pharma strategies and medication regimes. This should include any red flags for when escalation is required and emergency services called.

Supporting a person who is breathless can be very concerning, especially in non-clinical environments and having an awareness of treatment plan and usual pattern is beneficial. For example, a person with chronic respiratory disease could have dyspnoea when mobilising and they will need to rest at certain points of a journey to recover before continuing.



Katy Beckford, Vice Chair, Association of Respiratory Nurse Specialists

Summary

Dyspnoea is a complex phenomenon that impacts on morbidity, mortality and healthcare utilisation. Whilst physiological mechanisms are important it is also clear that psychological, social and environmental factors are also pivotal in the way that dyspnoea is experienced and controlled. Ideally treatments need to be individually tailored to meet concerns and priorities; the inclusion of family and carers in these needs is deemed an integral part of supportive care.

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Wendy Preston, RGN BSc(Hons) Msc Pgcert HE Chair, Association of Respiratory Nurse Specialists, Head of Nursing Practice, Royal College of Nursing

Katy Beckford, RGN BA

Vice Chair, Association of Respiratory Nurse Specialists, Lead for community cardiac & respiratory services (CARRS), Berkshire NHS FT

Association of Respiratory Nurse Specialists Tel: +44 (1)7740 117 902 info@arns.co.uk https://arns.co.uk/

Understanding the process of intravenous access

Virginia M Stewart, MD outlines when intravenous access may be needed and how the skilful process should be undertaken

atients coming to the Emergency Department (ED) with shortness of breath may have characteristics that impede intravenous (IV) access. Such characteristics may include hypotension, dialysis dependence, morbid obesity, history of diabetes, sickle cell disease, or IV drug use. One prospective observational study identified nearly 1 in every 9 to 10 adults coming to an urban ED had difficult venous access requiring 3 or more IV attempts.¹ If peripheral IVs are not established, patients may need a central venous catheter placed for life-saving medications administered. In addition to requiring physician skill, central venous catheter insertion carries a risk of complications including infection, arterial puncture or an aneurysm, and pneumothorax. Ultrasound-guidance for peripheral IV placement (UGPIV) has prevented the need for central venous catheter placement in 85% of patients with difficult intravenous access.² UGPIV has been performed by Emergency Medical Technicians (EMTs) in prehospital settings, as well as nurses and physicians. Patients who have been identified as having difficult access have higher patient satisfaction scores when ultrasound is used in peripheral IV access attempts.³

Frequently, the large veins of the antecubital fossa are sufficient to place large bore peripheral IVs needed for resuscitation. The brachial and basilic



Figure 1: Short axis view of a peripheral vessel visualised with Colour Doppler (blue). The scale on the right of the screen demonstrates a total depth of 2.6 cm. A guide (white dots) in the centre of the screen marks each 0.5cm of depth. Therefore the depth of the vessel is between 1-1.5cm deep to the skin surface.

veins are easy to locate. The brachial artery is generally flanked by 2 smaller veins and the median nerve. Anatomically, these structures are medial to the insertion of the medial biceps tendon. This tendon is palpable in the antecubital fossa as the patient flexes then extends the elbow. The basilic vein is located medial to the brachial vessels. Generally, it is more superficial, larger, and does not have an accompanying artery or nerve at the level of the antecubital fossa. As you move proximally up the arm (towards the head) the basilic vein dives deeper toward the humerus, and longer angiocatheters may be required for cannulation.

When considering vascular access, there is 2 views, a short and long axis view. Cannulation from the short axis is considered 'out of plane' since the needle is perpendicular to the probe. A short axis approach 'looks' at a cross section of the vessel. Long axis uses and 'in plane' approach with the needle entering from the probe marker end, and 'looks' along the length of the vessel. Figure 1 identifies a vessel using colour Doppler in the short axis view. Figure 2 demonstrates a long axis view with a hyperechoic angiocatheter. Figure 3 is the same vessel in long axis with the angiocatheter placed. While both approaches may be used for UGPIV placement, the



Figure 2: Long axis view of a peripheral vessel. The hyperechoic needle is visualized approaching from the top left of the screen into the vessel lumen.

benefit for the short axis is the ability to identify target veins as well as accompanying non-target (arteries and nerve) structures.

Identify the vein: remember the two C's

The two C's to remember for UGPIV access or for central venous cannulation are compression and colour (or Power) Doppler. Veins are thinnerwalled and more easily compressed than arteries. This author advocates for finding a vessel first in the short plane, and compressing the vessel to ensure it is indeed a vein, rather than a less or non-compressible artery. Colour or Power Doppler may be utilised to determine if the pulsatile flow is consistent with an artery or vein. Colour Doppler uses red and blue to determine flow towards or away from the probe respectively. Power Doppler detects flow without concern for direction. Colour should not be relied on alone to determine arterial or venous flow due to the colour scale setting can be flipped or reversed, or aliasing can occur. Arterial flow is more pulsatile than venous. Venous flow may require distal augmentation (by squeezing the forearm distal to the probe) to appreciate the blush of colour.

Once the target vein is identified, the

depth from the skin surface should be noted. A common mistake is to use an angiocatheter that is too long or too short. A general rule of thumb is to use a catheter length that is more than twice the depth of the vessel to ensure at least half the catheter lies within the vein. Sterile ultrasound gel should be used, with a covered probe to prevent infection. To prevent the risk of multiple punctures, this author advocates for first bouncing the needle on the skin over the point of entry. The tissue should deform at the top of the screen, and confirm the needle is over the target vessel. Once the skin is punctured, the needle tip is kept in view by angling the ultrasound probe until the target vessel is punctured.

To confirm placement, either a 'bubble study' with agitated saline may be performed or Colour (or Power) Doppler utilised to visualise saline flow through the cannulated vessel. A vessel that is not properly cannulated will demonstrate extravasation of saline around the vessel into the tissue before the tissue swells to a degree which is palpable on the surface of the skin. Figure 4 demonstrates confirmation of intraosseous (IO) lines utilise Power Doppler. A 10cc saline flush is rapidly pushed through the line, and flow is demonstrated beneath



Figure 3: In this long axis view of a peripheral vessel the catheter has been threaded and is seen within the lumen of the vessel.



Figure 4: Power Doppler (orange) confirms placement of an intraosseus line within the distal tibia. The bright white line of the tibia cortex (in long axis view) is visualised at the top of the screen, with flow confirmation from a 10cc saline flush immediately distal (below) to the hyperechoic cortex.

the bony cortex in this adult tibia. If the line is improperly placed, the blush of colour using Doppler would appear in the soft tissues. For further information about UGPIV placement, visit: <u>http://rmgultrasound.com/pivaccess/</u>

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Virginia M Stewart, MD Forsythe Emergency Services, PA PO Box 25447 Winston-Salem NC27114 askdrstewart@gmail.com www.fespagroup.com

The impact of stroke in young people

Jukka Putaala from the European Stroke Organisation outlines the effects of stroke in young people compared to stroke in the older generation

Stroke occurs due to disturbed blood flow to the brain, resulting in cell death and dysfunction in one or several parts of the brain. The 2 main types of stroke are ischemic, due to a blood clot in an artery, and hemorrhagic, due to bleeding into the brain parenchyma.

Each year a total of 17 million people of all ages are struck by a first-time stroke. Approximately a quarter of these strokes occur in people younger than 65 years of age and a tenth in people younger than 50 years of age. In absolute numbers, about 4.25 million annual strokes occur in working-aged individuals and 1.7 million in young people aged less than 50. About a third of all strokes in young people are hemorrhagic, as opposed to approximately 15% of hemorrhagic strokes in older people. Generally, men are at a higher risk for having a stroke and at younger age than women. Nevertheless, women younger than 30-35 years are at a higher risk of ischemic stroke than men at the same age.

Strikingly, recent studies have shown increasing incidence rates of ischemic stroke in young people while overall incidence has been declining. Worldwide, the number of individuals having strokes aged 20 to 64 has increased by 25% from 1980 to 2010. This startling observation may have many, yet only little explored explanations. For example, in parallel with this, increasing prevalence of vascular risk factors, substance abuse, sedentary lifestyle, and increasing time spent sitting, among the young has been observed. More workingaged people are also likely to suffer from psychological stress and consequences of 24/7 online lifestyle than they used to do 2 decades ago. Furthermore, diagnostic techniques and awareness of stroke in the young have been improved as speculated explanations. Whatever the reasons, the absolute number of young people having a first-time stroke has been increasing substantially. The overall burden of stroke in the young now represents almost half of the entire stroke burden.



Different outcomes between old and young

Compared to stroke in older people, young stroke is different in many respects. First, they are young, at productive age, making decisive career moves, having family and children to take care of. Stroke may have disastrous effects on all these domains. Second, risk factors and causes underlying young stroke have a different spectrum and thus may affect acute treatment and secondary prevention choices. Third, stroke outcomes have to be faced differently. For example, a good outcome for an elderly stroke survivor may be independence in daily duties, whereas a good outcome for a working-aged counterpart merely means a return to paid work. Young stroke patients, therefore, have unique rehabilitation needs and goals.

Unique spectrum of risk factors and causes

Identifying risk factors and pathogenesis form a cornerstone for secondary prevention after stroke. Traditionally, it has been thought that stroke in young people is associated with risk factors specific to young age or factors more commonly detected in younger patients. Such factors include coagulopathies, patent foramen ovale, pregnancy and puerperium, and illicit drug use. Recent evidence, however, shows that the risk factor profile of young stroke patients has changed and now more resembles that of older patients than 2-3 decades ago.

Regarding stroke pathogenesis, older-onset causes like atherosclerosis in the brain supplying arteries, small-vessel disease of the brain, and certain high-risk cardiac conditions such as atrial fibrillation cause a rather small proportion of ischemic strokes in the young. Dissection in the carotid artery is the most common (15-20%) solitary cause of ischemic stroke in the young, while it is rarely seen in the elderly. More than a hundred other rare causes can lead to ischemic stroke at a young age making the diagnostic workup in young stroke patients a real challenge. Another unique feature in the spectrum of causes of young strokes is the very high frequency of patients without any identified cause: 30 to 40% of ischemic strokes in people aged less than 50 years represent these "cryptogenic strokes", with the highest proportions observed in the youngest patients. Many of these cryptogenic strokes show an embolic pattern in neuroimaging, raising a suspicion of embolism from the heart, although no definitive source for the embolism can be detected with modern-day diagnostic work-up. Secondary prevention is problematic if the cause remains unclear. Regarding hemorrhagic strokes, structural conditions such as vascular malformations cause a notably larger proportion in the young than in the elderly.

Consequences of young stroke

Studies show at least 4-times higher mortality in young stroke patients as compared with background population of the same age. Young patients who survive a stroke have to face a considerable risk of recurrent stroke, other vascular events, and other consequences such as epilepsy and problems with cognition exceeding by far the risks among the stroke-free people. Very limited data exist on the long-term medical secondary prevention after stroke at young age. For instance, should every young patient eat aspirin and statin for the rest of their life is a question unresolved. Young patients tend to be excluded from or have represented a small minority in randomised trials of secondary stroke prevention so the trial results may not be always generalisable to younger patients.

Young people with stroke have unique rehabilitation needs, although only a few studies have systematically assessed these. Available data suggests that young stroke patients have 2-3 times a higher risk of being left without paid work in the long-term than their peers. Stroke affects the entire family and leads to socioeconomic consequences.

Research needs

Until recently, research on the area of young stroke patients has been based on relatively modest patient samples and suffered from methodological limitations such as single-center and retrospective nature. The key areas for future research include, investigating the reasons for the increasing incidence of ischemic strokes in young people, deciphering the risk factors and pathogenic mechanisms of cryptogenic ischemic strokes (being the largest group of young patients with ischemic stroke), delineating the specific needs of rehabilitation and how to efficiently deliver rehabilitation in young people after stroke, e.g. assisted with mobile devices. Economic impact of young stroke needs to be assessed. Large prospective studies should investigate the use and adherence of secondary prevention medication after young stroke. Randomised trials should be planned to assess the efficacy of secondary preventive medication in specific situations, e.g. statins in young people without atherosclerosis and oral anticoagulation in patients with cryptogenic strokes. Finally, given the already high and increasing impact of young stroke patients in society, primary prevention strategies deserve rethinking.

Jukka Putaala is an associate professor and stroke neurologist from the University of Helsinki and Department of Neurology at the Helsinki University Hospital.

Jukka Putaala, MD, PhD, MSc (Stroke)

European Stroke Organisation jukka.putaala@hus.fi http://eso-stroke.org/ www.twitter.com/ESOstroke

Imaging cerebral blood flow with single capillary resolution

Experts from the European Laboratory for Non-Linear Spectroscopy and the Neuroscience Institute reflect on cerebral blood flow (CBF)

The circulatory system of our body can be imaginatively described as a highway, through which oxygen and nutrients are carried to feed our organs. About 60,000 miles of blood vessels and a high degree of complexity, flexibility and efficiency make our body's transportation plan a super engineering work, with no rival among man-made roads. The blood flow ensures all the body districts to be continually supplied with all the substances needed for their activities.

However, loss of blood flow (ischemia) can occur, leading to organ dysfunctions. The severity of these events, depends on the site, with some organs being more sensitive than others to reduced blood flow. In particular, the brain is more depended than other organs on a continuous supply of blood. This dependence is due to the lack of fuel reserves and the high brain's energy demand. If cerebral blood flow (CBF) is interrupted, brain function ceases within seconds leading to irreversible damage to its cellular constituents within minutes.

Such interruption of CBF can come in different sizes and shapes, with consequences depending very much on the part of the brain affected. In what is called a transient ischemic attack (TIA), the blood supply to a part of the brain fails temporarily. The



Comparison between MRA and optical microscopy for imaging of blood vessels: (a) MRA on a whole human brain showing large brain vessels. (b) 3D reconstruction of 1mm3 brain tissue using an advanced optical microscopy technique.

symptoms of TIA resolve within 24 hours and include sudden dimming or loss of vision, aphasia, slurred speech and mental confusion.

A prolonged cut off of blood supply is called stroke, and can lead to irreversible damage. The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty speaking or understanding speech, difficulty seeing with one or both eyes, difficulty walking, dizziness, loss of balance or coordination, severe headache, fainting or unconsciousness.

Moreover, a very severe stroke can cause sudden death. The World Health

Organization estimated in 2012 cerebrovascular accident (another name for stroke), as the second leading cause of death and the third leading cause of disability worldwide.

Nowadays imaging techniques such as magnetic resonance angiography (MRA) and computer tomography angiography (CTA) represent important diagnostic means to identify vascular abnormalities or evaluate vessels occlusions. MRA and CTA yield images of brain vasculature with minimal invasiveness. For this reason, they keep a relevant role in the diagnosis of vascular diseases like stroke.

In addition to diagnostic use in humans, these methodologies have been applied in pre-clinical settings to

obtain full datasets of whole brain vasculature. Time of flight (TOF) angiography, for instance, is a noninvasive MR method which allows the visualisation of blood flow in whole mouse brains with a resolution close to 1 mm. Contrast-enhanced MRA and microscopic computed tomography (μ CT) take advantage of contrast agent injected into the blood flow to visualise smaller vessels (10 times smaller than TOF-MRA) in whole rodent brain.

On the other hand, these approaches are profoundly wanting on a microscopic level, which means that only large vessels are detectable (Fig.1a). The resolution needed for visualising single capillaries is instead achievable with optical microscopy (Fig.1b). Thanks to the advances achieved in optical technologies in the last years, we are now starting to unveil the intricate organisation of the brain vascular network on micrometric scale.

Imaging techniques

Optical imaging techniques like twophoton fluorescence or light-sheet microscopy allow evaluation of changes in vascular organisation, at the level of the capillary network in animal models of vascular impairments. In combination with recently developed optical clearing techniques, these methods provide fine morphological vascular details in large volumes of tissue, thus coupling high-resolution with brain-wide analysis.

This level of analysis is of remarkable importance to improve our understanding about metabolic processes, underlying both physiological and pathological conditions. Nevertheless, such a fine analysis requires considerable efforts to be accomplished in large volume. Indeed, with the purpose of obtaining a complete understanding of the brain vascular network, methodological developments involving computational analysis and microscopy technologies are currently ongoing.

The specific features of optical microscopy make it also a complementary tool when associated to other imaging methods. For instance, the coupling between MRA imaging with the latest optical methodologies will allow us to associate functional studies with a detailed vascular structure. Ultimately, the approaches described above will permit to step forward towards the achievement of whole-brain vasculature network reconstruction.

Such achievements will have implications – ranging from the generation of better diagnostic tools to the availability of innovative procedures to be used in the field of brain research – eventually leading to new treatments of vascular related pathologies including cancer, stroke, and Alzheimer's disease.

The tremendous efforts against this kind of pathologies are justified by the strong impact on the society. For instance, stroke and cancer often affect individuals at the peak of their productive life, while the spreading of neurodegenerative disorders entails an increasing burden on public health. It emerges that beyond the personal and familiar difficulties, these conditions have an enormous effect on countries' socio-economic development. For such reasons, improving our knowledge about physiological brain activities and abnormalities is necessary, with the purpose of getting effective therapies to up to now incurable brain related dysfunctions. In this frame, the use of optical techniques can be a valid strategy to extract fine morphological information and to better define disease phenotypes. This will potentially lead to the identification of new brain alterations associated with specific pathologies to be used as new targets for therapeutic treatments.



Antonino Paolo Di Giovanna Researcher

European Laboratory for Non-Linear Spectroscopy Tel: +39 (0)5545 72267 digiovanna@lens.unifi.it

Anna Letizia Allegra Mascaro Researcher

Neuroscience Institute, National Research Council Tel: +39 (0)5545 72504 allegra@lens.unifi.it

Francesco Saverio Pavone Full professor

European Laboratory for Non-Linear Spectroscopy and Department of Physics University of Florence Tel: +39 (0)5545 72480 pavone@lens.unifi.it

Heart valve Disease: The heart of the matter

Associate medical director of the British Heart Foundation, Dr Mike Knapton explores the fundamentals of heart valve disease

ardiovascular disease causes more than a quarter of all deaths in the UK, and is a major global health problem. The term cardiovascular disease is an umbrella term for diseases of the heart and circulatory system including heart valve disease, which can cause problems throughout the body. At the centre of it all is the heart, a complex organ, which supplies the entire body with the blood, nutrients and oxygen needed to survive.

The heart is made up of four chambers. The two right sided chambers pump blood to the lungs to oxygenate the blood. This blood is then pumped by the left sided chambers to the body. To ensure the blood flows in one direction there are valves between the chambers, the mitral and tricuspid valves, and where blood leaves the heart, the pulmonary and aortic valves. Disease or damage of any one valve will disrupt the blood flow in and out of the heart.

Valves can be narrowed, called stenosis, restricting the flow of blood across the valve, or leaky, called regurgitation, allowing blood to flow backwards though the valve. Either way, this places an extra strain on the heart and means it has to work harder to pump blood around the body effectively. The UK's ageing population means that the number of people diagnosed with heart valve disease is likely to increase.

Causes

There are many causes of heart valve problems, but common causes include being born with abnormal development of the heart, called congenital heart disease, following infection such as rheumatic heart disease, and following a heart attack. Problems are more commonly seen in older people, but heart valve problems can affect anyone at any age. The more common symptoms include breathlessness, swelling



Dr Mike Knapton, Associate medical director of the British Heart Foundation

of the ankles and feet and exhaustion, though it is possible not to experience any symptoms at all.

Further diagnostic tests will be recommended if someone presents to the doctor with heart valve disease symptoms or when their doctor hears a murmur whilst listening to the heart. Diagnosis of heart valve disease is confirmed by undertaking an echocardiogram, a scan which uses sound waves to build up a detailed picture of the structure and function of your heart.

Management

The management of heart valve disease varies. For some people, no treatment is necessary but the condition should be monitored to ensure it doesn't worsen. Most valve problems can be managed using medicines or by valve heart surgery. Treatment is dependent on the cause of the valve problem, the severity of symptoms, and the effect that it is having on the heart and circulation. Common medicines include blood pressure lowering drugs such as beta

blockers and ACE inhibitors and drugs to reduce the strain on the heart muscle, such as diuretics. Many people with heart valve disease need little or no treatment and can live a normal life for many years.

Heart valve surgery is also relatively common. Valves can either be repaired or replaced. Heart valve repair involves a surgical operation to improve the structure and function of the valve. The two types of replacement valves are mechanical (artificial) valves or biological (animal) valves.

"The term cardiovascular disease is an umbrella term for diseases of the heart and circulatory system, which can cause problems throughout the body."

Because an artificial valve can lead to blood clot development around the valve, recipients will have to take blood thinning medication for life. There are pros and cons to both types of valve and the choice of which valve is optimal will depend on your individual circumstances. The operation involves open heart surgery and is undertaken by specialist cardiac surgeons.

Replacement

Usually, a replacement valve can be expected to last for many years, typically 10 to 20 years. The BHF is funding research in Bristol to find ways to prolong the life of biological prosthetic heart valves. The aim is to develop a new biological prosthetic valve that lasts longer, because it is more resistant to mechanical damage and less prone to hardening by calcium buildup. Research like this is vital to the development of new and improved treatments and surgery for people with heart valve disease.

Some adults who need an aortic valve replacement and are not well enough to have open heart surgery can have a transcatheter aortic valve implantation (TAVI) procedure instead. TAVI is carried out in a cardiac catheterisation laboratory, and normally takes one to two hours to complete. The replacement valve is introduced and positioned though an artery, often through an incision in the groin, without the need for open heart surgery.

As a result of basic research, improved technology and material science, as well as the development of new surgical techniques, the prospects for someone living



with a heart valve problem are excellent and enable people affected to live a full and symptom-free life.

Find out about the BHF's life saving research at: www.bhf.org.uk/research .



Dr Mike Knapton Associate medical director British Heart Foundation supporterservices@bhf.org.uk www.bhf.org.uk www.twitter.com/TheBHF

Rebuilding tissues inside the human body

The creation of living tissues to replace or repair damaged tissues or organs in the human body has defied clinicians and researchers for centuries. Yet, only by the end of the last century, scientific progress and systematic approaches to grow or culture new tissues outside the human body led to the first market approvals of living tissue-engineered implants.

In its most fundamental paradigm tissue engineering entails the seeding of living cells, harvested from a donor, onto a pre-shaped biodegradable support material, or scaffold, of synthetic or natural origin. This cell-scaffold construct is generally cultured in a so-called bioreactor under conditions that favor cell expansion, tissue growth and tissue function. When the tissue has reached targeted functional properties, it can be implanted (Fig. 1A). Key to the success of this approach is the synthesis of substantial new tissue by the cells to take over the function of the degrading scaffold.

Compared to other approaches for tissue regeneration, like stem cell therapies, *in vitro* tissue engineering emerged as a promising therapy to replace tissues with a predominantly mechanical function that should withstand high dynamic loads immediately upon implantation. As such, research in our group concentrated on the creation of structurally organized load-bearing tissues for the cardio-



Fig 1. Paradigms of tissue engineering: A: in vitro tissue engineering (TE), where cells are harvested from a donor and seeded and cultured on temporary scaffolds inside a bioreactor. B and C: In situ tissue engineering, where tissues are created inside the human body at the site of destination using slow-degrading scaffolds. The example shown here aims at the creation of blood vessels from scaffolds that are either pre-seeded with cells harvested on the fly during the surgical procedure (B) or implanted as pristine materials (C).

vascular system: functional blood vessels, load-bearing heart valves, and supportive cardiac muscle tissues.

Heart valves

A prominent example is the heart valve. Heart valves control unidirectional flow through the heart and their damage or malfunction often leads to serious medical conditions. End-stage heart valve disease is commonly treated by replacement of the valve with a mechanical or bioprosthetic device. While these prostheses generally improve survival and quality of life, they have technical drawbacks that limit their long-term efficacy. These include thrombo-embolic complications requiring lifelong anticoagulation therapy in case of mechanical valves, and limited durability due to calcification and structural failure in case of bioprostheses. Most importantly, prosthetic valves, including donor valves, are non-living structures that do not grow, repair or adapt. As a consequence, the life expectancy of patients after heart valve replacement is substantially lower than that of age-matched healthy individuals. The creation of a living, tissue engineered heart valve could circumvent many prostheses-related complications and would be particularly beneficial to paediatric patients.

By merging insights from engineering, life sciences and medicine, our group, in collaboration with partners from the University of Zurich, was the first



to develop a living tissue engineered heart valve that could withstand systemic loading and hence could function as an aortic heart valve¹ (Fig. 2). Translation of this technology to the clinic, however, was hampered by suboptimal long-term in-vivo performance of these valves and valves from other labs - the biggest issue being valve leaflet retraction and consequent valvular leakage due to traction of the used cells. In addition, clinical introduction is hindered by the costly and laborious cell and tissue culture, associated high risks of infection, and the complex logistics and regulation of applying a living medical product.

In situ tissue engineering

Recently, in situ tissue engineering was proposed as a route to create living heart valves inside the body (Fig. 1 B, C). In this innovative approach costly and complex tissue culture is omitted and the body itself is used as bioreactor. Cell-free valvular shaped scaffolds are implanted at the site of destination where they gradually transform into living heart valves by recruiting cells from the bloodstream. Both synthetic and biological scaffolds can be used, provided that they can function as a load-bearing heart valve upon implantation and adequately guide and control neo-tissue formation.

Contrary to *in vitro* tissue engineering, the technology is compatible with current regulation for medical devices and offers off-the-shelf availability at substantially reduced costs.

Collaboration

While this technology would constitute a simple and clinically attractive procedure, starting with the implantation of a non-living device, it requires the design of slow-degrading scaffolds that provide meticulous control over (selective) cell recruitment, cell fate, and load-bearing tissue formation. We propose the use of supramolecular polymers that can be fine-tuned with respect to degradation and mechanical properties, and functionalized with bioactive moieties to communicate with host cells in the course of tissue development^{2,3}. It is hypothesized that neo-tissue formation follows the pathways of wound healing and to align this process interaction with inflammatory and immune cells, as well as balanced tissue formation in pace with scaffold degradation in the beating heart, is critical. To achieve the essential deep understanding of these interactions, multidisciplinary consortia of material scientists, engineers, clinicians and biologists have been established. Within larger (inter)national frameworks they

collaborate with industrial partners and patient organizations to translate the technology to the clinic⁴⁻⁷.

Outlook

In situ tissue engineering holds great promise for the regeneration of damaged tissues and is foreseen to be valid for a broad range of applications. It provides the opportunity to create living tissue replacements that improve quality of life of many patients and that can outrange existing replacement therapies in terms of effectiveness, durability, availability, and costs. When successful, its simplicity and compliance with current regulatory protocols may favor a relatively smooth route to clinic.

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Prof. Dr. Carlijn Bouten

Department of Biomedical Engineering & Institute for Complex Molecular Systems Eindhoven University of Technology Tel: +31 40 247 3006 c.v.c.bouten@tue.nl www.bmt.tue.nl

Cardiology: Prevention is better than cure

Joep Perk from the European Society of Cardiology talks about methods of preventing cardiovascular diseases and research into cures

The European Society of Cardiology (ESC) is an independent, non-profit organisation, representing more than 90,000 men and women in the field of cardiology from Europe, the Mediterranean basin and far beyond. We were fortunate to speak with the Joep Perk, member ESC press committee to learn about cardiovascular diseases, including heart attacks and strokes.

By way of an introduction, ESC's Joep Perk reveals that cardiovascular diseases were uncommon around the time of the nineteenth century, but peaked in the 1970's and 80's and is slightly declining in Europe today. It is among what is termed as non-communicable diseases and it is the main killer in Europe, as well as in developing countries such as Indonesia and China. No less than 80% of all premature deaths are occurring in the third world, Perk reveals, adding that cardiovascular diseases are still a huge global challenge today.

Perk then moves the conversation to focus on his thoughts concerning the progress made and opportunities ahead when it comes to tackling cardiovascular diseases. He highlights an old Chinese saying, which says that the poor doctors will wait for a disease to occur, but the best doctors are those who prevent diseases.

Prevention

According to the World Health Organization (WHO), "most cardiovascular diseases can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies" Perk then provides his perspective on the WHO's view that, "health policies that create conducive environments for making healthy choices affordable and available are essential for motivating people to adopt and sustain healthy behaviour."¹

"According to WHO, 80% of cardiovascular diseases are caused by human behaviour, including smoking, not being physically active, eating the wrong type of diet and being chronically stressed. Since the 1990's, we have known at the molecular level what causes cardiovascular diseases and how this links into lifestyle.

"Over the past few years, the thinking has been that we should be out there in the effort to prevent the disease happening at all. When I was working in Africa for several years, I wondered why nobody was having a heart attack. However, having recently returned to Zambia to work in a small rural hospital, I have still not seen any heart attacks. So, we need to focus on human behaviour to get a better hold of cardiovascular diseases."

Healthy lifestyle

On the extent to which tackling cardiovascular diseases in Europe has been a success story today, Perk highlights the disastrous effect of smoking on the vascular wall, which he tells us has completely exploded. The thinking here is that if you make a country smoke free, then 2 out of 3 heart attacks will disappear soon.

"There is continual load of new evidence, which shows that being sufficiently physically active has a tremendous preventative effect. By simply taking a walk or a bike ride, you can reduce the risk of having a heart attack by 50%. These are very simple messages that ESC wants to convey, such as using hedge clippers, and we certainly need to keep the political focus on staying physically active.

"The other part concerns diet, indeed a significant global study showed that our normal recommendations for



food in European countries are excellent. If you keep your weight under control, and eat enough fruit and vegetables, then you can positively influence the health of your vascular walls. Science from the last 10-20 years convincingly shows that if we want to be a good doctor, we should be encouraging people to look after their body in a healthy way.

"During the past two decades, we have seen in England, France, Holland and Sweden a dramatic drop in mortality where cardiovascular diseases are concerned. Now, the risk of dying of a heart attack in Sweden is only one-third what it was in the 1980's, so this is tremendous. While I am not against developing drugs and new techniques, this seems to be behind us, so in general there has been a shift in human cardiology to focus more on human behaviour."

Moving to his concluding thoughts, Joep underlines the importance of taking this message to decision makers, to put these recommendations into law. Simple measures such as restricting the amount of salt and hidden calories, reducing junk food advertising to children, are some of the measures that can be taken by politicians in government. "This is not easy due to a number of industrial interests, but we do feel that we are on track now to conveying these simple messages across" Joep adds.

1 http://www.who.int/mediacentre/factsheets/fs317/en/

Joep Perk Member ESC press committee

European Society of Cardiology Tel: +33 (0)4 89 87 24 83 joep.perk@ltkalmar.se www.escardio.org www.twitter.com/escardio

Early stage CARdio Vascular Disease Detection with Integrated Silicon Photonics

Lead Scientist EMEA, Mirko De Melis, Ph. D sheds light on cardiovascular disease detection research and prevention methods

ardiovascular disease (CVD) includes pathology of the heart and of the vessels (mainly arteries) supplying blood to organs and tissues from the heart. It primarily encompasses diseases of the arteries directing blood to the brain. CVD and their risk factors are the major contributors to global morbidity and mortality. They are responsible for over 17.6 million deaths per year worldwide, representing 31% of all global deaths. Early cardiovascular disease detection for individuals at risk allows early intervention to delay, halt or reverse the pathological process.

Assessment of arterial stiffness by measurement of carotid-femoral pulse wave velocity (PWV), as surrogate for aortic stiffness, is included in the latest guidelines for cardiovascular risk prediction in patients with hypertension and there is ample evidence that arterial stiffness is the strongest known biomarker for cardiovascular risk in general, with predictive power above and beyond all known conventional risk factors.

Early identification of arterial stenosis and heart dyssynchrony can be used to improve CVD risk classification. However, no tools are available today to screen a large population under primary care for these indicators. Individuals who are considered to be at low or moderate risk too often remain undiagnosed. Over the past few years the Universiteit Gent (UGent) and Queen Mary University of London (QMUL) and others have gathered evidence that mechanical vibrations induced by cardiovascular dynamics actually propagate up to skin level, where they can be detected using non-invasive contact or non-contact measurements such as laser Doppler vibrometry.

A laser Doppler vibrometer (LDV) is an instrument that is used to make non-contact vibration measurements of a surface. The laser beam from the LDV is directed at the surface of interest. Vibration amplitude and frequency are extracted from the Doppler shift of the reflected laser beam frequency due to the motion of the surface. Three approaches are followed to use LDV for cardiovascular risk assessment:

- Targeting the skin overlying an artery enables detection of skin vibrations induced by the flow in the artery. A stenosis in the artery will induce instabilities in the flow, change the flow pattern and thereby change the frequency spectrum of the vibration propagating to the skin level.
- Targeting two adjacent points on the skin overlying an artery enables measurement of the time it takes the pulse wave to travel between these two points, from which the pulse wave velocity at that specific location can be derived.

• Targeting the chest allows for detection of skin vibrations induced by the heart pumping action. Dyssynchrony will change the vibration pattern.

Overall objectives

Under the leadership of Medtronic, the objective of CARDIS is to investigate and demonstrate the concept of a mobile, low-cost CVD screening device based on a silicon photonics integrated laser vibrometer (see figure 1, panel A & panel B) and to validate the concept for the screening of arterial stiffness, detection of stenosis and heart dyssynchrony. It will be met by:

- Investigating, designing and fabricating optical subsystems and components:
 - A photonic integrated chip, with a multi-branch laser interferometer with integrated photo detectors and input port for an external micro-optical laser assembly;
 - A micro-optical laser assembly;
 - A micro-optical lens system.
- Integrating the subsystems and building a multi-beam laser Doppler vibrometer. Two rows of 6 beams are envisaged.
- Developing a process flow scalable to high volumes for all subsystems and their integration steps.



- Investigating and developing experimental and computational biomechanical models to translate optical signals related to skin-level vibrations into underlying CVD physiological events.
- Validating the system in a clinical setting.

Progress beyond the state of the art and expected potential impact

With Medtronic, SIOS, imec, Tyndall-UCC, the Universiteit Gent, Queen Mary University of London, INSERM and the Universiteit Maastricht, CARDIS is partnering European leaders in respectively medical devices, laser interferometers, silicon photonics and arterial biomechanics. CARDIS will help to secure their leadership by developing a new application that advances the existing background.

The possibility for earlier detection of risk for CVD makes it possible to start earlier treatment. In these early stages of the disease this could be achieved simply by a change in life style and/or relatively cheap cholesterol lowering drugs. Thus, more complicated treatments, like stenting and ultimately cerebral and myocardial infarction may be prevented.

"CVD and their risk factors are the major contributors to global morbidity and mortality. They are responsible for over 17.6 million deaths per year worldwide, representing 31% of all global deaths. Early cardiovascular disease detection for individuals at risk allows early intervention to delay, halt or reverse the pathological process."

CARDIS will enable Medtronic to enter a new market segment and extend its diagnostic business, currently focused on Implantable Cardiac Monitors. SIOS is a growing company and the project will enable them to enter the medical market.

The new knowledge and expertise developed by imec, UGent, Tyndall-

UCC and QMUL in CARDIS will be made available to EU companies in the medical diagnostics market and other markets. It will be used to bring integrated photonics to the next level, opening its use to all kind of applications. It is the corporate mission of these institutions to transfer technology to industrial partners, thus creating a significant economical and societal impact.

Medtronic

Mirko De Melis, Ph. D Lead Scientist EMEA, Patient Monitoring & Diagnostics Medtronic Bakken Research Center, research & technology department Endepolsdomein 5, 6229 GW, Maastricht, Netherlands Tel: +31 433 566 837 mirko.de.melis@medtronic.com www.medtronic.com

Achieving sustainable health in Europe

The World Health Organisation is working towards equitable and sustainable health in Europe, as Open Access Government finds out

H Better, more equitable and sustainable health for Europe" defines the primary aim that The World Health Organisation in the European Region (WHO/Europe) is working towards and striving to achieve. Responsible for public health within the United Nations System, WHO/Europe is comprised of 53-member states, encompassing a vast geographical region reaching from the Atlantic to Pacific oceans. WHO/Europe staff consists of public health scientific and technical experts, who are based in the main office in Copenhagen, Denmark, in 5 technical centres and in country offices in 29 Member States.

This goal of better overall health proves an exciting challenge, as it provides opportunities for innovative new approaches and collaboration across many countries. It will also encourage and enable multi-sector collaboration and will help countries to strengthen their capacity to deliver high quality, effective health services.

WHO regional director for Europe: Dr Zsuzsanna Jakab states in 2016 that it is a privilege to lead the WHO regional office for Europe, and that:

"Working with countries, the years ahead can bring even greater health gains, achieved through collaborative work on prevention, protection, promotion, appropriate management of diseases and rehabilitation."

2012 marked the adoption of HEALTH 2020 by the 53-member states of the European Region, resulting in a policy framework that provides a vision and a strategic path forward for health in general. In recent years, Europe has seen overall improvement and impressive progress in several areas of health, for example; overall life expectancy has increased by 5 years.

However, significant health inequalities remain. It is a large-scale problem, that many of Europe's recent policies have failed to benefit everyone equally, but under the unifying policy framework of HEALTH 2020, the regional office will support member states in developing, implementing and aligning national policies on health issues, to ensure, that these strategies are inclusive. This platform has supplied a way forward to meet those challenges and nurture successful results, offering a unique foundation on which to coordinate activities.

One example of health inequalities lies in cardiovascular diseases (CVD), of which people born in eastern Europe are almost five times more likely to die young due to a heart attack or stroke than those born in western Europe. Low- and middle-income countries are more exposed to CVD risk factors, and their populations have less access to preventive efforts than people in high-income countries.

Thus, CVD affect these countries disproportionately: over 80% of CVD deaths occur in low- and middleincome countries. This figure goes to show the extent to which imbalance can occur. However, one of the priorities of WHO and HEALTH 2020 is to improve health for all and reduce these inequalities.

Cardiovascular health in Europe

Cardiovascular diseases are a group of disorders of the heart and blood vessels and include:

- Coronary heart disease: disease of the blood vessels supplying the heart muscle;
- Cerebrovascular disease: disease of the blood vessels supplying the brain;
- Peripheral arterial disease: disease of blood vessels supplying the arms and legs;
- Rheumatic heart disease: damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;



- Congenital heart disease: malformations of heart structure existing at birth;
- Deep vein thrombosis and pulmonary embolism: blood clots in the leg veins, which can dislodge and move to the heart and lungs.

To address these inequities in cardiovascular health, the Regional Office for Europe and the Ministry of Health of the Russian Federation held an International Conference on Cardiovascular Diseases in Saint Petersburg in November 2015, at which policy-makers, technical experts and patient and professional associations could share knowledge, experience, challenges and successes. Member States, multiple partners including the largest nongovernmental organisations and professional associations in the field, and WHO could discuss the next steps in the response to these disparities.

Thus, a strategic focus for WHO is universal health coverage, a goal that guides the Regional Office's work of strengthening health systems in the context of Health 2020 including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all. Building on this, Dr Zsuzsanna Jakab highlighted in a recent press release that governments will now be able to implement the 2030 agenda. The press release, released in September 2017, marked the annual meeting of the WHO Regional Committee for Europe. It focussed on Europe's progress in the health sector, and stated that leaders will take decisions on health priorities that impact on the health and well-being of about 900 million people in the WHO European Region.

However, in closing it is worth underlining that there is still much more to be done, with the new roadmap to achieve 2030 Agenda and the discussion of new priorities and goals. "Much progress has been made to improve health in the European Region, but much work remains to be done. The Regional Office will continue to play a vital role in supporting countries to achieve ambitious health goals such as those outlined in Health 2020" Dr Zsuzsanna Jakab said.

For more information, please visit: <u>www.euro.who.int/en/home</u> .

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The geography of EURO-HEALTHY Population Health Index

Professor Paula Santana from University of Coimbra sheds light in the importance of capturing a holistic understanding of population health

espite the significant advances that have been made at the European Union (EU) level in terms of health inequality measurement, there is still a lack of comparable indicators able to capture the holistic understanding of population health, with multiple determinants involved. Existing measures and indicators of health status and quality of life are considered inadequate, especially when measurements focus on regional and local levels.

The EURO-HEALTHY project has contributed with a response to this challenge, by applying both a multi- and transdisciplinary approach and sound methodology to enable the appraisal and comparison of population health and inequalities in multiple dimensions.

Consequently, the project constructed the EURO-HEALTHY Population Health Index (PHI) – a multidimensional and multilevel robust measure – to evaluate and monitor European health as well as the interactions between health in a wide range of areas of concern, dimensions and indicators.

Presenting a bottom-up hierarchical structure, the PHI takes into consideration two main components of population health: health determinants and health outcomes, both disaggregated to areas of concern, dimensions and indicators. The indicators are presented for the following 17 health dimensions: employment, income and living conditions, social protection, security, education, demographic change, lifestyle and health behaviours, pollution, housing conditions, water and sanitation, waste management, road safety, healthcare resources, healthcare expenditure, healthcare performance, mortality, and morbidity.

Analysis

To provide a snapshot of the health of the European population and detect health inequalities, the PHI was applied to 269 NUTS 2 regions of the 28 EU countries. This level of analysis was chosen given that it is the statistical unit applied by the European Structural and Investment Funds (ESIF) to define regional boundaries and to determine geographic eligibility for receiving funding. Regional eligibility provides essential opportunities to address and invest in interventions that tackle health inequalities across NUTS 2 regions.

The PHI ranges from 0 to 100, where 0 represents the lowest value-score of population health and 100 the highest value-score. The findings demonstrate a high degree of variation in the geographical distribution of health determinants and health outcomes, emphasising that inequalities still persist in Europe. The identified inequalities can be understood through the analysis of environmental, social, economic, and lifestyle/ behavioural patterns.

The PHI has uncovered that the spatial distribution of the multiple health determinants of population health is heterogeneous, showing differences between Northern regions and Southern and Eastern Europe regions. Overall, the more developed regions of the Northern countries present value-scores that are significantly higher (Health Determinants index > 80) than those presented by regions in transition from Southern and Eastern Europe (where lives 167 million people) with worse population health (Health Determinants index < 50). This finding refers to all dimensions of Health Determinants component, except for the security, demographic change and education.

Inequalities in Europe

Economic conditions and social protection remain the most important domains for reducing the EU regional health inequalities. Income and living conditions present the largest inequalities (S80/S20): regions within the highest quintile (S80) have 11 times higher income compared with the regions within the lowest quintile (S20) where it lives around 100 million people (Map 1).

In general, Europeans are educated (Education index > 65), showing a positive contribution to overall population health; however, significant differences are observed between the highest valuescores in North-Central Europe, and the lowest value-scores concentrated in Southern European countries.

Different levels of development in the EU regions are presented through built environment indicators. Remark-

Map 1





ably, there are still populations in the EU28 that "live in households without flushing toilets", that are not "connected to public water supply", and are not "connected to wastewater treatment plants".

When looking at the within-countries inequality, the 28 EU capital regions present systematically better valuescores when compared with other regions in all health determinants. Nevertheless, capital regions struggle with increased rates of recorded crimes and air pollution. It was found that 50% of these regions registered a PM₁₀ concentration higher than the 2005 WHO recommendations (20 ug/m³per capita), and almost 80% exceeded the recommended (10 ug/m³ per capita) concentration of PM₂₅. Globally speaking, there are 157 million Europeans who live in regions of particular concern for physical environment indicators and are evaluated with the lowest population health value-scores (Physical Environment index < 50); mainly concentrated in East-Central Europe (Map 2).

Regarding lifestyle dimension, policies and interventions promoting more positive health behaviour changes and lifestyles need to be reinforced across the EU, particularly within the Baltic States and Eastern European countries. Even though amenable deaths due to healthcare dropped significantly in all EU regions showing an overall good healthcare performance, regional inequalities persist, which indicates noticeable differences between the regions with the highest and lowest values (ratio S80/S20 equals 3).

When analysing health outcomes, similarly to health determinants, there are clear differences between high scores (Health Outcomes index >70) observed in the Northern and Western regions of the EU and lower scores recorded in regions where ¾ of the EU population lives, with particularly low value-scores (Health Outcomes index <50) identified in the regions of Eastern Europe (Map 3).

Deaths from causes considered to be "avoidable" remain excessive, particularly in the regions of the Baltic States and Eastern European countries. These regions (where more than 100 million EU inhabitants reside) show significant low value-scores (average Mortality index <37) for population health (measured by preventable mortality, infant mortality and life expectancy at birth) and therefore require particular interventions to decrease observed inequalities. Despite the decline in preventable deaths and infant mortality among all the EU28 regions, chronic conditions Мар З



have increased, creating an ongoing challenge for healthcare systems.

The space-time analysis and comparison of the PHI is possible through a user-friendly web-based Geographic Information System (GIS) platform on: <u>http://healthyregionseurope.uc.pt/</u> (to be made available to public without cost by December 2017).

Reference: Santana P, Costa C, Freitas Â, Stefanik I, et al. Atlas of Population Health in European Union Regions. Coimbra, Portugal: Imprensa da Universidade de Coimbra; 2017. doi:10.14195/978-989-26-1463-2.

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Professor Paula Santana Project Coordinator University of Coimbra paulasantana.eurohealthy@gmail.com www.euro-healthy.eu www.twitter.com/euro_healthy

Dutch health targets for the future

The aims for Dutch health and Netherland's place in Europe from the Ministry of Health, Welfare & Sport are explored here by Open Access Government

The Netherlands Ministry of Health, Welfare & Sport promotes better health and wellbeing at home and internationally. It is currently leading the Dutch government's bid to become the new home of the European Medicines Agency post-Brexit and improve Dutch health.

The Netherlands Ministry of Health, Welfare & Sport (VWS) works towards the twin ambitions of keeping everyone as healthy as possible and to return the sick to health as quickly as possible. It also supports to people with physical or mental limitations and encourage their full participation in society.

Its public health remit focuses on promoting healthier lifestyles: exercising more, stopping smoking, drinking moderately, practising safe sex and eating healthily.

Together with health insurers, healthcare providers and patients' groups, the ministry also works to ensure there are sufficient facilities available for people if they need access to a GP, hospital or other form of care – and that they have sufficient choices in the care they receive.

On welfare, the Ministry of VWS works with other government departments focused on the economy, education, housing and the environment to strengthen the Netherlands' social infrastructure and ensure people who are not economically independent have an active role in society. Volunteer work and youth care are key elements of its social policy.

The ministry's "sports mission" is to make it possible for everyone to participate in sport, providing social contact and promoting health. In addition, it funds top-level sports so the Netherlands can compete at international tournaments.



Edith Schippers, Minister of Health, Welfare and Sport

Post-Brexit vision

Edith Schippers has been Minister of Health, Welfare and Sport since November 2012. She is currently leading the Dutch government's bid to become the new home of the London-based European Medicines Agency (EPA) once the UK leaves the EU.

The EMA is responsible for assessing the efficacy, quality and safety of new medicines before they are approved for the European market. It also monitors the safety of authorised medicines and promotes research into new treatments.

Briefing the House of Representatives on the bid along with foreign minister Bert Koenders in January 2017, Ms Schippers said: "EMA plays a key role in assessing and approving innovative and often life-saving medicines. This process must not be interrupted by Brexit.

"The Netherlands is ready to offer EMA and its staff a new and outstanding location. This would, of course, benefit the millions of patients in Europe but it would also give a boost to the healthcare sector in the Netherlands."



Koenders added: "Relocating EMA to the Netherlands would guarantee its continuity for Europe as a whole, in an environment and with secondary conditions that more than measures up to its current situation in the UK."

The government believes the Netherlands offers the EMA excellent international connections, as well as first-class housing, healthcare, education and public transport for its staff in an environment where English is spoken widely. A new, custom-built headquarters would be located in Amsterdam.

In July, Ms Schippers made the official presentation to host the EMA in Brussels. "We cannot jeopardise the continuity of EMA's vital work," she said. "We cannot afford to lose its vital expertise. Its independence. Its hard-earned authority" she added.

The bid is based on four key principles: commitment, continuity, connectivity and community. Commitment is demonstrated by the detailed plans already in place for the EMA's new HQ. A team of experts would also offer full support during relocation, including individual support for the families of the 900 or so staff employed by the agency.

The Dutch Medicines Evaluation Board is already increasing its capacity in order to offer the EMA the same scientific support it receives from UK regulators. The government has committed an extra €2m to this process.

A further €8 million has been set aside for a cooperation programme between the board and other national agencies to strengthen regulatory work on medicines across the EU.

"If the decision is made to relocate EMA to Amsterdam, it can keep on functioning without disruption, due to a quick, smooth and seamless operation," Ms Schippers said. "We offer continuity. That is the only way to ensure the needs and the rights of our patients in Europe."

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Modern research into rare diseases

Research infrastructure project manager at EURORDIS, Virginie Bros-Facer highlights the extent of rare diseases in Europe in this insightful article

here are over 6000 distinct rare diseases and each one affects fewer than 1 in 2000 people. All together, an estimated 30 million people are living with a rare disease in Europe.

Rare Disease Day takes place on the last day of February each year, with the primary objective of raising awareness of the impact of rare diseases on patients' lives amongst the general public and policy makers, public authorities, industry representatives, researchers and health professionals. Rare Disease Day 2018 will take place on 28th February and will focus on the theme of research.

Rare disease research contributes to the development of diagnostic tools, treatments and cures, as well as improved health and social care for patients and their families. The patient community needs researchers. They discover diseases and develop treatments and cures.

Researchers also need patients and reply upon their participation to ensure research is meaningful. Rare disease research is not done for the sake of creating knowledge; the knowledge generated is only useful if it is translated into real benefits for patients.

Patients are not only subjects but also proactive actors in research:

Patients kick start research: Patients convince researchers and companies to finance or engage in research. They also proactively raise funds for research through their own networks.

Patients drive research: Patients set the strategic agenda for research projects, helping to make sure research is truly relevant to patients' needs. For example, they participate in the design of clinical trials to

ensure that the safety and efficacy of medicines are measured in terms of the real benefit they bring to patients.

Patients organise research - they work tirelessly to build up a network around their disease. They connect with each other online, for example, through patient groups and at conferences. In doing so, they create the critical mass of patients needed for research on their disease to take place.

"There has been great progress in rare disease research, in big part thanks to the advocacy work of the rare disease patient community. Patients are already participating in research."

Patients also create a community of relevant stakeholders focused on their specific disease. They are at the centre of an ecosystem and bind together all relevant stakeholders involved in research, including researchers, companies, healthcare providers and policy makers.

Patients proactively provide data – they provide the data researchers need to discover rare diseases (providing for the development of diagnostic tools) and to learn about how the disease progresses (helping them to determine how to stop the disease or how to develop a therapy.)

Patients join registries and set up and help maintain registries themselves. They also directly provide data to researchers regarding their health condition (patient-reported outcomes).

Rare Disease Day 2018

There has been great progress in rare disease research, primarily due to the advocacy work of the



rare disease patient community. Patients are already participating in research. And in some cases, patients have taken the reins themselves to fund their own research. However, the fact remains that there are over 6000 rare diseases, an estimated 30 million people living with a rare disease in Europe and 300 million worldwide, but no cures and few treatments available for the vast majority of these diseases.

To help change this, patient involvement in research needs to be taken to the next level. Rare Disease Day 2018 offers participants the opportunity to be part of a global call on policy makers, researchers, companies and healthcare professionals to increasingly and more effectively involve patients in rare disease research.

Great efforts are being made to take rare disease research to an international level. Only by doing so can we guarantee rare disease research will be truly effective. In turn, this will contribute to increased and faster diagnosis of rare diseases and therefore reduce the number of people around the world who face the daily challenge of living with an undiagnosed rare disease.



Virginie Bros-Facer Research infrastructure project manager EURORDIS Tel: +33 1 56 53 52 61 5200 www.eurordis.org www.twitter.com/eurordis

The impact of clinical research in rare diseases

Kit C.B. Roes from the University Medical Centre, Utrecht outlines why clinical research in rare diseases requires swift implementation of new methodology

fficient clinical research in rare diseases is crucial for new (drug) treatments to reach patients for whom there is often no treatment available. Design and conduct of clinical trials in these diseases is challenging, due to the smaller number of patients available to participate. The European Union has made a substantial investment into research for new methodologies for clinical research in small populations, with three funded projects completing in 2017. Results were obtained, a network was built, and there is strong support both from patient organisations and regulatory authorities to implement innovative methods across industry and academic clinical research. A call for concerted action to all of us to make this happen.

Clinical trials as cornerstone for development of new treatments

The combined clinical and socio-economic impact of rare diseases is huge. An estimated 30 million European patients suffer from a rare disease. Of the more than 6000 rare diseases known, many are chronic, potentially very disabling and typically affect children. The unmet need for patients suffering from a rare disease is well recognised. Over the past decades, the European Union – as well as other jurisdictions such as the United States and Japan – have taken on numerous initiatives to stimulate the development of new therapies to treat rare diseases. These initiatives range from regulatory legislation to stimulate

research by pharmaceutical companies and accelerated regulatory pathways, to funding research and building strong research networks across Europe for rare diseases. The incentives towards industry appear to be successful, with many more drugs being granted orphan designation.

A cornerstone to bringing new drug treatments to patients are clinical trials to assess efficacy and safety, and ultimately, the benefit-risk balance. These trials still face substantial challenges. The first obvious challenge is the inherently small number of patients that can be recruited into clinical trials. Secondly, there is often a substantial heterogeneity in disease course between patients suffering from the same rare diseases. Thirdly, exploration of these challenges in clinical research for rare diseases has triggered a re-think in terms of whether the usual standards of evidence (number of trials, control of false positives (type 1 error rates), and the role of meta-analysis) are adequate.

This calls for innovative approaches, including: new concepts for clinical endpoints, more advanced data analysis, (pharmaco-metric) modelling, trial designs with multiple treatments and approaches to leverage the data from registries and routinely collected clinical data. And – specifically for very rare diseases – a fundamental rethink how much evidence is actually needed to make new treatments available to patients.

A joint meeting with regulatory authorities, patient representatives, academia and industry towards implementation

Three major EU funded projects in this area, <u>Asterix</u>, <u>IDeAl</u> and <u>InSPiRe</u>, have made major progress in these areas over the past 4 years. The progress was presented at the 'Seventh Framework Programme (FP7) small-population research methods projects and regulatory application workshop', March 29th & 30th 2017, which was jointly organised by the European Medicines Agency (EMA) and the 3 EU projects. At this meeting, it was clear that:

The progress across the 3 projects is impressive, and the joint challenge for patients stimulated collaboration across the 3 projects to a level that is unique for such programs.

The EMA is strongly supportive of innovative methods in this field.

Part of the results is ready for broad(er) implementation, which can be stimulated by regulatory instruments such as the EMA Guidance on Small Populations, and the EMA Qualification Procedure.

Innovative methods that may have even stronger breakthrough impact need further investigation, including real life application on a smaller scale.

Patient representatives appreciated the opportunity to truly engage actively in advancing research methodology for clinical trials.

There is a strong call from the patient perspective to move to implementation to accelerate the availability of new but proven, therapies for patients suffering from a rare disease.

Highlights and the action already envisioned

The full workshop is available online (see <u>www.ema.europa.eu/ema/</u>, under News and Events) and the results of the project are presented with a discussion. A few highlights are the following;

In view of the limited number of rare disease patients available for clinical trials, it is crucial that information on new treatments from other sources (animal experiments, earlier healthy volunteer trials, trials in different populations) can be used to infer efficacy and safety. Developments such as the 'scepticism' factor for extrapolation from one population to another and pharmacometric modelling now allow more quantitatively justified а approach to do so. This will strongly aid in researching new treatments within the constraints of small samples.

A second development that sparked discussion and enthusiasm, concerned a new approach to clinical endpoints. To accommodate the potential large heterogeneity between patients, Goal Attainment Scaling allows patient to have individualised outcomes that nevertheless can be summarised across comparative groups of patients to assess the treatment effect. This may resolve the problem of choosing appropriate endpoints for diseases such as Duchene's Muscular Dystrophy. Currently, the so-called 6 minute walking test is used as default endpoint. But boys suffering from Duchene's become wheelchair bound at the age of about 8-10, hence with such endpoints many patients are excluded from trials – although they might very benefit from treatment.

A look into the future

The network of experts across the 3 projects covers large parts of the EU, and many researchers are engaged in clinical research for rare diseases. Hence, new methods gradually find their way to practice. This is, however, not enough and not quick enough from the patient perspective. The three project leads, Prof. dr. R-D Hilgers, Prof. N. Stallard and Prof. K. Roes assessed that 2 crucial objectives can be pursued simultaneously. The first and foremost objective is to ensure broad implementation of the new findings in clinical research for rare diseases, across academia and company research and across all relevant types of interventions. This directly contributes to the IRDiRC objective of regulatory approval of 150 new drug therapies in the period 2017-2027. Secondly, aiming for truly breakthrough improvements requires continuation of the research network to expand on the most innovative methods, as well as tailor these to the specific nature of the vastly diverse rare conditions.

The first objective is already on its way. In addition to engaging in clinical research projects across the EU, it is anticipated that the project leads will submit a selection of methods – such as Goal Attainment Scaling - for EMA scientific advice, e.g. for qualification of methods. This will stimulate pharmaceutical companies to use the methodology. In addition, general guidance for trials in small populations will likely be revised to include the most recent findings. Furthermore we foresee that a target education program can be developed. The core principle is to link education directly with implementation: training is to be aimed at clinical research teams in the process of designing a clinical trials for a rare condition. Their protocol under development can then be actively used in the educational program to implement the learnings. Hence, clinical research protocols are optimised for real, important clinical trials. It can be highly beneficial if these efforts are connected to the recently established European Reference Networks for rare diseases.

Finally, the direction, content and urgency of the research has truly benefitted from patient representative involvement. Although we may not have found the optimal language and process yet, it is clear to all involved that we need to step-up our effort to include patients across all our clinical research phases, including the methodology underlying the design and ultimately the assessment of evidence from clinical trials.



University Medical Center Utrecht

Kit C.B. Roes

Professor of Clinical Trial Methodology University Medical Center, Utrecht Tel: +31 88 7568295 k.c.b.roes@umcutrecht.nl www.asterix-fp7.eu

Health, prevention, and long-term care in Germany

Germany's Federal Ministry of Health (BMG) is centred around health, prevention, and long-term care, as Open Access Government discovers

ermany's Federal Ministry of Health (BMG) is centred around three main focal points in which it aims to facilitate the overall improvement of the population's health. These specific areas of interest are health, prevention and long-term care.

'Health' stresses the significance of safeguarding and further developing the effectiveness of the statutory health insurance and with the 2007 major health care reform, the ministry could improve both efficiency and quality of the system itself, while also bringing the interests of the patients to the forefront of its policy.

Similarly, a reform of long-term care was conducted in 2008 in the hope that it would improve quality of life for staff and relatives, as well as persons in need of long-term care. It provided a series of new benefits such as the possibility of a legal claim to individual long-term care counselling (case management) for those who felt they needed it. In terms of prevention, this is an area, which in recent years has become increasingly vital to the Ministry and is continuing to do so, in fields such as exercise, eating disorders and women and children's health.

The Federal Minister for Health, Hermann Gröhe, is currently leading campaigns such as these. For example, Gröhe recently led Germany's delegation to the 2016 High Level Meeting on Ending Aids in New York, following Germany's many years of engagement with the prevention of HIV and AIDS.

The BMG manages and continually develops the HIV and AIDs control strategy that has been implemented, despite its low figures of infection by international comparison. It is measures such as these that are being taken that allow Germany to combine its responsibilities for national health care policies with both European and international health policy.

Federal Minister of Health Hermann Gröhe distinctly stated in a press release in Berlin on May 19th, 2017: "We have to confront global health crises." He has headed the Federal Ministry of Health in the third cabinet of Angela Merkel since December 2013, and has recognised International Cooperation as a priority and made it a driving force for the recent G20 Presidency. December 1st, 2016 marked Germany's one-year take-over of the presidency of the G20, the number one forum for international cooperation among the leading 20 industrialised and emerging countries.

Germany's place in global healthcare

Global health is now a priority of the German G20, and May 2017 brought its first ever G20 health ministers' meeting, at the invitation of Gröhe, in which the aim would be to tackle global health hazards. "The G20 represent two-thirds of the global population and three-quarters of global trade. We have to confront global health crises together", Federal Minister of Health Hermann Gröhe says.

In order to do this, countries must learn to be better prepared for further health issues (for example they hope to rehearse the event of a transnational outbreak), make sure that a fast-international response can be delivered, and strengthen the World Health Organisation (WHO) as it plays a vital role in dealing with this type of crisis.

It is clear that Gröhe is targeting this with an open, inclusive mindset, as he has brought to light the importance of supporting vulnerable, developing countries, not just those who have multiple resources available to



them through their national health systems. He stated at the conference that: "We have noted the importance of supporting poorer countries and promoting access to affordable antimicrobials for all patients in need."

"In terms of prevention, this is an area, which in recent years has become increasingly vital to the Ministry and is continuing to do so, in fields such as exercise, eating disorders and women and children's health."

Another area that needs to be tackled is the threat of antimicrobial resistance (AMR), and how it can be combatted. This affects all types of countries, whether they are industrialised or developing. According to the World Health Organisation, AMR is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it. As a result, standard treatments become ineffective, infections persist and may spread to others. Germany has shown the way with the German Antimicrobial Resistance Strategy (DART 2020), but many countries do not have the necessary monitoring systems.

Germany together with many countries and foundations has also recently pledged €56.5 million to help develop new treatments to fight against antibiotic resistance, during a fundraising event for the Global Antibiotic Research and Development Partnership (GARDP). Overall, Germany is leading with its best foot forward the path to excellent health, prevention and long-term care, in the hope that many other countries, particularly the ones within G20, will follow. ■

MF Warrender Writer

Open Access Government editorial@adjacentopenaccess.org www.adjacentopenaccess.org www.twitter.com/OpenAccessGov

PET imaging of neurodegenerative diseases

Prof. Dr. Axel Rominger from the Ludwig-Maximilian-University of Munich on how neurodegenerative diseases can be studied through PET imaging

ith its exponentially increasing incidence as a function of age, Alzheimer's disease (AD) has become the most common form of dementia, and is thus imposing an onerous burden on health care systems of societies with aging populations.

The disease is histopathologically characterised by the presence of cerebral protein depositions, notably intracellular neurofibrillary tangles and parenchymal β -amyloid plaques. The principal component of amyloid plaques, the amyloid β -peptide (A β), is a heterogeneous cleavage product of the β -amyloid precursor protein (APP) generated by the successive actions of β - and γ -secretases.

Of the several A β variants, the A β 42 species is widely believed to be a key factor of the disease. Current therapeutic options for AD include acetyl-cholinesterase inhibitors and NMDA receptor antagonists, both of which provide some transient amelioration of cognitive symptoms, but without any disease-modifying effects. Consequently, there is an urgent need for disease-modifying treatments such as those targeting amyloidosis or tau depositions.

In addition to these depositions, further pathological changes occur in the AD brain, especially involving neuroinflammatory processes. Microglia, the resident macrophages in the brain, are activated in response to pathogens (e.g. tau, β -amyloid, or white matter damage) and mediate the clearance of toxic protein aggregates and cell debris.

However, chronic microglia activation may lead to increased neurodegeneration by feed-forward mechanisms promoting further toxic protein deposition; as such, microglia present another important potential therapeutic target. The causal relationship and detailed interactions of the different disease mechanisms of AD are however not fully understood yet.

PET imaging allows the non-invasive investigation of molecular alterations in living brain. With the advent of novel molecular imaging markers (radiotracers) targeting specific pathological hallmarks of the disease, new options have arisen for monitoring neurodegenerative disease processes. The repertoire of available tracers now enables to map microglia activation along with primary pathologies such as β -amyloid and tau depositions. PET methods can be applied translationally, both in transgenic animal models and in humans.

In clinical AD trials, investigating disease-modifying agents, molecular imaging confirms the baseline state

and progression of pathology markers, and thus serves as a gatekeeper for including patients into clinical trials, e.g. EMERGE/ENGAGE study (clinical trials identifier: NCT02484547) or the A4-Trial (NCT02008357). Studies following individual cases with confirmed baseline pathology are superior to earlier approaches, where inclusion was based solely on clinical evaluation. PET studies of longitudinal design can then monitor the disease course as well as drug efficacy, with respect to objective pathological markers.

In the preclinical setting, there have emerged numerous transgenic AD mouse models expressing different hallmarks of the disease, which can be studied with respect to pathophysiology as well as from a therapeutic standpoint. In both respects, these models can be used to assess the effectiveness of novel treatment options on specific markers of AD disease progression.

Longitudinal investigations in living transgenic animals can be cross-correlated with terminal immunohistochemical and biochemical assessments, which constitute in vitro methods. This hybrid approach with serial microPET assessment throughout the course of a long-term treatment protocol in conjunction with histopathological and biochemical end-point



analyses, is inherently superior to conventional experimental paradigms, in which only the end-point readouts are obtained. Given the well-known inter-animal variability observed in transgenic mouse studies, parallel microPET monitoring during treatment as well as normalisation of results to individual baseline microPET findings inform the interpretation of biochemical findings at the studies' conclusion.

In an ongoing preclinical research project, we are currently investigating microglial activation in relation with abnormal protein deposition in different transgenic β -amyloid and tau mouse models, along with complementary behavioral/cognitive assessment using the Morris-Water- and Y-Mazes. After completion of the longitudinal PET/behavioural study, we shall confirm pathology by histopathological and biochemical assessments.

In the second stage of this project, we shall test the efficacy of acute and

chronic immunomodulatory therapeutics on the progression of β -amyloid- and tau-load in the AD mice, emphasising the predictive value of the neuroinflammation-PET on the effects of immunomodulation on the cognitive testing and in vitro histopathological outcomes.

In the final stage, we shall test the effect of an anti- β -amyloid vaccination on the neuroinflammatory response, and on the progression of amyloidopathy and impaired cognitive performance in AD mice. Given that anti- β -amyloid vaccines have already entered human trials, we are convinced of the translation relevance of the current project.

These preclinical projects are performed in collaboration with the German Center of Neurodegenerative Diseases, Biomedical Center (Head: Professor Christian Haass) and the Neuropathological Department (Head: Professor Jochen Herms), and are funded in part by the SyNergy Cluster with further support from industry partners. Further support comes from the Deutsche Forschungsgemeinschaft (Grant no. 348312276).



Prof. Dr. Axel Rominger Department of Nuclear Medicine Ludwig-Maximilian-University of Munich Munich, Germany axel.rominger@med.uni-muenchen.de

Tackling the UK's obesity epidemic

Professor Russell Viner from the Royal College of Paediatrics shares his thoughts on the UK Government's strategy to tackle the UK's obesity epidemic

Iittle over a year ago the government launched its Childhood Obesity Plan. This long-awaited plan (which in its formative stages had been called a 'strategy') had been eagerly awaited by health campaigners, following a consultation process. The talk was that it would be a comprehensive and far-reaching strategy to tackle the UK's obesity epidemic.

With one in five children overweight or obese by the time they arrive at primary school, and this number rising to over one in three by the time they leave, this was a strategy that was long awaited and much needed.

"A recent study by the Obesity Health Alliance found that the top spending crisp, confectionary and sugary drinks manufactures put more than £143 million into advertising their products each year. When you compare that to the government's £5.2 million spend on its flagship healthy eating campaign, Change4Life, it is perhaps not surprising that obesity rates continue to climb."

Unfortunately, when it came to launch, the strategy had become rather watered down. Having a Childhood Obesity Plan clearly signals a commitment from government that it has a strong focus on obesity. However, the Plan as published was disappointing in its reach. The only real structural element was the Soft Drinks Industry Levy.

Otherwise it relied on physical activity, personal responsibility and voluntary product reformulation as the solution. There was nothing on restrictions to junk food marketing at children or indeed more dramatically changing the unhealthy environment in which our children are growing up.

Sugar and soft drinks

The Soft Drinks Industry Levy – commonly referred to as the 'sugar tax' – was certainly the biggest positive from the plan. The levy seeks to encourage manufacturers to remove sugar from soft drinks or face a financial levy dependent on added sugar content. Passed by Parliament in April this year and coming into force next year, the soft drinks levy has already encouraged big name companies to significantly reduce sugar from their drinks – which typically contribute the most sugar to children's diets.

Another promising aspect of the government's plan is the sugar reduction programme. Led by Public Health England, this programme is working with retailers, manufacturers and restaurant sector to reduce sugar from foods commonly eaten by children by 20% by 2020.

In addition, to coincide with the Obesity Plan's oneyear anniversary, Public Health England announced plans to begin a new programme of work to make everyday food less calorific. This is very welcome – but targets must be ambitious and meaningful sanctions have to be imposed on those companies that don't comply. But as we've said previously, these measures alone will not be enough, and tackling obesity requires concerted action on a range of fronts.

Junk food

Getting a handle on childhood obesity will not happen unless we prevent the junk food industry from advertising to our children. There is a wealth of evidence to show junk food advertising encourages unhealthy food choices in children, yet children continue to be bombarded with sophisticated advertising techniques during programmes they watch on TV and online.



A recent study by the Obesity Health Alliance found that the top spending crisp, confectionary and sugary drinks manufactures put more than £143 million into advertising their products each year. When you compare that to the government's £5.2 million spend on its flagship healthy eating campaign, Change4Life, it is perhaps not surprising that obesity rates continue to climb. Existing Ofcom and Committee of Advertising Practice regulations need to be strengthened and expanded and the introduction restrictions on junk food advertising on TV and online media before the 9pm watershed would send a strong signal of intent and leadership from the government.

Coronary heart disease, type 2 diabetes, stroke and eight different types of cancers are clearly linked to overweight and obesity. And obese children are five times more likely to grow into obese adults with not only a lifetime of health complications ahead but also a lifetime of costs incurred by the NHS. The government must ensure children have the best possible start in life and parents and families are enabled and encouraged to make healthy food choices. At the moment, making the healthy choice often very difficult, particularly in the light of the so-called obesogenic environment in which we live.

As has been said time and again, obesity is a complex problem with no silver bullet solution. But any solution must be comprehensive and crucially long term. Tackling obesity should not fall victim to political short termism or industry lobbying. Obesity is a killer – just as smoking is. The government took on the tobacco industry effectively and there's no reason why they can't do the same with junk food.

Professor Russell Viner Officer for health promotion

Royal College of Paediatrics and Child Health Tel: +44 (0)20 7092 6000 enquiries@rcpch.ac.uk www.rcpch.ac.uk www.twitter.com/RCPCHtweets

The continuous improvement of care

European Association of Hospital Pharmacists (EAHP) on developing the hospital pharmacy profession and the improvement of care for patients in Europe

n accordance with its mission, the European Association of Hospital Pharmacists (EAHP) aims to represent and develop the hospital pharmacy profession within Europe to ensure the continuous improvement of care and outcomes for patients in the hospital setting.

The goals of the association – which represents more than 21.000 hospital pharmacists in 35 European countries – are achieved through EAHP's educational activities – such as the annual congress and the Academy Seminar events – sharing of best-practices via the Good Practice Initiatives and the publication innovative and practical research in the European Journal of Hospital Pharmacy.

The desire to continue raising the standards of the hospital pharmacy profession has guided EAHP towards the adoption of the 44 European Statements of Hospital Pharmacy and the creation of a Common Training Framework (CTF) for hospital pharmacy specialisation.

The European Statements of Hospital Pharmacy express commonly agreed objectives which every European health system should aim for in the delivery of hospital pharmacy services. They were adopted via a methodical consultation process involving EAHP's member country associations as well as 34 patient and healthcare professional organisations.

Focusing on core competencies of the profession including but not limited to production and compounding, clinical pharmacy services as well as education and research, the European Statements were designed to become the key benchmark for measuring the extent to which hospital pharmacy is developing around Europe, and where precisely improvement efforts should be focused. Implementation is driven by motivated and enthusiastic hospital pharmacists. The efforts of both the EAHP implementation team and national member associations in terms of awareness raising are currently measured by means of EAHP's statement survey which provides a glance on how hospital pharmacies within EAHP's 35-member country associations implement specific sections of the statements.

A more tailored review will be possible once EAHP's new self-assessment tool is fully operational. The tool allows hospital pharmacists to assess the level of implementation within their hospital and provide them with an individualised action plan, that guides their progress in implementing individual statements. Through the tool and the resources available on the statement implementation website, EAHP hopes to drive implementation forward to ensure continuous improvement of care and outcomes for patients in the hospital setting play in Europe today.

Making further improvements

To further foster patients equal access to safe highquality pharmaceutical care, EAHP has worked towards improving the mobility of its profession in Europe by seeking to put in place arrangements for specialties of pharmacy to move between countries. Enabled by the most recent revision of the Professional Qualifications Directive, EAHP has taken initiative to enhance the labour mobility perspectives of hospital pharmacists on European level, and to align educational standards throughout the EU by means of the establishment of a CTF for hospital pharmacy education.

Allowing qualified hospital pharmacists to move freely throughout Europe will not only increase the access to health information and pharmaceutical expertise in the European Union, but it will also provide benefit for



patients. By setting a benchmark for all European countries to strive for, the CTF will also function as a strategic tool for realising the European Statements.

Free movement of persons - one of the EU's four freedoms - has been specifically analysed by EAHP, since it currently seems to be one of the main challenges of the profession. In exploring the impact of a CTF on labour mobility, EAHP gathered information on the attitudes and perspective of hospital pharmacists by means of a survey. The findings showed that development of the profession, facilitation of exchange of expertise, standardisation in the quality of education and increase of mobility opportunities are benefits to be gained by creating a new tool for automatic recognition of specialisation across borders which would encourage 85% of the survey participants to make use of a CTF once it is established. A report summarising the findings and showcasing the journeys of hospital pharmacists that tried to move within the EU will be published by the end of 2017.

As the profession that strives to continuously maintain and improve the medication management and pharmaceutical care of patients to the highest standards in a hospital setting, EAHP also actively advocates for the use of the unique skills and knowledge that hospital pharmacists possess. In particularly, the uptake of new medicines, such as biosimilars and the fast-paced developments in the field of eHealth and mHealth necessitated the recent adoption of position papers by the association on these topics.

Focusing on the safe, effective and efficient use of medicines and new technology, both papers underline the importance of hospital pharmacists' involvement in eHealth/mHealth discussions and decisions concerning selection, procurement, logistics, information, education and collection of real life experience for biosimilar medicines.

Stephanie Kohl Policy Officer

European Association of Hospital Pharmacists (EAHP) Tel: +32 (0)2 669 25 12 Stephanie.Kohl@eahp.eu www.eahp.eu www.twitter.com/EAHPtweet



Fostering and supporting excellence in clinical pharmacy practice

Islam Elkonaissi and Zahra Laftah from the UKCPA explore the British model of supporting excellence in clinical pharmacy practice

n the UK, evidence that pharmacists can provide better clinical outcomes and more efficient, consistent and sustainable services for patients, is increasing. In this article, key themes are discussed to showcase the importance of empowering pharmacists and fostering leadership in clinical pharmacy practice.

Context

The vision in the National Health Service (NHS) 5-year forward view (FYFV)¹ is for a sustainable NHS that continues to be tax-funded, free at the point of use and that is fully equipped to meet the evolving needs of its patients, now and in the future.

To deliver this vision, pharmacists are supporting efficiencies in the NHS and improving patient care by undertaking person-centered medicine reviews in a range of different care settings and as part of care pathways and multidisciplinary teams.

Medicines optimisation

Within the context of an NHS struggling to cope with an ageing population, prolonged life expectancy, large numbers of patients managing co-morbidities and polypharmacy, the National Institute for Health and Clinical Excellence (NICE) published a medicines optimisation guideline².

Key recommendations from NICE include efficient medicine-related communication across different settings of care, medicines reconciliation in addition to medication reviews. Pharmacists across the country have been leading on projects within the remit of these recommendations. This includes antimicrobial stew-
Summary of the four principles of medicines optimisation



Figure 1 provides summary of the four principles of medicines optimisation as defined by the Royal Pharmaceutical Society of Great Britain

ardship, diabetes referral tools as well as polypharmacy stop-start tools.

The four guiding principles³ (figure 1) outlined by the pharmacy professional body, the Royal Pharmaceutical Society of Great Britain (RPS) in 2013, describe medicines optimisation in practice and the outcomes it is intended to impact. These principles can be used by pharmacists as well as other healthcare professionals and this simply shows the level of influence by pharmacists through their professional body.

Medicines optimisation and cost efficiencies

Lord Carter's efficiency review⁴, which shed light on significant variations across NHS pharmacy services, was fundamental in paving the way for pharmacists to lead in new models of care in a financially sustainable manner. The Carter review highlighted that unwarranted variation in the use and management of medicines cost the NHS at least £0.8 billion, that could be reinvested. Amongst other recommendations, Lord Carter recommended a Hospital Pharmacy Transformation Programme to ensure hospital pharmacies achieve their benchmarks such as increasing pharmacist prescribers, e-prescribing and administration, accurate cost coding of medicines and consolidating stockholding. The main objective of these activities is to ensure pharmacists and pharmacy technicians spend more time on patient facing medicines optimisation activities.

The Commissioning for Quality and Innovation (CQUIN) scheme⁵ aids this vision by incentivising NHS organisations which achieve specific targets. Of particular relevance to pharmacists is the medicines optimisation CQUIN scheme. The goal of this scheme is to optimise use of high cost drugs, tackle variation and reduce waste.

The scheme highlights pathways to achieve this through:

- Adoption of biosimilars and generic switches.
- Improved drug data quality.
- Utilising most cost efficient dispensing channels.
- Compliance with policies/guidelines to reduce variation and waste.

The future of what is known as Carter is envisaged through the "Top ten medicines" list identifying further productivity opportunities, as recommended by Lord Carter, opening up more roles for pharmacists. The list itself was developed in collaboration with a small group of Chief Pharmacists working in NHS organisations, with the aid of a tool known as "Define". Savings targets for individual trusts are based on a baseline period and represent either a simple reduction in spend or on the uptake of a less costly alternative medicine. The following example demonstrates the huge role played by pharmacists in developing and delivering cost saving efficiencies.

Learning from the Cancer Vanguard⁶ **in the UK** At the core of the FYFV strategy is the development of new models of care, or the vanguards. It recognises that there are universal levels of care provision that require a degree of conformity. It has, therefore, proposed many new care models that are being explored and implemented via the vanguards.



The Cancer Vanguard⁶ through a collaboration led by The Christie, The Royal Marsden, and University College London Hospitals, has provided a platform for pharmacy to develop new models of cancer care that are replicable and transformational, which would ultimately act as blueprints for the NHS nationally. For example, a process timeline for adoption of biosimilars has been developed with accompanying guidance, resources and template documents to enhance biosimilar uptake within the NHS.

The replicability of both the process and the new models developed, means that the national impact is substantial. With the support of pharmaceutical industry, other examples include adverse event monitoring of patients receiving immunotherapy, developing models of care for home delivery of chemotherapy, taking delivery of Denosumab out of hospital settings and the use of patient apps in metastatic colorectal pathways of care. Future opportunities are increasingly focused on prevention and early diagnosis with hospital-community pharmacy collaborations. The Cancer Vanguard has therefore provided an example of collaborative and systems leadership in terms of how quickly results are being produced as well as its replicability. Openings for further joint work with industry and involvement in early diagnosis are key learning outcomes.

Initiatives towards resilient and competent pharmacy workforce:

To deliver leadership in practice, there is a certain need for workforce resilience and competence which are necessary to improve parity amongst different sectors of care. The following explores two examples of such efforts.

National training programmes

The Royal Pharmaceutical Society alongside the United Kingdom Clinical Pharmacy Association (UKCPA) and other affiliated partners are in the final stages of developing National Training Programmes for pharmacists for all levels and sectors. This will support pharmacists, addressing pharmacy clinical training needs up to

consultant level. It consists of components to suit each pharmacist's scope and level of practice.

Each component of the programmes will be mapped to professional curricula and the Advanced Pharmacy Framework of the RPS⁶. Featuring an assessment within each module, pharmacists would be able to receive a certificate of completion to demonstrate evidence of their training to employers, commissioners, patients, the General Pharmaceutical Council and the Faculty Scheme⁶ by the RPS.

"Lord Carter's efficiency review, which shed light on significant variations across NHS pharmacy services, was fundamental in paving the way for pharmacists to lead in new models of care in a financially sustainable manner."

Pharmacy fellowship schemes

Established in 2015, the Chief Pharmaceutical Officer Fellowship schemes provide pharmacists at their early career with a unique opportunity to spend a year working with senior pharmacy leaders in national healthcare organisations. It enables fellows to lead on key projects which contribute to national healthcare priorities around patient safety, medicines optimisation, transfer of care, digitalisation and pharmacy workforce training. Host organisations for this scheme include, amongst others, Care Quality Commission (CQC), NICE, NHS England, Public Health England, NHS Digital and the Centre for Pharmacy Postgraduate Education (CPPE).

Take-home message

This article summarises a few examples that demonstrate a central role for pharmacists in new models of healthcare in the UK. Empowering pharmacists and equipping them with the necessary training is yielding exceptional results. The future path is to foster community engagement in preventative strategies. The essence of clinical leadership can ultimately be summed up in the vision provided by Jatinder Harchowal, the Chief Pharmacist at the Royal Marsden Hospital in London, as he says: "Leadership is when it is easier to do nothing". Therefore, leadership is not simply a title, but merely an action. References

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UKCPA CLINICAL PHARMACY ASSOCIATION

Islam Elkonaissi

Lead Lung Cancer and Clinical Commissioning Support Pharmacist, UKCPA General Committee Member

Zahra Laftah Clinical Pharmacist & UKCPA Member

The United Kingdom Clinical Pharmacy Association (UKCPA) Tel: +44 (0)116 2714 894 general.enquiries@ukcpa.com http://ukclinicalpharmacy.org/ www.twitter.com/UKCPA

Dose-finding trials: why not to use algorithmic designs

Prof Thomas Jaki from the Medical and Pharmaceutical Statistics Research Unit at Lancaster University sheds light on dose-finding trials

he primary aim of dose-escalation trials (Phase I trials) is often to find the largest dose of a treatment that can be administered safely, often called the maximum tolerated dose (MTD). Phase I studies are crucial in the development of a novel treatment as the agent is often being given to humans for the first time. To ensure the safety of the patients in the study, they tend to start at doses much lower than the anticipated highest safe dose and only slowly increase the dose until the target dose is found. Dose-escalation studies have been described by Edler² as "first-into-human studies where safety is paramount and close monitoring essential".

Algorithmic designs

Rule-based designs, such as the 3+3 design¹ (illustrated in Figure 1), continue to be popular even though they can perform extremely poorly. The alternative to these rule-based designs are (Bayesian) model based approaches which use a statistical model to describe the dose-response relationship³. Here we list the main arguments why 3+3 and similar rule based A+B designs should not be used for phase I dose escalation studies.

 A+B designs lead to more patients being treated at sub-optimal doses (i.e. patients either receive a subtherapeutic or an overly toxic dose);



- There is only a one in three chances to obtain the correct dose at the end of a 3+3 design, compared to better than 1 in 2 for model based designs;
- In contrast to model based designs, A+B designs do not offer a measure of variability in the final recommendation and hence do not provide any measure of confidence in the recommendation;
- A+B designs are highly inflexible and therefore need ad-hoc changes to cope with many situations observed in practice (e.g. drop-out of patients);

- A+B designs use only the information from the last cohort of patients whereas model-based designs make use of all data accumulated.
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The MPS Research Unit is pleased to announce our programme of short courses for 2017/2018 on advanced concepts in the design and analysis of clinical trials. Our courses are aimed at statisticians working in clinical research. Courses take place in the attractive accommodation of the Postgraduate Statistics Centre at Lancaster University. Presenters will be Thomas Jaki, Andrew Titman and Fang Wan.

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12 Mar – 15 Mar 2018	Adaptive Methods in Clinical Research
4 June – 5 June 2018	Designing Early Phase Trials

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Tel: +44 (0)1524 593064

Email: a.j.mercer@lancaster.ac.uk



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Prof Thomas Jaki

Professor of Statistics Medical and Pharmaceutical Statistics Research Unit, Lancaster University Tel: +44 (0)1524 59 23 18 mps@lancaster.ac.uk www.mps-research.com

Chemical biology: A chance conversation but an important question

Research professor Prof Colin J Suckling OBE DSc FRSE discusses his engagement with medicinal chemistry and chemical biology

was asked a little while ago by a member of the governing body of the University of Strathclyde what the significance of my current research is. He had some idea of my interests in medicinal chemistry and chemical biology, but clearly no real understanding of what was involved or indeed of the aims. Explaining my commitment to the discovery of new antibacterial and other anti-infective compounds raised some interest, but also the somewhat disheartening comment: "Surely big pharma does that", whereupon I was drawn into a defence of the value of academic research in drug discovery. I tried to put over many points with examples and evaluations.

Since I was talking to a businessman, the first argument I raised was that when it pays off, it pays off big. Perhaps the best example of this in the last 15 years or so is Ted Taylor from Princeton University, whose work in the heterocyclic chemistry of pteridines I have known for many years, having contributed to the same field myself. Ted and his team discovered the hugely important anticancer drug known as Alimta (pemetrexed). It was developed in partnership with Eli Lilly and successfully treats some types of lung cancer, in combination with other chemotherapeutic drugs.

Interestingly, and significantly in terms of antibacterial therapy, pemetrexed has more than one biological target (see below). The financial outcome for Ted and Princeton was huge, providing sufficient resources to build a new chemistry department building. I went on to explain that we had raised a much smaller but nevertheless significant sum from the chemistry of leucovorin, a compound of the same chemical class as Ted's pemetrexed, and it had contributed to the establishment of a new chair and had provided for direct reinvestment in my own research, notably in the field of DNA minor groove binders, which make up our portfolio of anti-infective compounds.

Happily, I had now raised sufficient interest in our member of Court to take the discussion forward and positively. It was interesting that whilst the 'antibiotic apocalypse' challenge was well enough understood the commercial challenges of developing and marketing a new drug under stringent antibiotic stewardship conditions of use were not. Some areas of antiinfective research such as malaria and TB treatments, do attract the interest of big pharma because of their global market importance and the serious current resistance to many available drugs. For example, in South Africa, it has been argued that we are back to 19th century medicine, because of the lack of effective drugs to treat TB. But, as was once pointed out to me by a senior scientist in the former Wyeth company, despite its size and skill power, big pharma can't do everything;

it has to make choices, which naturally favour of those projects that seem to have the most financial comfort and confidence and market opportunity to them.

Anti-infectives

To go into this more fully I had to explain the standard ideal paradigm for drug discovery, which is concisely expressed as 'one target, one drug, one effect'. In other words, a single drug molecule acts at a specific biological target (typically a protein but also DNA like many anti-cancer drugs) and produces a discrete and beneficial biological response. This summarises a clean and systematic way approach, but is not the only way to think about new drugs. Indeed, quite the reverse can be argued in the context of antibacterial and other anti-infective compounds because of the serious problem of antimicrobial resistance (AMR), which of course is what is behind the antibiotic apocalypse of which TB mentioned above is an example.

There are many ways in which bacteria and other pathogens become resistant to drugs, for example they can evolve to modify the biological target so that the drug no longer binds, thereby losing the beneficial effect. It would be a good idea, therefore, if the drug had more than one target so that it would still work even if one target were resistant and lost. A beautiful recent example of this was

published earlier this year by the Boger group, from the Scripps Research Institute in California, a nonindustrial laboratory. Boger's team synthesized a derivative of the 'last resort' drug, vancomycin, that targeted three mechanisms of resistance (www.pnas.org/cgi/doi/10.1073/pnas. 1704125114). It's not yet in the commercial realm, but experiments showed that resistance simply could not be induced. Our approach is different chemically and biologically, but has similar consequences. Indeed, avoiding the development of resistance has been at the heart of our minor groove binders (MGB) project from the beginning.

"Graduates with a good chemistry degree are valuable, versatile people. This is especially true in fields such as medicinal chemistry and chemical biology, which are intrinsically multidisciplinary..."

Our anti-infectives programme has DNA as its molecular target; formally this is a single biological target but in practice contains hundreds of sites on which a drug molecule can touch down. In this way, it is equivalent to a collection of targets all held together in a strand. The key challenge for a successful anti-infective drug is selectivity; we want to kill the pathogen not the patient. Since patients like ourselves also have DNA we must ensure selectivity for the pathogen, which can be done.

In the anti-infective therapeutic field, where the evolution of resistance to drugs is critical to their long-term effectiveness and more broadly to public health, a drug molecule that touches down on many sites of an infectious organism's DNA is likely to be highly resilient to the evolution of resistance. It is a situation equivalent to one drug's having many targets and many effects, analogous to the discoveries at Scripps. The Scripps vancomycin derivative was shown to be resilient to the development of resistance. This is exactly what we have found too in our antibacterial compounds being developed by our partner company, MGB Biopharma (http://www.mgb-biopharma.com). We've not been able to generate resistance in one of our target pathogens, the bacterium Staphylococcus aureus, despite hundreds of consecutive challenges.

Moreover, we know from experiment that our drug causes many different biochemical effects when it kills S. aureus. So, we have single drug, multiple targets (all on DNA, of course), and multiple effects, just what is needed to combat the 'antibiotic apocalypse' (see The Antibacterial Drug MGB-BP3: from discovery to clinical trial. C. J. Suckling. Chemistry & Biology Interface, 2015, 5,166-174). It was now clear to my University colleague that this approach to anti-infective therapy was not typical of what would be done in industry. University research adds value and creates opportunity.

Working in the university environment, I then pointed out to our member of Court, that we also have a primary responsibility for education and training. In chemistry degrees there is clearly a component of training, but arguably more important is the range of skills that a good chemistry curriculum provides, analytical, conceptual, practical, mathematical, and many more. Add this to the range of knowledge and connections with other fields and the value of a chemistry degree stands out. Graduates with a good chemistry degree are valuable, versatile people. This is especially true in fields such as medicinal chemistry and chemical biology, which are intrinsically multidisciplinary, and this is essentially where that conversation ended.

I will end this piece with a question and an anecdote. Will modern studies of particle physics will directly affect our daily lives? Perhaps they will and I think it's good to know more about the fundamental properties of matter anyway. Simply understanding more subtle details about biology won't on its own make something useful happen although it can make an opportunity. We need that key translational component, chemistry, the science that can create the objects in the form of new molecules that make the difference. What other science has room for discovery, creativity, and applicability? As the former chancellor of the University of Strathclyde and Nobel Prize winner, the Lord Todd put it at a meeting that I organised many years ago, 'Chemistry is the Queen of Sciences. Get your chemistry right and everything else follows'.



Prof Colin J Suckling OBE DSc FRSE Research professor of chemistry Department of Pure & Applied Chemistry, University of Strathclyde Tel: +44 (0)141 548 2271 www.strath.ac.uk/chemistry

Europe can lead curing asthma

Susanna Palkonen of the European Federation of Allergies and Airways Diseases Patients' Associations underlines research around asthma in Europe today

sthma is a common chronic disease that causes inflammation of the smaller airways of the lungs (bronchioles). The disease can develop at any age, although very often it starts at childhood. Asthma is the most common chronic disease in children, leading cause of school absences, emergency visits and hospitalisations in Europe. It accounts for more than €70 billion annually.

Recent research has confirmed that asthma not only appears because of simple predisposition to develop it, but it can also be linked to environmental factors, like exposure to air pollution or to tobacco smoke during pregnancy.

Everything contributes to respiratory health

To decrease asthma rates and provide better care for patients, governments need to promote policies that include respiratory health concerns everywhere.

In the case of the European Union, there is a wide spectrum of policies impacting asthma care and prevention that go from chemicals exposure to tobacco consumption and marketing, and from medical devices approval to the management of indoor air quality. A European Parliament Interest Group on Allergy and Asthma works to embed asthma considerations into sectoral policies beyond healthcare.

Although no cure has been found for asthma yet, we know measures that are effective in controlling symptoms. The European Union has a clear role to play to reduce asthma. For example, EU institutions are adopting mandatory prevention standards to improve air quality by reducing the emission of pollutants from transport and industry sectors. However, still some progress needs to be done towards the establishment of a smoke-free Europe – implementing the WHO Framework Convention on Tobacco Control – or the establishment of a pollen monitoring system, both measures implying better health and savings.

We also hope that the EU will reinforce its labelling rules to better inform consumers about their choices,

especially in those products that might impact asthma and respiratory patients, like cleaning products, fragrances and cosmetics.

Patients need to be at the core of asthma research

Our knowledge about asthma has increased in the past decades leading to the development of important therapies to control the disease. However, those therapies have demonstrated their limitations in many patients, especially those with severe or difficult-to-control asthma, who experience lower quality of life and are even scared to die.

Independently of its severity, asthma as most of chronic diseases, depends on having the right treatment at the right time. While, researchers have clustered data to better understand the underlying causes of the disease and develop treatments, the scientific community is now calling for a clinical redefinition of the methods to diagnose and control asthma.

A leading group of pneumologists proposes a further revision and measurement to find out how exactly asthma develops in our bodies and what is happening in our lungs. They are calling for a deeper analysis of the patients' demographics, daily life and management of their disease.

In short, we see their positioning as a global call to put patients at the centre of medicine, while developing disease-specific measurement guidelines to propose personalised and more effective medicine, and we think this is the only consistent way to optimise asthma treatment and prevention, and improve patients' quality of life and, indeed, finding the cure.

The future asthma management plan is digital While personalised medicine promises to improve health outcomes, it needs tangible changes to operate. First and foremost, a safe and secure data privacy environment, to enable patients to safely share health data to model and predict disease changes. Governments would need to fully embrace eHealth possibilities, allowing to move from face-to-face consultations and paper health records to virtual assistance from healthcare professionals, alerts settings for out-patient care but also matching health budgets towards digital healthcare, including fair honorariums for healthcare professionals across diseases and reimbursement for patients. The European Union has the opportunity to lead European countries on this with policy, tools and innovative projects, like the ongoing myAirCoach mobile application to help patients keeping up with their asthma from a smartphone.

Like our former President Breda Flood, who has severe asthma, said: "After decades of having asthma I am only now starting finally to control asthma, knowing that my lungs are permanently damaged". At EFA we work to spare patients from going through everything people like Breda had to.

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Susanna Palkonen Director

European Federation of Allergies and Airways Diseases Patients' Associations Tel: +32 (0)2 227 2712 info@efanet.org www.efanet.org www.twitter.com/EFA_Patients

Pre-disposition to chronic inflammatory lung diseases

Michael Roth, Research Group Leader, Pulmonary Cell Research at University Hospital Basel & University Basel sheds light on lung diseases

he prevalence of asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases are increasing worldwide and represent a major issue for daily life for all patients. According to the World Health Organization, 280 million people suffer from asthma and up to 40% of children suffer from asthma symptoms.

In 2015, 65 million people were diagnosed with severe COPD with a death rate of 3 million per year. Both diseases are characterised by chronic airway inflammation, which can be controlled by pharmaceutical drugs and airway wall remodelling, which is insensitive to drugs. The American Thoracic Society stated in 2016 that chronic inflammatory disease may not be cured unless the cause of airway wall remodelling is understood.

Gene linkage analyses suggested that the susceptibility to asthma or COPD is inheritable, but out of 182 candidate genes, none had been proven as a cause. Family studies showed heritability; while twin studies indicated that genetic conditions contribute less than 50% likelihood to develop asthma.

Recent studies on gene regulation suggest that epi-genetic mechanisms may be inheritable and present as pre-conditions to develop asthma or COPD. There is evidence that the lung is sensitive during embryogenesis and early childhood to develop asthma or COPD later in life. The nature of this imprinting process seems to be epigenetic, but is not well understood.

Several epi-genetic mechanisms can imprint the lung for asthma or COPD, including chemical modifications of histones and DNA. These events lead to over-expression of inflammatory proteins or block anti-inflammatory proteins. Epi-genetic events are modified microRNA regulation and stability, which is associated to mitochondrial activity. The activation of epi-genetic mechanisms can occur through asthma or COPD risk factors such as inhaled allergens, chemicals, cigarette smoke, and dust, as well as by physical and psychologic stress factors.

Computer models based on large data collections from the USA, Europe and Asia showed that outdoor air pollution caused 3.3 million premature deaths worldwide in 2015, which is expected to double by 2050. Indoor pollution (open fire cooking, heating) killed another 3.5 million people. Air pollution can also be caused by fine dust (<10 pm) from agriculture in less industrialised countries.

A survey by the European Union in 2016 stated that in Europe 50% of chronic inflammatory diseases are misdiagnosed and inadequately treated. Thus, more investigations into the pathogenesis of chronic inflammatory lung diseases are urgently needed if we want to reduce the burden for the patients and the society. Only if the origin of the diseases is understood, new disease specific diagnostic tools and personalised therapies can be developed. To achieve this, investigators need access to data and tissue banks generated from human asthma and COPD lungs.

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Genetic origins of chronic inflammatory lung diseases

Candidate genes for asthma susceptibility included the glucocorticoid receptors, ADAM33, TGF- β receptors, IL-33, surfactant protein D, IL-4 and interferon- λ . In COPD, the most recent candidate genes were surfactant protein-D, alpha-1-antitrypsin, hypoxia inducible factor-1, TGF- β 1 and Matrix metalloproteinase 12.

Moreover, specific gene alleles may only be relevant to the disease in Caucasians or Asians. None of the candidate genes had ever been proven to be a single cause of the diseases. There is evidence that modified gene



generational pre-dispositioning of the lung to chronic inflammatory lung diseases

regulation during embryogenesis imprints the lung to develop asthma or COPD later in life. Family studies performed over three generations suggested that, the imprinting of the embryonal lung by cigarette smoking mothers increased the chance for their children to develop COPD by over 40%. This epi-genetic imprinting of the embryonal lung was also correlated to cigarette smoking grandmothers, with the possibility of skipping one generation. Cigarette smoking lastingly altered DNA and histones methylation, thereby increasing the chance of children to develop COPD (figure 1).

Early studies analysing the effect of inhalable compounds on the structure of the airways - showed that lung structure pathologies were induced during embryogenesis. The studies showed that a second event was needed to initiate chronic lung inflammation in the offspring. In rhesus monkeys, the exposure to allergens during pregnancy and the new-born resulted in disturbed interaction of epithelial cells with smooth muscle cells, smooth muscle hypertrophy, cytokine expression, and vascular remodelling of the

airway wall. Importantly, none of these pathologies could be corrected later in life. Thus, once damaged, the lung stays damaged for the entire life. These observations suggest that epigenetic plays an important role in the pathogenesis of chronic inflammatory lung diseases.

Epigenetic events as a cause of chronic lung inflammation

In mothers and children cohorts, the susceptibility to develop asthma was associated with the exposure of mothers and children to the same risk factors during late embryogenesis (last trimester) and early childhood (0-6 years), as summarised in figure 2.

Another risk factor to pre-dispose the lung for chronic inflammation later in life, was low levels of zinc ions in mothers and children during pregnancy. This correlated with an increased risk of asthma in children (odds ratio >0.57). Zinc deficiency affects the function of a large number of proteins related to asthma, including the glucocorticoid receptors, matrix metalloproteinases and DNA methylating proteins. Furthermore, zinc finger proteins regulate

hormone-dependent gene activity, RNA transcription and protein synthesis, all of which are epi-genetic regulators.

Malnutrition during pregnancy increased the risk for the child to develop asthma, wheeze, and atopic diseases later in life. Risk factors for asthma can be transmitted by breast feeding. There is also evidence for multi-generation transmission of asthma susceptibility, as mothers exposed to phthalates during pregnancy increased the risk for the next two generations to develop asthma. The exact mechanism of this transgenerational asthma susceptibility is unknown, but experimental and clinical data suggested that it is due to DNA and histone methylation and modified microRNA expression.

DNA methylation was studied in 527 children (5-12 years) born to cigarette smoking mothers and identified 20,578 methylated DNA sequences. Most of the genes were methylated at stretches of CpG repeats with unknown function.

In a second study (572 children), DNA methylation caused by cigarette smoke was linked to respiratory symptoms at the age of 3-5 years. Tobacco smoke increased gene specific methylation by 10-fold in 26 different genes, including the aryl hydrocarbon receptor repressor (AHRR) and cytochrome P450 (CYP).

However, 50% of the affected genes encode for unknown proteins or microRNAs. In another study (245 females, 10-18 years), DNA methylation affected mainly genes encoding for Th2 cytokines, which are known to be increased during asthma. It is unknown if DNA methylation patterns in children exposed to risk factors are identical to those in adult asthma.

Allergens, smoke, dust

The importance of epithelialmesenchymal-trophic-unit (EMTU) in lung function

The EMTU describes the interaction of different cell types that form the bronchi. Animal models implicated that airway wall remodelling originated from over-active fibroblasts/myofibroblasts, which produced and deposed pro-inflammatory components of the extracellular matrix and proliferated faster. However, in the human lung, this pathogenesis was never fully confirmed and more recent studies on human tissues and isolated cells suggested a different mechanism.

Epithelial cells are a key regulator of the sub-epithelial mesenchymal cells. In case of epithelial injury or loss of the epithelium, the sub-epithelial cells start to proliferate, to compensate the loss of the epithelium. As a result, the thickness of the airway wall increases, leading to local hypoxia, followed by the formation of new micro-vessels and infiltration of pro-inflammatory immune cells (figure 3).

In our own asthma studies, the epithelium obtained from asthma patients controlled the function of fibroblasts and airway smooth muscle cells. Most of the available drugs for asthma and COPD can well control the secretion of pro-inflammatory cytokines, while they have no effect on proliferation or the deposition of pro-inflammatory extracellular matrix components.

Recent studies indicated that epithelial cells specifically control mitochondrial activity in sub-epithelial cells. Mitochondria can be linked to the abovementioned epi-genetic mechanism, leading to chronic lung inflammation. However, a search by Pubmed (keywords: asthma, mitochondrial, NOT



Figure 2: Hypothesised mechanism of two-event pre-dispositioning of the lung to chronic inflammatory lung diseases

review) found only 219 publications focused on this topic. Similarly, 205 publications in COPD investigated the role of mitochondria. The inheritance of epi-genetic events would be most effective if they occur in mitochondria genes, which are forwarded to the next generation only by the mother.

"Computer models based on large data collections from the USA. Europe and Asia showed that outdoor air pollution caused 3.3 million premature deaths worldwide in 2015, which is expected to double by 2050."

Malfunction of mitochondria was reported in human asthma and correlated with airway smooth muscle cell hyperplasia and increased secretion of pro-inflammatory cytokines. Epigenetic deregulation of mitochondria genes was associated with aging, resetting gene regulation during embryogenesis, inflammation, proliferation, and cell differentiation. Interestingly, the function of mitochondrial genes or mitochondria regulating genes is controlled by microRNAs. Thus, more investigations are needed to clarify the role of mitochondria in chronic inflammatory lung diseases.

The contribution of microRNAs to chronic inflammatory lung diseases

MicroRNAs are short strands of RNA which had been regarded as useless elements for a long time. Only recently, microRNAs were recognised as essential post-transcriptional regulators of protein production. MicroRNAs act as epi-genetic regulator of RNA-protein translation, RNA stability and mitochondria activity. Regarding asthma and COPD, 47 different microRNAs have been linked to organ malfunction and disrupted cell-cell interaction.

MicroRNAs can be detected in body fluids such as plasma and serum. which makes them candidates as new biomarkers. However, there is a lack of evidence microRNAs are specific for asthma or COPD as many have been described earlier as markers for various tumours.

However, microRNAs may present a novel form of therapy, as they are functional and stable under certain conditions in plasma and serums. As a biological drug, microRNAs can be protected by peptide envelopes and even can be taken up by cells from the



Figure 3: Cell – cell- communication between the different cell types forming the EMTU. Immune competent cells will infiltrate the inflamed tissue from micro-vessels

blood stream. Some on-going investigations explore the possibility to create such peptide enveloped microRNAs as a therapy for diseases where specific proteins are overexpressed.

"A survey by the European Union in 2016 stated that in Europe 50% of chronic inflammatory diseases are misdiagnosed and inadequately treated. Thus, more investigations into the pathogenesis of chronic inflammatory lung diseases are urgently needed if we want to reduce the burden for the patients and the society."

One problem with the use of microR-NAs as therapeutics is the fact that the same microRNA can be highly expressed in one cell type, while being down-regulated in another cell type under disease conditions. For example, microRNA-19 is up-regulated in immune cells, while it is down-regulated in smooth muscle cells and fibroblasts of asthma patients. Similar problem was described for microRNA-21 in COPD versus lung cancer.

Further attention must be given to the fact that microRNAs have many mRNA

targets. For example, microRNA-19a down-regulates the mRNA of Erk1/2 mitogen activated protein kinase as well as the microRNA of the TGF- β receptor 1, TGF- β associated protein and tyrosin kinase. Therefore, its high expression in immune cells should result in reduced production of pro-inflammatory cytokines.

In contrast, the lack of microRNA-19a in mesenchymal cells in asthma – should lead to increased production of pro-inflammatory factors and stimulate the cell proliferation. The later observation by our group can explain the mechanism underlying the regulation of asthmatic mesenchymal cell behaviour, which has been described by others earlier. Therefore, the use of microRNAs as therapeutic must be carefully studied to avoid unwanted side effects.

Conclusion

Lungs are vulnerable to be pre-disposed for developing chronic inflammatory lung diseases during two-time windows in late embryogenesis and early childhood. These critical phases determine the lung's maturation, function and structure for the rest of the life. The susceptibility to develop asthma and COPD may not be inherited through a genetic pre-condition, but rather by irreversible epi-genetic events. Future studies need to investigate how epi-genetic modifications become "fixed" and inheritable.

Mothers should be better informed about these risk factors and that they can do more to prevent their children from suffering lifelong malfunction of the lung.

Finally, the interaction of basic, clinical and epidemiological research is needed for better understanding the cause of asthma and COPD to find new therapies.



Michael Roth Research group leader pulmonary cell research University Hospital Basel & University Basel Tel: +41 (0)61 265 2227 Michael.roth@usb.ch https://biomedizin.unibas.ch/nc/about-us/ people/profil/profile/person/roth-3

Workplace mental health: Healthy workforce, healthy society

The European Brain Council (EBC) highlights the challenges around workplace mental health, following World Mental Health Day on 10th October

obs and careers are an important part of our lives. Along with providing a source of income, they help us fulfill our personal aims, build social networks, and serve our professions or communities. They contribute to development of a healthy European population. However, the pace and nature of work is changing which can make job a major source of emotional strain, affecting our workplace mental health.

A growing body of evidence shows that many workplace mental health issues like job stress, work-life conflict, harassment, and violence exert a human toll, lead to significant social costs and impede productivity. Prolonged job-related stress, for example, can drastically affect physical health. Constant preoccupation with job responsibilities often leads to erratic eating habits and not enough exercise, resulting in weight problems, high blood pressure, and elevated cholesterol levels. It can cause burnout that can lead to depression, which, in turn, has been linked to a variety of other health concerns such as heart disease and stroke, obesity and eating disorders, diabetes, and some forms of cancer. Chronic depression also reduces immunity to other types of illnesses, and can even contribute to premature death.

Depression in the workplace is a leading cause of lost work productivity, sick leave and early retirement worldwide. In Europe alone, mental health conditions like depression place a heavy burden on society as a whole:

- One in ten working people have taken time off work because of depression, and around 350 million working days are lost in the EU each year due to stress and depression;
- Mental disorders are highly prevalent in Europe and impose a major burden on individuals, society and the economy. They represent 22% of the EU's total burden of disability;

 The overall financial costs of mental disorders, including direct, as well as indirect, medical costs through care and lost productivity, amount to more than €450 billion per year in the EU.

Stigma also accounts for a big part of the problem. The misunderstanding that surrounds mental health problems or illness contributes to preconceived notions, misperceptions and fears. Employees facing mental health challenges often choose to suffer in silence and/or avoid getting help rather than face the stigma and discrimination.

The opportunity

The workplace culture, including good psychosocial management practices, contributes considerably to an organisation's success. It has been observed that it improves sense of wellness and overall satisfaction among employees, service quality and subsequent client satisfaction, strengthens reputation in the community and increases brand awareness.

Mental health and well-being of the workforce is a key resource for productivity and innovation in Europe as well as critical asset for companies. There is no doubt that a wide variety of working conditions are powerful determinants of health, for better or for worse. Employers can make a major contribution to the wellbeing of society by their actions, therefore businesses have an important role to play, not only as employers, but also as advocates for health in society.

The European Brain Council (EBC) – a non-profit organisation gathering patient associations, major brainrelated societies as well as industries, to promote the improvement of the quality of life of those living with brain disorders in Europe – is strongly convinced that mental health and well-being of the workforce is a key resource for productivity and innovation in the EU.

Employment not only involves focusing on more jobs, but also on better jobs, therefore key existing recommendations should be consolidated and tangible preventive measures need to be developed to improve wellbeing of the workforce. This should be done in collaboration with relevant stakeholders, including employers and employee organisations, to be implemented in human resources policies within the workplace.

The initiative

A strong opportunity exists to reach deeper into the "silent majority" suffering from the burdens of mental health disease in the workplace and broaden the reach of mental health education. Most organisations advocating for mental health today cannot claim to have started the conversation on mental health in the workplace, however, collectively, we do want to strengthen it, and make all employees feel safe and comfortable enough to "not feel okay" in their work environment or at times in their career.

"Not Myself Today" was introduced to workplaces in Canada in 2013, to encourage employers and employees to transform mental health at work, and is now being piloted by EBC in Europe. Over the past three years, the campaign has informed, engaged, recruited, mobilised and partnered with people and organisations to successful and meaningful change in the improvement of mental health. The initiative provides comprehensive resources and tools to organise events and activities that engage employees and aims to reduce stigma and create cultures of acceptance and support for mental health and for those who are facing mental illness.

1 in 5 people at the workplace experience a mental health condition, and with issues like stress and burnout becoming more and more prevalent in this day and age, this statistic can only be predicted to worsen if early intervention and education is continuously avoided. It is vital to have the voices of leading companies and organisations, policymakers and community leaders spread awareness of a campaign that helps employees and employers better understand mental health, reduce stigma and foster a safe, open and supportive workplace environment.

Frédéric Destrebecq Executive Director

Stephanie Kramer Communications & Advocacy Coordinator The European Brain Council (EBC) Tel: +32 (0)2 513 27 57 www.braincouncil.eu www.twitter.com/EU_Brain

Supporting measures that improve health for all

The Wellcome Trust backs ideas from all over the world to improve health for everyone, as Open Access Government learns

The Wellcome Trust traces its roots back to the entrepreneur and philanthropist Sir Henry Wellcome, a man born on the American frontier who, with his partner Silas Burroughs, built a multinational pharmaceutical giant.

Wellcome's laboratories, one physiological and one chemical, proved research could develop better medicines. During his lifetime, Wellcome funded scientists who produced antitoxins to combat tetanus, diphtheria and gas gangrene.

On his death in 1936, Wellcome's will established a charity for the "advancement of medical and scientific research to improve mankind's wellbeing".

Today, the Wellcome Trust's funding supports over 14,000 people in more than 70 countries thanks to a £20.9 billion investment portfolio. It has set a target of investing up to £5 billion over the next five years alone to explore new ideas in science, population health, medical innovation, social sciences and public engagement.

The trust's wide-ranging work is intended to reflect the breadth of its founder's scientific and pharmaceutical interests.

Since 1993, the trust has funded the Wellcome Trust Sanger Institute, which played a major role in the Human Genome Project, mapping 30% of the human DNA sequence as part of a collaborative international effort. The trust's backing kept the data public, meaning researchers have permanent access to it.

The trust also runs the Wellcome Collection, a free London-based exhibition space and the home of the Wellcome Library, one of the world's leading resources for the study of medical history. Much of the trust's research funding aims to address major challenges in a number of different ways, bringing different activities together to create something greater than the sum of its parts. This approach is evident in its work to help the world prepare for the next major epidemic.

The trust has supported activities ranging from vaccine development to tackle Ebola through to public health interventions, such as providing insecticide-treated bednets to prevent malaria, behavioural training for health workers to minimise potential infections and advocacy work to encourage governments and business to secure global health.

Preparing for epidemics is one of a few priority areas and the trust is constantly assessing new issues to see where its work could have an impact.

Mental health

The latest area in development is mental health. The trust is exploring how the mental wellbeing of young people could be improved by supporting alternative approaches to better understanding mental health and the development of new interventions to prevent and respond to mental health problems.

In October, the trust co-funded a £200,000 investment to help 14 public libraries in England, Scotland and Wales find new ways of engaging communities on the issue of health.

The Engaging Libraries project, a collaboration with the Carnegie UK Trust, will back a range of pilots, some fun and some serious, looking at mental health at all stages of life. They include a project to create a "wellbeing sanctuary" focused on the mental health of men working in the City of London. Another scheme in Oldham,



Greater Manchester, will use comics and cosplay to engage young people on mental health issues.

"Today, the Wellcome Trust's funding supports over 14,000 people in more than 70 countries thanks to a £20.9 billion investment portfolio. It has set a target of investing up to £5 billion over the next five years alone to explore new ideas in science, population health, medical innovation, social sciences and public engagement."

Elsewhere, the trust has worked with the Simons Foundations to fund a £10 million International Brain Lab.

This ambitious project – described as a "world-premiere" for neuroscience – will see 21 neuroscience groups from the UK, the USA, France, Portugal and Switzerland work together to map brain activity in mice to understand the sequence of steps used to make decisions, such as the best way to obtain food.

It is hoped that bringing together leading experimental and theoretical neuroscientists will deliver greater insight into learning and decision-making than any single lab could achieve on its own. The work is one of the first steps towards identifying the brain network dysfunctions behind mental health disorders. The lab officially launched on 19 September 2017.

Dr Andrew Welchman, Head of Neuroscience and Mental Health at Wellcome, said: "Even the seemingly simple decisions we take for granted in everyday life involve the coordinated activity of many thousands of brain cells.

"A longstanding barrier in understanding the brain has been capturing and teasing apart this activity. The International Brain Lab will deploy state-of-the-art technologies in a collaborative setting, with input from some of the leading experimental and theoretical neuroscientists on the planet. This could be transformative in helping us understand how the brain works."

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Newborn brain injury – innovations in early diagnostics

A new direction in the monitoring of brain injury in babies, pioneered by a team of physicists, engineers and doctors in University College London (UCL) and University College London Hospitals (UCLH)

n this profile, Dr Ilias Tachtsidis, Wellcome Trust Senior Fellow, Reader in Biomedical Engineering at UCL and Dr Subhabrata Mitra, Consultant Neonatologist at UCLH introduce MetaboLight, explain how physicists, engineers from the department of Medical Physics and Biomedical Engineering at UCL, working together with medical doctors from the Neonatal Unit at UCLH have demonstrated innovation concerning the monitoring of newborn brain injury, with the development of technologies and instruments that allow early diagnostics of brain injury severity.

Early insults to brain development can result in significant long-term morbidity and mortality. Unfortunately, many infants are born in difficult conditions, with a lack of blood and oxygen supply to brain around the time of birth. Brain function becomes deranged in this group of infants and they develop hypoxic ischaemic encephalopathy (HIE). In developed countries, 2-3 infants per 1000 live births suffer from this condition and unfortunately, this incidence can be up to 10 times higher in countries of sub-Saharan Africa and Asia.

Therapeutic hypothermia (total body cooling) is the only clinical treatment option that has been shown to improve outcome (death or disability) following this condition. It has become a standard of care from 2010 in UK. During this treatment, the infant is cooled for 72 hours and then gradually warmed back to the normal temperature, over a period of 14 hours.

The clinical challenge

Following HIE, significant changes are noted in brain metabolism. The energy state of the brain changes through stages of energy depletion and apparent recovery, before going through final depletion, if not acted on early. These stages are called primary and secondary energy failure. Most of these neuro-metabolic cascade of changes occurs within the powerhouse of cell, mitochondria.

In addition to HIE, other neurological conditions like neonatal stroke and seizures are also known to cause disturbances in brain metabolism and oxygenation. So, it is important to focus on attempts to monitor mitochondrial metabolism, along with brain oxygenation continuously at baby's cotside to understand the degree of injury and response to treatment in different neonatal neurological conditions.

There is an unmet demand for developing an early cotside biomarker – that will give us the information regarding changes in the pathophysiological state of the brain function during and following treatment; and it will relate to future outcome.

The engineering challenges

Once the infant becomes stable after the cooling treatment, an MRI (Magnetic resonance imaging) and a MRS (magnetic resonance spectroscopy) of the brain is performed (normally between day 5-8 of life) to assess the degree of injury and to predict the future neurodevelopmental outcome.

MRS derived brain Lac/NAA (lactate/ n-acetyl aspartate) peak area ratio is a robust biomarker of outcome. MRI and MRS are expensive instruments that require dedicated staff, can only be used several days after the injury, when the infant becomes stable and because they require the infant to be moved from the intensive care unit, they carry significant risk in sicker infants.

Given the complexity of the other monitoring in place for these infants, any new monitoring needs to be easily applicable from day one following birth and can be monitored by clinical staff.

Our technology and Measurements

To answer these challenges, we employ an optical technique using harmless near infrared light that can probe the brain tissue. The technology is known as near infrared spectroscopy (NIRS) and has been used to monitor accurately the changes in brain haemodynamics and oxygenation, using simple optical probes placed over the surface of the scalp.

NIRS instruments transmit a couple of different wavelengths (colours) of near-infrared light to the surface of the head; the reflected light from the brain tissue has been attenuated by the haemoglobins in the blood vessels that carry oxygen. The amount of oxygen carried by the haemoglobins will affect the colour of the blood in the brain tissue; that is why arterial blood is red (fully oxygenated) and venous blood is blue/purple (less oxygenated). NIRS can quantify this colour and hence measure oxygenation.

But we had to go further and develop solutions that allow us to monitor the mitochondrial function. To achieve this, we have developed and used broadband NIRS technology, which means that instead of using only two or three different colours of nearinfrared light we use hundreds.

This allows us to monitor many optical signatures, besides the haemoglobins within the brain tissue. One unique optical signature comes from within cytochrome-c-oxidase, an enzyme inside the mitochondria. This enzyme is one of many responsible in converting glucose and oxygen to energy; by facilitating this process it changes colour and means that we can detect it with our novel broadband NIRS technology. We now have technology that can continuously measure brain oxygenation and mitochondrial metabolism using harmless near-infrared light.

Broadband NIRS instrument

We have developed instruments that use white light sources, similar to the headlights in cars to transmit many colours of near-infrared light through optical fibres attached on the head of the infant. We collected the reflected light from the head with another fibre optic cable, that is connected to a detection unit that is called a spectrometer.



A spectrometer is an instrument often used in biology and astronomy, that is capable of splitting the light to its many colours. It then uses sensitive digital cameras to measure the changes in light intensity for every colour. As oxygenation and metabolism changes, the measured colour intensities will change. The broadband NIRS is made of easily sourced and relatively cheap components, non-invasive, harmless, highly portable and can be positioned by the cotside in the neonatal intensive care unit to measure the changes in brain tissue oxygenation and mitochondrial metabolism, continuously in real time from early on after a suspected brain injury.

Our current research results

Using our novel broadband NIRS instrument, we have now monitored nearly one hundred babies suffering from different neurological conditions including HIE, seizures and neonatal stroke. We have demonstrated that using metabolic biomarkers, sicker infants can be identified early after HIE, and how the injured brain metabolism respond differently to available oxygen delivery following injury. We have also identified new insights in the brain metabolic changes during neonatal seizures and following neonatal stroke. These results have brought us a closer to a robust biomarker of neonatal brain injury. This work is part of our feasibility study supported by the Wellcome Trust and further information can be found in our public engagement and dissemination web platform <u>www.metabolight.org</u>.



Wellcome Trust Senior Fellow and Reader in Biomedical Engineering University College London i.tachtsidis@ucl.ac.uk www.twitter.com/IliasTachtsidis

Dr Subhabrata Mitra Consultant Neonatologist University College London Hospitals Subhabrata.Mitra@uclh.nhs.uk

www.metabolight.org www.twitter.com/metabolight



The challenge of mental disorders: European neuroscience answers the call

Executive Director of the European College of Neuropsychopharmacology (ECNP), Alexander Schubert looks at how science is unravelling the complexity of the human brain

The human brain is the most complex and improbable arrangements of matter known to mankind. That this one-and-a-half-kilogramme pudding of salty water and fat manages to achieve anything at all must count as one of nature's great surprises. That is does so using electricity – firing trillions of electrical signals back and forth, like e-mails, every second – is amazing. That from these signals it is able to conjure up consciousness is utterly miraculous.

Appreciating the miracle though is not the same as understanding it. After centuries of sustained research by some of humanity's brightest minds, the secrets of this astonishing organ remain stubbornly elusive. The more we learn about it, the more we realise how much there is to know. Science's last great frontier, it turns out, is the one inside our own heads.

Not surprisingly, when this extraordinary organ does misfire, it does so in ways that are complex and baffling. All of the major psychiatric disorders – despite the enormous progress being made in identifying and treating them – remain at the level of their causes stubbornly mysterious. We can mitigate many of their symptoms, often with life-saving effect, but where these disorders come from – out of what secret mix of biology, heredity, environment, experience, personality and lifestyle – and exactly what triggers them are conundrums we are still years away from getting to the bottom of.



Unravelling the mystery of mental illness is not only a daunting scientific challenge but an urgent moral imperative. The brain's utter centrality in the cockpit of our being means its malfunctions are unusually dangerous and far-reaching, attacking not just our health but our whole sense of self in particularly damaging and debilitating ways. The effects are not only devastating on the individual level, with serious conditions such as major depression and schizophrenia inflicting enormous suffering, curtailing life choices, and reducing life expectancy¹. They also have a huge social impact.

According to the best estimates, during any given 12month period more than one third of the EU population suffers from a mental disorder of some sort, most of which go untreated². As well as the untold human misery that lies behind these statistics, there is an enormous social cost, estimated in brute economic terms at €798 billion per annum. Of these, indirect costs 'hidden' in lost productivity, accidents, early retirement, premature mortality, disability and care-seeking account for an enormous 40%³.

Globally, mental illnesses constitute by far the heaviest burden on world health, responsible for fully a third of all years lived with disability (YLDs)⁴ adding up to a cumulative economic output loss between 2011 and 2030 projected to be in the order of US\$ 16.3 trillion worldwide⁵. These are very big numbers.

So, what is to be done? At the public health level prevention will be key, with investments in training, treatment and education high on anyone's list of priorities. But science will also play a critical role, and in this Europe, is unusually favoured.

"Today's neuroscience does not just transcend borders, it is also leapfrogging disciplinary boundaries. Psychiatry and neurology used to be different zones of expertise, but like tunnellers coming in from different sides of the hill, the leading researchers in these fields are now starting to link up underground, at the level of the brain's fundamental mechanisms."

Brain research is one of the glories of European science, with no less than 16 Nobel Prizes to its credit. The field is so vibrant that a special award was deemed necessary to do it justice, and the million-euro Brain Prize was accordingly launched in 2011⁶. Unusually deep and rich, the region's scientific infrastructure is supported by a sophisticated ecosystem of universities, research institutes, innovation-driven companies, government agencies, medical societies and scientific associations.

As the obstacles of distance and difference are overcome, European diversity is proving a powerful advantage. Organisations such as the European College of Neuropsychopharmacology (ECNP), the Federation of European Neuroscience Societies (FENS) and the European Psychiatric Association (EPA) regularly bring thousands of researchers and clinicians together to share new findings, insights and ideas, and push against the limits of what we know.

The result is an exciting shift in how mental disorders are conceived. Today's neuroscience does not just transcend borders, it is also leapfrogging disciplinary boundaries. Psychiatry and neurology used to be different zones of expertise, but like tunnellers coming in



from different sides of the hill, the leading researchers in these fields are now starting to link up underground, at the level of the brain's fundamental mechanisms. Two major new pan-European research enterprises point to where these exciting new developments are taking us.

The PRISM (Psychiatric Ratings using Intermediate Stratified Markers) Project, funded under the Innovative Medicines Initiative, an imaginative attempt by the European Union to foster ground-breaking cross-sector collaboration, is one such example. A landmark multimillion-euro project to find the biological basis for social withdrawal, PRISM seeks to open a window onto the underlying pathologies that connect such major disorders as depression, schizophrenia and Alzheimer's. The potential long-term payoff is enormous. If a common biological mechanism for behavioural markers such social withdrawal can be found, linking apparently very different diseases, the possibility arises not only of understanding brain disorders and the processes that drive them in profoundly new ways, but of developing whole new avenues of treatment.

Eat2beNICE (Effects of Nutrition and Lifestyle on Impulsive, Compulsive and Externalising Behaviours), another multimillion project, this time under the EU's Horizon 2020 funding programme, is a pioneering exploration of the nervous system highway that connects our brain to our digestive organs to understand how nutrition interacts with mental health, and in particular whether diet can be linked to control disorders such as impulsivity, compulsivity, addiction and aggression. Perhaps the most comprehensive and ambitious project of its kind yet, Eat2beNICE is shining a new light into the darkness that separates what we consume as organisms from how we behave as humans.

Projects such as these are the great scientific expeditions of our age, the twenty-first century's version of the voyage of the *Beagle* or the search for the source of the Nile. Organisational tours de force that mobilise

hundreds of researchers from countries across the region, they are pushing science deep upriver into some of humanity's most impenetrable unknowns, and placing European research at the very forefront global discovery.

But scientists are also working to bring the benefits of these new approaches into the clinic. The Neuroscience-based Nomenclature (NbN) project is an international collaboration, led from Europe, to bring the way medicines for psychiatric disorders are organised in line with what we are learning about how the brain works⁷. The implications here are extremely significant. By reorienting our understanding of these treatments away from the largely pharmaceutical conventions that have predominated in the past, towards principles based on the modes of action of the underlying compounds, NbN gives clinicians a much more robust and rational tool with which to make their medication choices.

"According to the best estimates, during any given 12-month period more than one third of the EU population suffers from a mental disorder of some sort, most of which go untreated."

It also helps doctors not to confuse and alarm patients by treating their depression with "second-generation antipsychotics" or their anxiety with "antidepressants." So far 20,000 psychiatrists around the world have taken up this new system, an outstanding example of how the latest insights from neuroscience are being translated into better care for those suffering from mental health difficulties.

What steam was to the nineteenth century and electricity to the twentieth, cognition will be to the twentyfirst. How well we understand, manage and optimise this critical resource, in a world in which knowledge and innovation are the founts of wealth and well-being, may very well determine our future.

A major recent review of research progress in applied neuroscience concluded with "rekindled optimism" that the effective treatment and even prevention of psychiatric disorders may soon be within our reach. But it "will require a sustained commitment by all the major partners concerned by this venture, from industry to academia, clinicians to patients, regulators to public policy makers and, indeed, from society at large."⁸ European neuroscience is stepping up.

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Alexander Schubert, PhD Executive Director

European College of Neuropsychopharmacology (ECNP) Tel: +31 88 756 9555 a.schubert@ecnp.eu www.ecnp.eu www.twitter.com/ECNPtweets

Time for a change of tack on drug development for neurodegenerative diseases?

UCB's Duncan McHale outlines why reclassification might be a good idea to boost drug development for neurodegenerative diseases like Alzheimer's and Parkinson's

eurodegenerative diseases are a growing global challenge, as medical advances ensure more individuals live longer. By 2020 there will be more than 40 million people in the world with Alzheimer's disease (AD) and by 2040, without the development of disease modifying drugs, this will rise to more than 80 million. Discovering and developing disease modifying drugs is proving very challenging, with many programmes failing. November 2016 saw another phase 3 failure with Lilly's solanezumab failing at the final stages of development. Is this the end of the amyloid hypothesis or a case of too little, too late and too broad?

"AETIONOMY is an Innovative Medicine Initiative (IMI) funded consortium established to develop a mechanistic based classification of neurodegenerative diseases, with an initial focus on Alzheimer's and Parkinson's disease."

The amyloid hypothesis

Alzheimer's disease is a chronic neurodegenerative disease which usually presents in the seventh or eighth decade of life. However, earlier onset is not uncommon. The cause(s) of AD are not fully understood but the presence of amyloid (protein) plaques in the brain was demonstrated in 1911 and since this time the disease has been thought of as a disease of amyloidosis. Multiple potential therapies targeting amyloid processing have been developed and studied, with several still in the development stages. These therapies have all demonstrated an ability to reduce amyloid load in preclinical models, but this has so far not been beneficial to humans.

Amyloid is undoubtedly associated with AD and its presence has been a core part of the diagnosis, either post mortem or, more recently, through imaging techniques. However, the amount of amyloid does not correlate with disease severity and many subjects have significant amyloid deposits but no symptoms. Despite these anomalies, the majority of current potential therapies have been targeting this mechanism. The community eagerly awaits the results of a clinical trial using Biogen's aducanumab as the most promising agent so far, but given the failure of other admittedly less potent molecules targeting amyloid deposition, many are pessimistic about a good result.

Drug development for neurodegenerative diseases at a turning point

The failure of these therapies to date could be because the amyloid hypothesis is flawed and, despite the



association, amyloid is a downstream consequence of the disease process and not pathogenic in its own right. However, the presence of familial forms of the disease caused by genes involved in amyloid processing make this unlikely. For example, the presenilin 1 gene is part of a protein complex which degrades amyloid, creating the pathological 42 amino acid peptide.

"By 2020 there will be more than 40 million people in the world with Alzheimer's disease (AD) and by 2040, without the development of disease modifying drugs, this will rise to more than 80 million."

It is much more likely that, for most individuals, amyloid is not the sole cause and additional pathological mechanisms are involved. Indeed we now know that the Tau protein is one of these additional mechanisms. It is therefore time to start focussing on some of these other mechanisms to find the causes of AD, which we can then target with new therapies. We need to look for mechanisms that are important in later stages of the disease process and/or can still be successfully modified once the very early symptoms appear. AETIONOMY is a consortium with the sole purpose of identifying these other mechanisms involved in AD and reclassifying neurodegenerative disease using these discriminatory mechanisms, which will help us develop new treatments.

At AETIONOMY we have been taking the totality of research in AD and, using our knowledge base, integrating this information into a common framework to search for other potential mechanisms. By looking for these other mechanisms we hope to find sub-populations of patients who can be treated by targeting the cause in



them which is present with the amyloid plaques. Success will result in a new way to classify AD beyond just the presence of memory problems and plaques. Success will also result in new mechanisms for targeting and precision medicines for AD.

AETIONOMY

AETIONOMY is an Innovative Medicine Initiative (IMI) funded consortium established to develop a mechanistic based classification of neurodegenerative diseases, with an initial focus on Alzheimer's and Parkinson's disease. This public private partnership is co-led by myself and Martin Hofman-Apitius from SCAI Fraunhofer. The premise behind the project is that, although large sums have been invested in research in neurodegeneration and a lot of data generated, the co-ordination and integration of this data across the community has been less well addressed. The consortium has brought together experts in

informatics, computing, engineering, mathematical modelling of disease, neuroscience and clinical neurology from leading academic centres, as well as neuroscience, informatics and neurology drug development experts from the EFPIA Industry partners.



Duncan McHale Head of Global Exploratory Development UCB Duncan.McHale@ucb.com

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Dementia as a progressive condition

Alzheimer's Society in the UK provides a fascinating glimpse into the most common types of dementia, all of which are progressive

The most common types of dementia – Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia – are all progressive. The structure and chemistry of the brain become increasingly damaged over time and the person's ability to remember, understand, reason and communicate will gradually decline. As dementia worsens, the person will need more support with daily living. Their behaviour and mood will also change.

Health professionals often use scales to measure these changes. They may assess a person's mental ability, daily living skills (such as dressing or managing medication), behaviours, overall functioning or quality of life. Some of these scales were developed specifically for Alzheimer's disease and work better for that compared to other types of dementia.

Assessment of the extent of someone's dementia should take account of these scales, but should also take a broader view of the person, including their capabilities and needs. Looking at dementia as a series of three stages – early, middle and late – can be a useful way of understanding the changes that occur over time. However, it is important to realise that this view of dementia can only provide a rough guide to the course of the illness.

This is because:

- Some symptoms may appear earlier or later than indicated here, in a different order, or not at all;
- The stages may overlap the person may need help with one task, but may be able to manage another activity on their own and;
- Some symptoms, such as irritability, may appear at one stage and then vanish, while others, such as memory loss, will worsen over time.

The way that a person experiences dementia will depend on many factors. These include their physical make-up, other illnesses they may have, emotional resilience, medication and the support they can rely on.

Before dementia develops

There is good evidence that, by the time most people develop any symptoms of dementia, the underlying disease has been causing damage to their brain for years. Researchers are very interested in this 'pre-symptomatic' period and have developed tests to look at the brain chemistry, function and structure now. It is likely that any medication designed to slow down or prevent the diseases that cause dementia would work in this early phase, before the disease is fully established.

Over time, the changes in the brain will begin to cause mild symptoms. Subtle problems such as memory, reasoning, planning or judgement may cause difficulties with more demanding tasks (such as preparing a meal), but they will not yet significantly affect daily life. A person at this stage may be given a diagnosis of mild cognitive impairment (MCI). About 10–15% of people with this diagnosis will go on to develop dementia each year.

Rate of progression

The speed at which dementia worsens varies. There are differences between the different dementias – Alzheimer's disease seems to have the slowest progression on average – but much of the variation is from person to person. A wide range of factors influence how quickly someone's dementia will progress, including age – people who develop symptoms before 65 often have a faster progression.

Evidence also suggests that a person's genes play a role, as does someone's overall physical health. People with poorly controlled heart conditions or diabetes, those who have had several strokes, or those who have repeated infections, are all likely to have a faster



deterioration. There is some evidence that keeping active and involved can help a person with dementia retain abilities for longer. Regular physical exercise seems to slow the rate of decline.

Some of these factors affect the underlying disease processes in the brain, while others do not but still help with dementia symptoms. People supporting someone with dementia should help them to stay active – physically, mentally and socially.

The person with dementia should also try to eat healthily, get enough sleep, take medications as advised and not smoke or drink too much alcohol. It is also important for the person to keep a careful eye on underlying health conditions. A sudden change in the person's abilities or behaviour could indicate a physical or psychological health problem or an infection.

Early ('mild') stage

Alzheimer's disease usually begins with very minor changes in the person's abilities or behaviour. At the time, signs can often be mistakenly attributed to stress or bereavement or, in older people, to the normal process of ageing. The loss of short-term memory is a common early symptom. The person will have difficulty recalling things that happened recently and with learning new information. Someone with Alzheimer's may:

- · Mislay items around the house;
- Forget recent conversations or events;
- Struggle to find the right word in conversation or lose the thread of what is being said;
- Become slower at grasping new ideas, become confused or lose track of the day or date;
- Have problems judging distance or seeing objects in three dimensions (for example, when navigating stairs or parking the car) and;
- If you are caring for someone with Alzheimer's disease, there's a lot you can do in the early stages to help them maintain their independence. It may be tempting to do things for them, but they are more likely to retain their sense of self-worth and independence if they are given the chance to do things for

themselves, with support if necessary. Focus on what the person can do, rather than what they cannot. Explore how things can be achieved in a different way.

The person may also become anxious, irritable or depressed. They may experience distress over their failure to manage tasks and may need some reassurance. If this is the case, talk to them and give them as much emotional support as you can.

Middle ('moderate') stage

As Alzheimer's disease progresses, the changes become more marked. The person will need more support to help them manage their day-to-day life. They may need frequent reminders or help to eat, wash, dress and use the toilet. They are likely to become increasingly forgetful – particularly of names – and may sometimes repeat the same question or sentence. They may also fail to recognise people or confuse them with others.

"There is good evidence that, by the time most people develop any symptoms of dementia, the underlying disease has been causing damage to their brain for years."

Some people at this stage become very easily upset, angry or aggressive – perhaps because they are feeling frustrated or because they misinterpret what is happening – or they may lose their confidence and need a lot more support or reassurance.

Other symptoms may include: becoming confused about where they are, or walking off and becoming lost; muddling up time and getting up at night; behaving in ways that may seem unusual, such as going outside in their nightclothes; becoming very agitated or unknowingly behaving in socially inappropriate ways.

Changes in behaviour tend to be most common from the middle stage of dementia onwards – and are one of the most challenging aspects of dementia for carers.

Late ('severe') stage

At this stage, the person with Alzheimer's will need even more help and will gradually become totally dependent on others for nursing care. Loss of memory may become very pronounced, with the person unable to recognise familiar objects, surroundings or even those closest to them, although there may be sudden flashes of recognition. The person may also become increasingly weak. They may start to shuffle or walk unsteadily, eventually spending more time in bed or a wheelchair. Other symptoms may include:

- · Difficulty eating or swallowing;
- Considerable weight loss, or eating too much and putting on weight;
- Continence losing control of their bladder and sometimes their bowels and;
- Gradual loss of speech.

The person may become restless, distressed or aggressive, especially if they feel threatened in some way. Angry outbursts may occur during close personal care, usually because the person does not understand what is happening. Those caring for the person should try not to take this personally – the person is not being deliberately aggressive. It is also important to consider that the person may be experiencing pain which they cannot express verbally.

Although the person may seem to have little understanding of speech, and may not recognise those around them, they may still respond to affection and to being talked to in a calm, soothing voice. They may also enjoy scents, music or stroking a pet.

On average, people with Alzheimer's disease live for eight to ten years after their symptoms begin. However, life expectancy does vary considerably depending on how old the person is and other factors as mentioned above. The length of time that someone with Alzheimer's can expect to live for, also depends on whether they were diagnosed early on or later in the course of the disease.

Alzheimer's Society Tel: +44 (0)330 333 0804 press@alzheimers.org.uk www.alzheimers.org.uk www.twitter.com/alzheimerssoc

Tackling cognitive decline in Alzheimer's disease

Ai-Ling Lin PhD, of The Lin Brain Lab talks about the reversal of cognitive decline in Alzheimer's disease with comprehensive and personalised nutrition

Izheimer's disease (AD) represents the most common cause of dementia, accounting for 60% to 80% of all dementia cases. There are currently only a few interventions that have been approved for the treatment of AD, but none have shown a clear effect on disease progression. Between 2002 and 2012, 99.6% of clinical trials on AD failed, showing the highest failure rates of any disease area. In the last 14 years, no new drugs have been released and existing drugs only stabilise symptoms temporarily in some patients, but do not slow progression of the disease. One of the major contributors for the failure is to focus on the wrong target. Until now, companies have mostly gone after the same target – amyloid-beta (Aβ) proteins that form aggregates or plaques in the brain of AD patients. This has led some to question whether treating AD with a single target-based approach is an optimal one.

Accumulating evidence shows that decades before the aggregation of Aβ, cognitively normal individuals had developed metabolic deficits, including significantly reduced brain glucose utilisation. Failure to maintain brain metabolism has been shown to lead to neuronal death, brain volume shrinkage, and ultimately, dementia. Therefore, interventions that are able to restore brain metabolism would be critical to preserve cognitive functions. In particular, therapies that target on



multiple metabolic networks, rather than a single target-based approach, may be potentially more effective for the treatment of cognitive decline due to AD.

MEND

In a recent exciting study, Dr. Dale Bredesen (Buck Institute, CA, USA) demonstrated that cognitive decline due to AD is reversible using comprehensive and personalised nutritional interventions (Bredesen, 2014). The report described a therapeutic programme that involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilised this program include patients with memory loss associated with AD, amnestic mild cognitive impairment, or subjective cognitive impairment. Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3 to 6 months, with the one failure being a patient with very late stage AD. Six of the patients have had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Take one case as an example - a 67-year-old woman presented with 2 years of progressive memory loss. She held a demanding job that involved preparing analytical reports and traveling widely, but found herself no longer able to analyse data or prepare the reports, and therefore was forced to consider quitting her job. She noted that when she would read, by the time she reached the bottom of a page she would have to start at the

top once again, since she was unable to remember the material she had just read. She was no longer able to remember numbers, and had to write down even 4-digit numbers to remember them. She also began to have trouble navigating on the road: even on familiar roads, she would become lost trying to figure out where to enter or exit the road. She also noticed that she would mix up the names of her pets, and forget where the light switches were in her home of years.

She enrolled in the MEND program with the following therapeutic protocols:

- Eliminated all simple carbohydrates, leading to a weight loss of 20 pounds;
- Eliminated gluten and processed food from her diet, and increased vegetables, fruits, and non-farmed fish;
- Began yoga to reduce stress;
- Began to meditate for 20 minutes twice per day to reduce stress;
- Took melatonin 0.5mg po qhs;
- Increased her sleep from 4-5 hours per night, to 7-8 hours per night;
- Took methylcobalamin 1mg each day;
- Took vitamin D3 2000IU each day;
- Took fish oil 2000mg each day;
- Took CoQ10 200mg each day;
- Optimised oral hygiene using an electric flosser and electric toothbrush;

- Fasted for a minimum of 12 hours between dinner and breakfast, and for a minimum of 3 hours between dinner and bedtime;
- Exercised for a minimum of 30 minutes, 4-6 days per week.

The MEND programme has helped her restored systematic metabolism, including the brains. After 3 months she noted that all of her symptoms had abated: she was able to navigate without problems, remember telephone numbers without difficulty, prepare reports and do all of her work without difficulty, read and retain information, and, overall, she became asymptomatic. She noted that her memory was now better than it had been in many years. Two and a half years later, she remained asymptomatic and continued to work fulltime. Similarly, in another 8 patients, improvements were sustained; even after 2 and a half years follow-up, the patients still showed sustained and marked improvements.

The results suggest that at least early in the course, cognitive decline is driven in large part by metabolic processes. With comprehensive and personalised nutrition, memory loss in patients with early phase of AD, may be reversed, and improvement sustained, with the therapeutic program such as MEND. Given the failure of monotherapeutics in AD to date, the results raise the possibility that MEND might be a future solution for restoring cognitive functions and preventing the onset of AD.

As mentioned in our previous reports, brain metabolic function changes can be early detected using non-invasive neuroimaging. The combination of neuroimaging technology and personalised nutritional interventions could be a powerful strategy to prevent AD in the future. To achieve these innovative and paradigm-shifted treatments compared to the monotherapeutics (e.g., with single-targeted drugs), there is an urgent need to increase funding for epidemiological and clinical studies, focused on the impact of metabolic dysfunction in relation to progression of AD. With awareness in society as a whole (researchers, governments, and general population), it is our hope that the risk of AD can be reduced and the onset of AD will ultimately be prevented.

Reference:

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Ai-Ling Lin, PhD Assistant Professor

The Lin Brain Lab Sanders-Brown Centre of Aging Department of Pharmacology and Nutritional Sciences and Department of Biomedical Engineering University of Kentucky Tel: +18593236671 ailing.lin@uky.edu https://.med.uky.edu/users/ali245

Malaria kills over 1000 people a day – technology and transparency offer the solutions

Peter Sherratt, executive chairman of AMF explains how novel ideas are being applied to a well-tested intervention in the battle against malaria

The fight against malaria follows a similar pattern to many human struggles against the seemingly insurmountable. Before Mount Everest was climbed repeated attempts were beaten back, the summit remained in clear sight, every year progress was made. Technology – the portable oxygen tank – finally solved it.

Malaria has many similarities. Death rates are coming down, eradication seems achievable, but we are still a long way from eradication and progress has slowed. Even on conservative estimates well over 400,000 people die every year, most of them children, and over 200 million become ill. It is the world's no.1 killer of pregnant women⁽¹⁾.

Malaria remains one of the world's greatest health problems

These are staggering levels for a preventable disease. It is as if, annually, every person in Germany, France, Italy and Switzerland became ill, and three quarters of Luxembourgians died. Should we respond differently because this happens in sub-Saharan Africa? AMF and a fast-growing community of 'effective altruists' think not.

Huge strides have been made. Twenty years ago, the numbers dying were far higher. But in the last few years the pace of eradication has slowed, even stalled – along with funding to fight the disease – leaving us with numbers that are totally unacceptable.

The burden of malaria goes well beyond the loss, pain and misery. The costs of health services to diagnose it, drugs to treat it, lost days at work, long lasting lethargy – all drag down levels of economic activity in the poorest countries of the world. For those who want to make the world a better place, preventing malaria is one of the most effective ways to start. At AMF we want to help reduce malaria from its current plateau, to very low levels, then eradication.

How easy is it to prevent?

Malaria is easier to prevent than most diseases, since it is transmitted by anopheles mosquitoes feeding on humans. And these particular mosquitoes feed between dusk and dawn, typically 10pm to 2am. After many randomised control trials (RCTs) over the last 20 years, it is clear that the best and most effective way to prevent malaria is sleeping under an insecticide treated bed net. It protects people, but also crucially kills anopheles mosquitoes. This is why it is far more effective to provide universal coverage, where everyone at risk receives a net, rather than distribute nets just to children and pregnant women.

Still, millions at risk do not sleep under a bed net

We estimate that more than 250 million people sleep at risk because they can't afford to buy a net. Yet providing them with a net is not expensive – they cost around \$2 each when bought in bulk. A typical fully loaded cost, including all distribution and monitoring, is about \$3.30. So, saving a life is shockingly cheap – which is why the independent charity evaluator GiveWell argues that funding nets through AMF is the single most effective altruistic intervention. The main barrier to reaching the summit of malaria eradication is funding.

Eradication beaten back by the mosquito

The second barrier is the incredible mosquito. Each time a new insecticide has been developed, the

mosquito fights back by developing resistance. It is now beginning to do this with the class of insecticide used in bed nets – pyethroids. If we let this develop, resistant mosquitoes are likely to become dominant through natural selection, threatening the use of nets that are currently so effective.

One way to fight this is through indoor residual spraying (IRS), where a variety of insecticides are sprayed on surfaces to help kill mosquitoes. Unfortunately, IRS is far more expensive than using bed nets, so exacerbates the funding constraints.

So how do we reignite attempts to drive down malaria?

The key lies in technology and transparency.

Technology

Getting nets to the people who need them is a significant operational challenge given the countries in which malaria is a problem. 90% of malaria cases are in sub-Saharan Africa. However, technology can now help solve this. We now use technology to radically improve analysis of net needs, in distribution management and in post-distribution monitoring. All help ensure distributions are carried out effectively and the impact of each net is maximised. To deal with the threat of insecticide resistance we are trying out a new type of net, which includes a second safe chemical, a 'synergist' which prevents the mosquito using its defence mechanisms against the pyrethroid insecticide. We are trialling the synergist PBO (piperonyl butoxide) for the first time at scale by providing 6 million PBO nets in Uganda, a country suffering badly from increasing numbers of insecticide resistant mosquitoes.

To truly discover whether this new net works, an RCT is being conducted across half of the country, led by the Liverpool School of Tropical Medicine. We and many others are hopeful it will provide the evidence needed that there is an important new tool in the fight against insecticide resistance.

Transparency

Transparency, we believe, is the key to increasing the



Peter Sherratt, Executive Chairman of Against Malaria Foundation (AMF)

funding available. Donors can now follow where the specific nets they fund are distributed, giving them confidence that their funds make a difference. We are getting ever closer to true 'end to end' transparency between funder and delivery, as the location of every person who needs a net can be collected using smart phones and GPS mapping, and each funder can see exactly what has happened through every link in the delivery chain. Using these and other elements of transparency through fundraising, the number of people who are in the 'against malaria community' continues to grow sharply.

So very low levels of malaria that are fundamental, lifechanging and life-saving are in sight. The last push to the summit – the ideal of eradication – is the hardest, but by applying technology to well tested solutions, encouraging funding through better transparency, we can get there.

1 Annual WHO Malaria Report, December 2016

Peter Sherratt Executive Chairman

Against Malaria Foundation (AMF) psherratt@againstmalaria.com www.AgainstMalaria.com/NetDelivery www.twitter.com/AgainstMalaria

Malaria Drug Resistance: Evolving and Moving in the Mekong Region

Professor of Chemistry at Portland State University, David H Peyton. PhD turns the spotlight on malaria drug resistance in the Mekong region

Recent news has come to light about malaria drug resistance. From the Thailand/Cambodia/Vietnam region comes the report that a particularly worrisome strain of Plasmodium falciparum malaria has moved into Vietnam from the Pailin region in Western Cambodia (Imwong M, Hien TT, Thuy-Nhien NT, Dondorp AM, White NJ. Spread of a single multidrug resistant malaria parasite lineage (PfPailin) in Vietnam. The Lancet Infectious Diseases. 2017 Oct;17(10):1022–3).

"This is a time of conflicting views regarding malaria. Some people see the great progress that we have made. This is true: Perhaps one-fourth of the deaths occur per-year as they did fifteen years ago. Still, we need to keep the pressure on this disease..."

A New York Times editorial by Christopher Plowe provides an intelligent perspective on this report (Plowe C. Taking the Battle Against Malaria to the Mekong - The New York Times. New York Times. 2017 Sep 26;1-5). This PfPailin, and its related strains, have the dominate "C580Y" mutation in the PfKelch gene of the malaria parasite that we now know to leads to resistance to artemisinin drugs, which have become the cornerstone of current (and now the best) combination therapies (artemisinin-based combination therapeutic drugs are known as ACTs) for malaria across the globe. This particular PfPailin-lineage is



particularly worrying, because it also harbors resistance to the artemisininpartner drug, piperaquine, which has been used extensively in this region as dihydroartemisinin-piperaquine.

More sophisticated ways of implementing the use of even combination therapies in the field can be envisioned (Nguyen TD, Olliaro P, Dondorp AM, Baird JK, Lam HM, Farrar J, et al. Optimum population-level use of artemisinin combination therapies: a modelling study. The Lancet Global Health. 2015 Dec; 3 (12): e758–66), but may not be easy to implement from policy and implementation perspectives.

Others have even suggested using 'triple-combinations' of an artemisinin drug with two 'partner drugs', to

protect the artemisinin drug against the evolution of even more resistance. But the problem here is that most of the proposed 'partner drugs' have already been in use, had so malaria has developed resistance against them. So, these 'triple' drugs may work for a while, but their long-term use may be doubtful. There are also potential side effects from each of the drugs, and these may be cumulative (although reports so far are hopeful in at least some cases).

Resistant strains

So, what to do about the migration of artemisinin-resistant malaria parasites? In his New York Times editorial cited above, Christopher Plowe suggests that the endgame must be to eliminate the parasites from the Mekong region. Indeed, this must be



the strategy for the long-term elimination from each region – then (total) eradication of malaria from humans. Any other strategy will ultimately become a strategy of losing one drug, then another, as the parasites evolve resistance over and over.

Drug resistance is a problem for humans as we treat ourselves against all sorts of infectious diseases – not just malaria – as we have been doing on a large-scale for well over half a century. We are facing these challenges in the cases of bacterial infections such as MRSA (methicillin-resistant staphylococcus aureus), and extensively drugresistant mycobacterium tuberculosis (XDR-TB). Carbapenem-resistant enterobacteriaceae (CRE) are extremely concerning class of drug-resistant bacteria.

For reasons that we probably still don't fully understand, the Mekong region is a place where drug resistance in malaria has happened multiple times. It happened with chloroquine, and then moved across Asia into Africa – leading to tragic consequences over the last few decades. It is now happening again with the artemisinin-based combination therapeutic drugs (ACTs). If we just try to contain malaria, it will happen to us. Will we have the resolve to take charge of the situation?

The answer to that question will become evident, but probably not for a few years. As with all facets of global health, the scope is large, the investment will need to be substantial, but most of all, the commitment will need to be unrelenting without significant interruptions, and maintained across national boundaries. Failure is as close as the border of India.

Once the parasites breach that border, it is not difficult to envision their movement quickly through India, and then across into Africa. That would change the situation badly against us. These commitments will need to be sustained irrespective of who is in power in those countries touched by the parasites directly, as well as by the rest of us who will surely continue to need to help finance and maintain the efforts. This won't end in the Mekong region, but the Mekong region cannot be neglected.

"Drug resistance is a problem for humans as we treat ourselves against all sorts of infectious diseases – not just malaria – as we have been doing on a large-scale for well over half a century."

This is a time of conflicting views regarding malaria. Some people see the great progress that we have made. This is true: Perhaps one-fourth of the deaths occur per-year as they did fifteen years ago. Still, we need to keep the pressure on this disease, from research to implementation, or the disease will come back. That is the way parasites are; parasites grow quickly and they evolve.



David H Peyton. PhD Professor of Chemistry Portland State University Tel: +1 503 725 3875 peytond@pdx.edu https://www.pdx.edu/chemistry/profile/ dr-david-h-peyton www.twitter.com/dmi_doc

Effective prevention and control of infectious diseases

David Partridge from the British Infection Association provides a comprehensive overview of effective infection prevention and control in the UK today

n 1967, US surgeon-general William Stewart proclaimed, "It is time to close the book on infectious diseases. The war against pestilence is over." 50 years later, healthcare associated infection is estimated to cost the NHS £1 billion per year. What Stewart underestimated was the extraordinary ability of microbes to adapt to their environment and the power of natural selection to ensure that favourable genetic traits evolve and are propagated. With an acceptance that we cannot simply develop new drugs to obliterate any pathogen, the speciality of 'infection prevention and control' has become our front-line defence.

"When infection control risks are present, healthcare facilities must resist the transfer of relevant organisms between patients, staff and the environment but this must be balanced against a need to ensure that the patient does not have their care or mental well-being unnecessarily compromised."

Effective infection prevention and control relies on:

- Identification of an infection risk, either human or environmental;
- Understanding the mode by which that infection may be transmitted to patients and;
- Implementation of interventions to remove the risk or interrupt transmission.

MRSA

To illustrate this, we can reflect on our successful efforts to reduce the burden of Meticillin Resistant Staphylococcus aureus (MRSA) with bacteraemia rates in England and Wales falling by 82% since 2007. For MRSA, risk identification was facilitated by predictable epidemiology and easy, accurate screening tests and management by interventions such as enhanced cleaning, antibiotic stewardship, alcohol hand gels and barrier nursing plus the possibility of eradication therapy for affected patients, and alternative treatment options for those with established infection. Equally vital was public recognition of the problem and consequent political pressure for action which ensured that appropriate resources were dedicated to tackling it.

The same focus is now required on other, more formidable foes. Carbapenemase producing Enterobacteriaceae (CPE) are resistant to nearly all current antibiotics and have emerged rapidly over the past decade, such that over 2500 such organisms were referred to the Public Health England in 2016. CPE and similarly resistant germs threaten to reverse the huge medical advances that have been supported by antibacterial therapy, not least in ensuring the safety of surgery and of anti-cancer chemotherapy.

Other organisms, such as Middle East respiratory syndrome coronavirus have the capacity to result in high mortality outbreaks if imported and then unrecognised and not contained. More familiar viral infections such as norovirus and influenza still close countless hospital wards each winter.

Diagnostics

Diagnostic laboratory provision has a major bearing on control of infection and the best model for the UK is currently the subject of debate. NHS Improvement's suggested hub and spoke model of pathology services has recently been published with the £200 million carrot from Lord Carter's report on healthcare efficiency, but any real savings need to be built on the foundation of effective transport and IT links between laboratory and bedside.
HEALTH & SOCIAL CARE

Without these fundamentals, diagnostic delay and resultant suboptimal decision-making is likely to result in inappropriate resource use or breakdown of infection control strategies. Point of care testing with molecular diagnostic devices can provide rapid results for organisms such as MRSA and influenza. These tests currently cost more than existing laboratory-based methods but the benefits of more timely results may mitigate some of the problems related to off-site laboratory provision as an increased repertoire of tests becomes available.

When infection control risks are present, healthcare facilities must resist the transfer of relevant organisms between patients, staff and the environment but this must be balanced against a need to ensure that the patient does not have their care or mental well-being unnecessarily compromised. This is a particular challenge in community healthcare where the facility is also the patient's home.

Comforts such as carpeted floors have long been eliminated from hospitals due to their potential to harbour infection, but their removal from residential care is much more contentious. Infections related to medical devices, especially urinary catheters, are a major burden in both hospital and community.

Smart materials may be employed in both patient devices and the environment. Surfaces which resist the development of biofilms (slime encased microbial communities), may coat orthopaedic implants or protect against infection of intravenous lines and urinary catheters. On a wider scale, high contact point surfaces in the hospital environment such as commodes and toilet door handles should be designed to resist contamination or to provide some indication that they have a significant level of organic soiling, such that cleaning time can be targeted more effectively.

NHS resources

In addition to the human misery caused by infection control threats, they and the measures introduced to prevent them have an enormous operational and financial impact on the NHS. Added to this, our era of budget restraint mandates that we attempt to reduce this drain



David Partridge, Communications secretary

on scant resource. The challenge for policy makers and infection prevention and control providers is identifying interventions which achieve greatest benefit for each pound spent. This task is complicated by the fact that, like other safety disciplines, the obvious outcomes tend to be failures as it is rarely possible to measure infections prevented as they haven't happened!

During the West African Ebola outbreak in 2014-15, trusts put significant resource into education, policy development, diagnostic strategies and isolation facilities. As a country we were lucky – only 1 case was diagnosed in the UK and this was identified relatively promptly with no secondary infections. Was the money and time spent on preparedness wasted? Clearly not, as a different throw of the dice could have had catastrophic consequences without it and the work will serve us well should another similar threat emerge in the near future. Investment in infection prevention and control therefore must be resolutely defended when there are so many competing priorities.

David Partridge

Consultant Microbiologist and Infection Control Doctor Honorary Senior Clinical Lecturer

Florey Institute for Host-Pathogen Interaction, University of Sheffield

Communications Secretary

British Infection Association Tel: +44 (0)1565 632 982 david.partridge@sth.nhs.uk www.britishinfection.org www.twitter.com/biainfection

Maintaining high standards of infection prevention and control

Elaine Ross, board member of the Infection Prevention Society (IPS) details the key issues around infection prevention and control (IPC) in the UK today

By way of an introduction, infection prevention and control (IPC) covers both the hospital and the community environment, Elaine Ross, board member of the Infection Prevention Society (IPS) explains. She says that infection prevention and control (IPC) should take place wherever care is being delivered, often in health and social care settings. Ross then expands this point in her own words.

"This will cover things from hand hygiene, cleanliness of the environment as well as encouraging personal hygiene and responsibility and careful antibiotic prescribing. We should also be undertaking surveillance, which looks for the types of infections that are going to cause a threat and helps us to design our services appropriately."

It is of course important that high standards are maintained when it comes to cleaning hospitals, despite pressures on tight budgets and growing workloads. Ross is keen to share her thoughts on this important point.

"We cannot underestimate the importance of the environment and the part it plays in infection prevention and control (IPC). People cared for in an environment where they might touch a surface that has been contaminated by microorganisms for example vulnerable people being cared for in hospitals are much more likely to contract an infection.

"It is therefore really important that hospitals and other settings where care is delivered are kept as clean as possible, because we are dealing with vulnerable people. Numerous studies have been made where you can link somebody's infection to a contaminated environment, whether that is equipment or the room itself."



Elaine Ross, board member of the Infection Prevention Society (IPS)

Concerning the main issues today facing teams working in infection prevention and control, in both health and social care, Ross points out that it comes down to having appropriate levels of qualified specialists.

"We need to invest in ongoing education around infection prevention and control (IPC) because the areas we are dealing with are evolving, including the environment and organisms. The nature of healthcare is changing and as such, Infection Prevention Society (IPS) believes that we need to adapt, but we need people in the infection prevention and control teams to have specialist knowledge around infection prevention and control (IPC)."

Infections and healthcare

Ross also reveals the main policy challenges around infection control in the UK and is keen to tell us that there have been massive gains made in tackling healthcare associated infections particularly methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile (C. difficile) over the past 10 years.

HEALTH & SOCIAL CARE



"Infection Prevention and Control teams are now being asked to tackle the infections in blood streams such as E. coli, which we should rightly do, to tackle infections that may not occur in hospitals, but in community settings. What we see in hospitals is the end-result of a community infection and particularly concerning urinary tract infections (UTIs).

"The nature of healthcare is changing and as such, Infection Prevention Society (IPS) believes that we need to adapt, but we need people to have access to specialist knowledge around infection prevention and control (IPC)."

"It's therefore very important to educate the community on how to avoid urinary tract infections in the first place, plus when and how to seek help so that they get assistance before it becomes a bloodstream infection (BSI) and sepsis – which can kill."

In closing, Ross underlines what needs to be done to prevent infections occurring in the future, stressing

that surveillance needs to be pursued and points to a greater number of antibiotic resistant infections occurring.

"If we don't look for them, then we don't know how to tackle the cause of them. Another key aspect of IPS' work is to help educate the public and ensure they can best protect themselves against infection, through simple steps such as thorough handwashing. They can do that outside of the hospital environment – and they can help with those who work in hospitals as well."

Elaine Ross Board member

Infection Prevention Society (IPS) ips@fitwise.co.uk www.ips.uk.net www.twitter.com/IPS_Infection

The unrealised benefits of an ATP cleaning verification system

An ATP cleaning verification system can help ensure cleaning is thorough and effective, saving money and lives in healthcare settings

he financial impact of poor cleaning is huge, yet the delivery of this vital underpinning service is not measured at all. By contrast, in almost all other aspects of healthcare, a multitude of diagnostic tests are performed to monitor and diagnose the conditions to aide recovery, prevent infections and cure the problem. There are many cost effective benefits to be gained across the hospital from the adoption of simple objective measurement of cleaning efficiency and delivery of service.

Cleaning is a fundamental preventative principle of good hygiene, as promoted by campaigns such as WHO's 'Clean Your Hands' initiative, but it does not stop there. The recognition that healthcare associated infections (HCAIs) are preventable has driven many different interventions that have resulted in a decrease in MSRA and C. Diff infections since 2008. Over 15 years ago it was proven that effective cleaning had a cost benefit of £56,000 per ward, per annum (excluding the cost of lost bed days and additional domestic and maintenance staff). The concern for increasing antimicrobial resistance means that cleaning practices need to be more vigilant and effective to prevent the spread of infection.

Cleaning costs the NHS £725m per annum, but research shows that only 40% of hospital cleaning policies are delivered in practice, resulting in the potential wastage of more than £400m. The NHS Productivity Review 2016 showed that a small improvement in cleaning practices alone would save £93m.

The cost of failure is high. A single infection is estimated to cost £5,000- \pounds 10,000. The National Patient Safety Association states that there are more than 200,000 slip injuries per annum, resulting in 26 deaths. It estimates that the average trust spends £92,000 per annum on these types of injuries.

Most hospitals rely on a subjective visual assessment of cleanliness, which is not fit for purpose and only detects gross lapses of practice. Visual assessment gives a misleading overestimate of cleaning that undermines infection control strategies.

The National Institute of Health Research (NIH) recognises that the NHS places greater reliance on visual assessment of surface cleanliness. However, reliance on observational evidence in judging cleaning efficacy is subjective and may be of questionable validity [...] the use of ATP bioluminescence can provide this, giving an instant indication of total surface contamination and importantly, an objective assessment of cleanliness. ATP detects invisible contamination and tells us that the surface has been cleaned.

The complex design of endoscopes makes them very hard to clean and



studies have shown that more than 30% are not adequately cleaned. In sterile services, the cleaning process is measured by an inadequate protein test where a single-minded focus on the potential unrealised hazards from prion proteins is driving an impractical, expensive, in situ, non-specific protein detection method; in total disregard for the more immediate and real biological hazards, that are quicker and easier to measure, as well as giving a broader reassurance.

The use of ATP bioluminescence for cleaning verification is well established and comes highly recommended in support of the fight against HCAIs. The test is also recognised by the CDC in USA and is written into a standard for cleaning in Denmark and Sweden. The test is simple and easy to use giving a numerical result in 15 seconds. ATP bioluminescence is a simple rapid



method for measuring organic soil. It requires a small handheld instrument and an all-in-one sample collection and testing device.

Earlier adopters, such as North Tees and Hartlepool NHS Foundation Trust have shown a consistent and marked improvement in cleanliness and reductions in infection rates since its introduction in 2008. The results have shown a more than 20% improvement in pass rates and a large reduction in fail scores to fewer than 5%, with a corresponding decrease of 35% in C. difficile cases, as well as a 39% reduction in infections per 10,000 occupied bed days. Monitoring officers, independent from nursing and environmental services staff, are assigned to act as project champions for individual facilities, reporting to departmental managers, wherever poor cleaning was discovered and where corrective action is required. Monthly reports are circulated for cross-functional team meetings of nursing, facilities and infection control staff. This allows for open discussions on all cleaning and maintenance related issues and stimulates actions for improvement.

The benefits of the ATP cleaning verification system include a dramatic improvement in hospital cleanliness, optimised cleaning performance and personnel training, increased productivity commitment and moral of cleaning staff and reduced infections rates.

Southport and Ormskirk NHS Trust have been using the ATP technology for more than 5 years, for several applications and departments from medical equipment library, ITU, IP&U, domestic services, planned care, catering and operating theatres. It is also used for hand hygiene training and compliance monitoring. Andrew Chambers explained: "We also use Hygiena ATP monitoring when we may have had an incidence of VRE, for example. After a clean, the area might look clean but a number of spot ATP tests could show that the area is, in fact, not clean."

"ATP gives you a clean hospital," said Val Hulme, Team Leader Domestic Services). "When you're doing a deep clean the staff know they are going to be tested, but they do everything to a very high standard now. ATP has helped us to achieve that. When you have a number – like the ATP machine gives you – it's more objective than subjective. You can't argue with it. ATP makes the staff competitive. They all want to score five or below, or ideally zero."

Regular objective monitoring of cleaning increases compliance of cleaning policies from 40% to 82%. This decreases contamination levels, reduces infection rates, maximises the use and value of existing resources thus saving time, money and lives.



Martin Easter General Manager Hygiena International Ltd Tel: +44 1923 818821 contactus@hygiena.com www.hygiena.com @HygienaInt

























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Living with lung disease in the UK

The British Lung Foundation's research findings are explored here on lung disease in the UK and their 'battle for breath' campaign

The British Lung Foundation's statistics on lung disease in the UK were compiled as part of their Respiratory Health of the Nation project by teams at St George's University of London, Nottingham University and Imperial College London.

Surveys of the general population suggest that approximately 12.7 million people in the UK (approximately 1 in 5) have a history of asthma, COPD or another longstanding respiratory illness. Half of these (about 6.5 million people) report taking prescribed medication for lung disease in the last year.

Estimates based on general practice records suggest that 8 million people have been diagnosed with asthma, 1.2 million with COPD, and over 150,000 with interstitial lung diseases (pulmonary fibrosis or sarcoidosis), with numbers generally similar for males and females.

From GP records, an estimated 86,000 people in the UK have ever been diagnosed with lung cancer, and over 5,000 (mainly men) have ever been diagnosed with mesothelioma.

Estimates based on general practice records suggest that in 2012 there were about 160,000 new cases of asthma, with numbers slightly higher among females than males, and over 110,000 people who developed COPD, with more males than females. There were about 10,000 new cases of pulmonary fibrosis and 4,500 of sarcoidosis.

According to GP statistics there are over 32,000 new cases of lung cancer and over 2,000 new cases of mesothelioma annually. However, these are likely to underestimate the true incidence of cancer, because the diagnosis may be made in hospital during terminal illness, or post-mortem.

According to cancer registration statistics, during 2011, there were 43,463 new cases of lung cancer (23,770 among males and 19,693 among females), and 2,570 new cases of mesothelioma (2,172 among males and 398 among females).

Lung diseases are one of the leading causes of death in the UK. During 2008-12, lung diseases were responsible for 20% of all deaths in the UK each year. In 2012, there were 114,225 deaths from lung diseases compared to 158,383 from cardiovascular diseases. However, over the 5-year period 2008–12, the proportion of deaths from cardiovascular diseases declined, whereas the proportion due to lung diseases remained constant.

Acute respiratory distress syndrome (ARDS) or shocklung, is a life-threatening condition in which the lungs become severely inflamed. It can be triggered by an infection such as pneumonia. You'll usually need to be admitted to an intensive care unit to be treated.

Over half of the deaths from lung disease in the UK are due to lung cancer and COPD. Both conditions are strongly linked to tobacco smoking, which is also a risk factor for pneumonia, another leading cause of death. In 2012, 6.2% of all UK deaths were due to lung cancer, 5.3% to COPD and 5.1% to pneumonia.

Male and female deaths from lung disease

In 2012, 57,621 males and 56,604 females died from lung disease. Of the 35,419 people who died from lung cancer, 19,333 were males and 16,086 were females. The picture was similar for COPD. Of the 29,776 who died, 15,245 were males and 14,531 were females. However, with pneumonia, of the 28,952 who died, 16,713 were females and 12,239 were males.

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The number of deaths from lung disease varies greatly according to age. The lowest numbers of deaths are among those aged 0–14 years and the highest among those aged over 65.

Children aged 0-14 years

In 2012, there were 2,435 deaths in children aged 0–14 years. Of these, only 262 were due to lung diseases and 102 to cardiovascular disease. Most of deaths (74%) were from other causes.

Of the 262 deaths from lung disease, 115 were the result of perinatal conditions (present in the time immediately before and after birth) and congenital respiratory conditions (present at birth, either inherited or caused by environmental factors). Large numbers of deaths in this age group were caused by pneumonia (58) and acute LRTI (25).

Adults aged 15-64 years

In 2012, in people aged 15-64 years, lung diseases

caused 16% of all deaths among the major disease groups. Cardiovascular disease was responsible for 20%, non-respiratory for 31% and other causes for 33%.

Of the 13,739 deaths from lung disease in this age group, lung cancer caused 8.4%. Deaths from cystic fibrosis were higher in young adults (105 deaths) compared with children (four deaths) and people over 65 (two deaths).

Adults over 65 years

In 2012, 476,510 people over the age of 65 died. Of these, 100,224 died from lung disease – the highest number among all age groups. In people over 65, among major disease groups, lung diseases cause 21% of deaths and cardiovascular disease causes 30% – higher figures than for any other age group

The number of deaths from pneumonia (27,520) and COPD (27,056) were high in this age group compared with others. There were 28,053 deaths from lung

HEALTH & SOCIAL CARE

cancer among people over 65. However, the proportion of lung cancer deaths in this age group (5.9%) is lower than the proportion for young adults (8.4%).

Death rates from lung disease vary across the UK

Death rates are affected by many factors, including:

- Population structure;
- Whether people live in urban or rural settings;
- Standards of living;
- The numbers who smoke;
- Exposure through work to the causes of some lung diseases and;
- Air pollution levels.

Hospital admissions and bed-days due to lung disease

Lung diseases place a heavy burden on health services. One way of attempting to measure the scale of this burden is to calculate the number of hospital admissions and bed-days due to lung disease.

However, it should be noted that these figures are only the tip of the iceberg. Because of the nature of conditions such as asthma and COPD, many patients are managed in the community and are never admitted to hospital because of their lung condition.

In 2011, there were 694,000 hospital admissions for lung diseases in the UK – 8% of all admissions, like cardiovascular disease at 9%. There were 6,120,400 bed-days due to lung disease – 10% of all bed-days, compared to 12% for cardiovascular disease.

Relative risk is used to compare risk in different groups of people. In medical research, all sorts of groups are compared to others to see whether belonging to one group or other puts you at greater risk of something. In this instance, relative risk has been used to see how people's risk of being admitted to hospital for any lung disease varies according to where they live in England, Scotland and Wales. You can find out how these figures <u>were calculated</u>. To find out more, please visit: <u>https://statistics.blf.org.uk/</u><u>lung-disease-uk-big-picture</u>

The battle for breath – the impact of lung disease in the UK

For the past 3 years, the British Lung Foundation has been investigating the impact of lung disease in the UK. Their report, the <u>battle for breath</u>, examines the overall extent and impact of lung disease across the UK. It also takes a closer look at the impact of 15 major lung conditions.

The new report is a valuable resource for policymakers, researchers, health care providers and more. It explains in detail the new findings, and the changes that need to be made to tackle them. You can view the statistics website <u>here</u>.

The key findings were:

- Lung disease is one of the top three killer diseases in the UK;
- 115,000 people a year die from lung disease 1 person every 5 minutes;
- Mortality figures are roughly the same as 10 years ago, yet heart disease has fallen 15%;
- 1 in 5 people in the UK have been diagnosed with a lung disease and;
- Every day, 1,500 new people are diagnosed with a lung disease.

You can read more and see BLF's 6 point action plan for change in the full report, <u>here</u>. ■

British Lung Foundation Tel: +44 (0)3000 030 555 www.blf.org.uk www.twitter.com/lunguk

New biomarkers of lung injury in ARDS

Associate professor at CHU Clermont-Ferrand, Université Clermont Auvergne, Matthieu Jabaudon highlights the hopeful future for ARDS

fter nearly a decade of trials reporting negative results, research in the past few years has provided new hope for the further reduction of mortality from acute respiratory distress syndrome (ARDS), with positive clinical trials of neuromuscular blockade and prone positioning, and exciting new directions in regenerative medicine and molecular phenotyping, among others (see www.openaccessgovernment.org/acu te-respiratory-distress-syndrome-2/34971 and www.openaccessgovernment.org/taura-project/33259).

However, ARDS is still an under recognised and undertreated syndrome, with high mortality and morbidity. Pharmacological approaches of ARDS treatment are limited, with ineffective clinical translation, and further mechanistic explorations are still needed to identify novel biomarkers and to develop innovative therapeutic approaches. Two major features of ARDS contribute to mortality and response to treatment: impaired alveolar fluid clearance (AFC), i.e. altered capacity of the alveolar epithelium to remove edema fluid from distal lung airspaces and phenotypes of severe inflammation.

The receptor for advanced glycation end-products (RAGE) is a transmembrane pattern-recognition receptor of the immunoglobulin superfamily that is constitutively and abundantly expressed by lung alveolar type (AT) I



epithelial cells, among other cell types (e.g. monocytes/macrophages, AT II and endothelial cells).

RAGE stimulation modulates several cellular signalling pathways including phosphorylation cascades and modulations of transcription factors such as NFkB. Advanced glycation end-products (AGEs) are not exclusive ligands for RAGE and other ligands include high-mobility group box 1 protein (HMGB1), calgranulins/S100 proteins, amyloid peptides and macrophage adhesion ligand-1 (MAC-1), among others. There is growing evidence supporting a pivotal role for RAGE in ARDS pathophysiology through the initiation and perpetuation of inflammatory and immune responses, but the roles of RAGE pathway during lung injury and repair remain underexplored to date.

The soluble receptor for advanced glycation end-products (sRAGE, the main soluble isoform of RAGE), consisting of the extracellular domain of RAGE, is a marker of AT I cell injury that is associated with the diagnosis of ARDS in critically ill patients. In particular, a biological phenotype of elevated sRAGE, HMGB1 and S100A12 combined with decreased esRAGE and AGEs was found to distinguish patients with ARDS from those without the syndrome.

In both preclinical and clinical studies, plasma sRAGE was associated with severity in ARDS, as assessed by the partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂) ratio, among other indices of alveolar capillary permeability and of lung injury. It has also been reported, in humans, mice, and in an *ex vivo* model of perfused human lung, that sRAGE

could be a good surrogate for net AFC rates, thus possibly providing a biological tool to monitor the function of the alveolar epithelium. In addition, baseline plasma sRAGE has been independently associated with mortality of ARDS in recent clinical studies.

Furthermore, plasma sRAGE is a good marker of lung imaging patterns in patients with early ARDS, distinguishing patients with focal ARDS from those with non-focal ARDS. New data supporting the notion that AFC may differ between lung imaging-based ARDS phenotypes, as well as mechanistic relationships recently described between RAGE pathway and mechanisms of AFC (such as the expression and function of lung epithelial channels), further suggest a role for RAGE pathway in an underlying endotype of impaired AFC.

Plasma sRAGE could therefore be useful for risk stratification in ARDS, i.e. to identify subgroups of patients who may experience better (or worse) outcome when exposed to an intervention, a condition, or a risk to develop a condition. Although plasma sRAGE was not predictive of ARDS development in an unselected population of all critically ill patients, measurements of plasma isoforms of RAGE could accurately predict the onset of ARDS in specific high-risk populations.

Evidence from trials

Our group has also found that variations in plasma RAGE levels occur shortly after a recruitment manoeuvre (RM, which is a ventilatory intervention used in hypoxemic patients)), and sRAGE is associated with response to RM (i.e., improved oxygenation), in patients with non-focal ARDS. Furthermore, in patients without preexisting lung injury undergoing major abdominal surgery, plasma sRAGE could reflect a lesser degree of epithelial injury when a lung-protective ventilation strategy (including low tidal volume, positive end-expiratory pressure and RM) is used, compared with non-protective ventilation with higher tidal volume and zero end-expiratory pressure.

"...ARDS is still an under recognised and undertreated syndrome, with high mortality and morbidity."

Although sRAGE has never been assessed in clinical trials of biomarkerguided therapies, plasma sRAGE, along with improved oxygenation and attenuated systemic and alveolar inflammation, decreased significantly over 2 days when patients with ARDS were sedated with inhaled sevoflurane, compared to intravenous midazolam, in a prospective monocenter randomised controlled trial from our group. Such findings reinforce the value of sRAGE to monitor therapeutic response in patients with ARDS.

A biomarker may serve different roles: it may provide a diagnosis, assess/monitor severity, assess the response to a therapeutic intervention, predict a disease, and/or identify subgroups of patients with a severe form of a disease associated with an increased probability of death or severe outcome. Most useful biomarkers are those that reflect underlying pathophysiological processes of injury and/or repair.

Therefore, sRAGE has most features of a validated biomarker that could be used in clinical medicine. It has values for ARDS diagnosis, assessment of severity and prognosis, monitoring the response to therapy, and possibly identifying subgroups (or phenotypes) of patients that would benefit from tailored therapy. Rapid point-of-care tests for circulating levels of biomarkers could lead to clinical trials of biomarker-guided, cell-specific ARDS therapy testing epithelial-targeted therapies such as innovative cell-based therapies.

The development and validation of an assay for bedside measurement of sRAGE, or of a panel of biomarkers including sRAGE, is therefore highly desirable. However more validation studies, as well as comparisons with other biomarkers, are warranted to ultimately support the application of personalised or precision medicine in patients with ARDS.



Matthieu Jabaudon Associate professor of medicine, anaesthesiology and critical care CHU Clermont-Ferrand, Université Clermont Auvergne, CNRS UMR 6293, INSERM U1103, GReD Tel: +33 473 750 476 mjabaudon@chu-clermontferrand.fr www.taura-project.com www.gred-clermont.fr www.twitter.com/TAURA_project www.twitter.com/mj0b



The role of education and educational research for a sustainable future

The European Educational Research Association stresses the important role of education in helping people to participate in a democratic society

The problems that afflict humankind today are complex, pervasive, and affect all of us. We have legitimate ambitions for a happier, fairer and more humane life. Addressing these issues represents a major challenge that calls upon the active and collaborative effort of all sectors of society, and a clear awareness of the central role of education.

Education is crucial in helping people at all age levels to participate fully and responsibly in a democratic society, in its discourse and its institutions. Education for such European citizenship, or even better for world citizenship, needs to include the competence to participate and deliberate. The essential elements of education for world citizenship are knowledge, skills and attitudes that help students become fully informed through an open flow of ideas. Students must be empowered to use critical reflection and analysis to evaluate ideas, problems and policies. They need to develop a concern for the welfare of others, the common good, and for the dignity and rights of individuals and minorities.

As advocated by the high-level group appointed by the European Commission and chaired by Pascal Lamy education can help students to develop creativity, innovation and entrepreneurship. We would contend that it also enables young citizens to cope with a range of



other highly important matters that concern European citizens, for example, in responding to the challenges of (youth) unemployment, migration, terrorism, (social) inequalities, and political extremism. These have been listed recently, in the Eurobarometer as central

challenges from the citizens' perspective.

More research is needed on the development of an approach to education that will help students to become active and critical citizens in a challenging and changing world. Educational research is the crucial link between educational reform and the effects envisaged. Only educational reforms that are based on sound educational research can lead to the societal changes we all strive for.

Research into improving education

Educational research in many domains has already demonstrated the capacity to improve student learning and overall development and develop more efficient approaches to a range of specific educational challenges. An example is the area of education for key competencies in Europe. Educational research has shown clear evidence of the essential role of well-being and social and emotional competencies in pupils' school success and success in later life (e.g. employment, active citizenship and personal fulfilment).

The development of The Common European Framework of Reference for Languages is another example that would not have been possible without educational research. This framework encourages the development of educational practices that encourage the emergence of tolerance, respect towards otherness and the valuing of cultural diversity, arguably resulting in the diminishing of realities such as human conflict, racism or xenophobia.

Educational research is not limited to a narrow focus on empirical research and statistical results. It also has the capacity to look behind the statistics and to answer- through qualitative and mixed methods research-questions on key processes in education. Why and under what conditions do some interventions work and others not? Which approaches work best with which students and why? The fact that education in so many different countries has been at the forefront of policy experimentation means that there has been ample opportunity for educational research to learn about system change, and the differences that national contexts make. Thus, educational research results can be of great help in moving towards the introduction of an educational agenda for world citizenship.

Problems in education are often complex, multidimensional and contextualized and to solve such problems interdisciplinary and multidisciplinary approaches are needed. Educational research by its very nature is interdisciplinary and multidisciplinary bringing together insights from disciplines as diverse as politics, economy, psychology, sociology, and anthropology and applying them to educational.

Thus, educational research makes an essential contribution to solving the enormously challenging problems in the areas of educational and social reform. Collaboration between educational research associations in different countries helps tremendously in building teams that are able draw on different modes, methods and traditions to solve the multifaceted challenges facing European education.

The European Educational Research Association is proud to have developed platforms not only for the collaborations between associations, but also between educational researchers from all over the world. Over 2,500 researchers from over 60 countries participate in EERA's annual conference to critically engage with each other's work and build networks for collaborative ventures.

Theo Wubbels Maria Figueiredo Herbert Altrichter Jani Ursin Joe O'Hara Members of the executive board European Educational Research Association (EERA) Tel: +31 6121 95122 T.Wubbels@uu.nl www.eera-ecer.de www.twitter.com/thwubbels

Why should we trust science?

Carlos Moedas, Commissioner for Research, Science and Innovation recently unveiled his thoughts in a speech on the whether we trust science itself

arlos Moedas, Commissioner for Research, Science and Innovation depicted a scene to illustrate exactly what the problem is concerning trusting science today. During his speech on 26th September 2017, Moedas takes us to 1979 and asks us to imagine a man about to sit down and eat a meal in his kitchen, when a time-travelling scientist from the future suddenly appears. The scientist warns the man that to avoid eggs, as they are high in cholesterol and could significantly increase the risk of a heart attack. "Happy with the thought that he has saved the hungry man from future health problems, he is quickly on his way" Moedas goes on to explain, before continuing this compelling story in his own words.

"Then the scientist appears again saying he was wrong, and that actually there are two types of cholesterol, one bad, one good. So, he advises the man to only eat the egg whites, but not the yolks. So, he leaves a second time. But he is back again straight away. This time he tells the hungry man that they are now unsure in the future about how cholesterol in food effects cholesterol in the body. And that the eggs are probably fine to eat!

"This scene shows us exactly what the problem is when it comes to trusting science today. Diverging scientific opinion is confusing. It is overwhelming. It causes the citizen to lose trust in the whole body of evidence. And to lose trust in science."

Modern approach to truth

Moedas then directs the thoughts of his audience to the phrases – "Post-fact", "Post-truth" and "Science skepticism" "Crisis of faith" – all of which simply tell us that the integrity of science is being questioned. Moedas then has some kind words to say about JRC (The European Commission's science and knowledge service) who for over 60 years have created excellent science that supports the European Union.

"Every day, JRC helps my colleagues and I to take the crucial decisions that affect all European citizens. I can truly say that JRC have helped shape European science. And they will be one of our champions when it comes to restoring trust in science in the years to come" Moedas explains.

Vladimir Šucha, played a huge role in defending the reputation of science and encouraging people from all over the world to trust it, Moedas goes on to explain. After decades of public trust in science, a crisis of confidence is facing us due to the fact that the reputation of science itself is in danger, Moedas warns.

Strengthening trust

Moedas then tells his audience that there are three essential steps required to safeguard trust in science. Firstly, to explain the process of science. Secondly, to create places of trust and thirdly – to toughen-up on research integrity.

"Firstly, explain the process of science, Sir Peter Gluckman has consistently made this point. In the digital age, citizens no longer accept being told what to believe. They want to know why they should believe it. Explaining the process of science will do that.

"Scientists must be honest about the limitations of the evidence. They need to show the full picture of what the scientific evidence tells us. To bring us on the journey of how they reach their conclusions. To explain the process so people can reach the conclusions themselves.

"This open process has been at the heart of the new Scientific Advice Mechanism. Or SAM as I call it. SAM has



now produced its first two Opinions – on CO_2 emissions in transport and on cybersecurity. In both cases, the journey to reach the Opinion has been incredibly important. That journey has always involved the JRC as the first stop. And I have to thank Commissioner Navracsics and Vladimir Šucha for this great collaboration.

"But the development of SAM Opinions has also involved the Academies of Europe and the wider scientific community. And in each Opinion, the evidence is clearly present. The process is explained. And every care is taken to ensure scientific accuracy and easy access for non-experts. Even politicians!"

Medical help

Moedas then reveals his pleasure that these first opinions are already having a major impact on policy. The European Commission's new strategy on cybersecurity draws heavily from SAM he tells us, adding that future proposals for CO_2 emissions are using the SAM Opinion as the basis of the impact assessment. Moedas then offers his reflections on explaining the process and also highlights the vital issue of trust concerning science. "I believe that explaining the process is important. But in my view, it is not enough. In the past, when someone was worried about their health, they used to go to the doctor. Now, often, they go online. But often they find a cacophony of confusing advice online. A mixture of fact and fiction.

"Scientists must be honest about the limitations of the evidence. They need to show the full picture of what the scientific evidence tells us. To bring us on the journey of how they reach their conclusions. To explain the process so people can reach the conclusions themselves."

"Increasingly, people are looking for sources that they trust. Like the Mayo Clinic or WebMD. And this trust comes from the scientific basis of the information they find.

"So, we need to develop these places of trust for scientific advice. Where citizens know that science is genuine. Where the process is explained. Where they can check the sources. Where they can access the data



themselves. So, I believe in the future there will be two types of internet. The one you trust and the one you don't."

"So, the reputation of science is threatened now. But I'm an optimist. I believe we must find the opportunity in this crisis of faith. Because it is only when we lean into the problems of today, that we can better create the world of tomorrow."

Carlos Moedas then takes us to his final point, which is that the European Commission need to be tougher where research integrity is concerned. Research integrity goes hand in hand with trusting science he stresses, pointing us to a fitting example of how this happened in 2016 at the Karolinska Institute, Sweden in his own words.

"Karolinska is one of Europe's most prestigious institutes. Its research in biomedicine is renowned, not just here in Europe, but across the globe. Like the Mayo Clinic, it was one of the places of trust where people go for biomedical information. "But then there was a case of scientific misconduct. It concerned one of the institute's researchers, in just one of the 22 departments. But it cast doubt on the whole institution. In a survey of public opinion of universities in Sweden, the Karolinska Institute dropped from 4th place to 12th place. The trust was broken.

"So, we cannot afford to be soft on research integrity. It is that simple. There are many things we are doing right now to make sure of this. Together with ALLEA (ALL European Academies), we have updated the Code of Conduct for research integrity. A single Code for all of Europe. And we have embedded this Code in every single Horizon 2020 grant agreement. Every single research institution needs to apply and enforce the Code."

The reputation of science

Moedas then congratulated the JRC (The European Commission's science and knowledge service) for leading by example, as they are a shining example of an organisation who place research integrity as their central value. They do this by preparing a "statement on scientific



integrity", that applies to all scientific staff, Moedas went on to say before adding his closing remarks.

"So, for citizens to regain their trust in science, we must do three things: Bring citizens on the journey of science; create places of trust and champion research integrity. We are taking a lead in the Commission on all these points. In the JRC. With the Scientific Advice Mechanism. In the standards, we set for all Horizon 2020 projects. But I would like us to go much further in future.

"So, the reputation of science is threatened now. But I'm an optimist. I believe we must find the opportunity in this crisis of faith. Because it is only when we lean into the problems of today, that we can better create the world of tomorrow.

"Let's try use this moment to create a better world of science for all of us, not just the citizens. If we take this opportunity, there are only two outcomes. Either we will succeed at involving citizens; we will evolve, transform and create a science for everyone. This is exactly what I hope to see in the years to come.

"Or, ultimately, we will fail. Losing the trust of the citizens, perhaps for good. Losing what inspires passion in citizens and the strongest link we have between European citizens and European policy. For me, the failure scenario is not an option. Because every time we mistrust science, it undermines the progress of humanity."

To read more about EU4Facts: Evidence for Policy in a post-fact world Session Titled: "Why Should We Trust Science?", please visit: https://ec.europa.eu/commission/commissioners/2014-2019/moedas/announcements/eu4facts-evidence-policy-post-factworld-session-titled-why-should-we-trust-science_en.

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Rubbing shoulders with frictional metamaterials

Julien Scheibert, researcher at CNRS/Ecole Centrale de Lyon explores the fascinating world of frictional metamaterials and their potential

magine a world where pushing a sofa with your friends sitting on it would be easier than pushing it unloaded! Imagine a world where you could adjust the grip of your running shoes just with a jogwheel! Imagine a world with frictionless surfaces, enabling transport of objects with a negligible lateral force! Such extraordinary objects are not just science f(r)iction, they can soon become reality in the rising world of frictional metamaterials!

Metamaterials are materials featuring un-natural capabilities, due to a specific engineering of their micro-structure. In optics, researchers can now create objects that cannot be seen, nearly matching the invisibility cloak of Harry Potter. In acoustics, they can create walls that do not reflect sound, or design cities that would not shake during an earthquake. In mechanics, they can prepare materials that become thicker when stretched. So far, nothing similarly exciting has been achieved in the field of friction.

Friction is recognised to be one of the most challenging topics of mechanical science, because it is a multi-scale (from your tyre, down to its molecular compounds) and multi-physics problem, tightly coupling mechanical, thermal, chemical and electrical phenomena. And indeed, after more than 500 years of investigations, pioneered by Leonardo da Vinci, no one is currently able to predict the resistance to motion of a given interface from first principles. However, I claim here that we currently know enough to design and create surfaces with unprecedented frictional properties.

Understanding friction

To understand how this is possible, let

us have a look at the way real surfaces make contact and rub on one another. The main point is that all surfaces are rough, at a scale or another, be it the atomic roughness of a cleaved crystal.

Thus, true contact between a slider and a track only occurs at the summits of their highest asperities. In such multi-contact interfaces (made of a large number of individual microcontacts between antagonist asperities), true contact typically involves as little as a few percent of the apparent contact area (for instance the few cm² of the feet of your sofa). The area of true contact increases with the weight of the slider, as each existing microcontact grows and new microcontacts are formed. A first remarkably robust feature is that weight and true contact area are found to grow proportionally.

NATURAL surfaces

META surfaces



What happens now when the contact is pushed laterally and driven towards sliding? Each micro-contact will deform, until it ruptures and starts to slip. The second robust result is that the total lateral force necessary to rupture all the micro-contacts (the friction force) is proportional to their overall surface, which is precisely the true contact area. Combining the two above-mentioned results leads to the friction force being proportional to the slider's weight. The proportionality constant is the so-called friction coefficient, which is most often considered sufficient to quantify the frictional properties of a pair of materials in contact.

Instead, it is clearly insufficient to describe the desired situations mentioned in opening, where one would like to have a sofa with various friction coefficients depending on the weight, or to tune reversibly the friction coefficient of his running shoes. Is there a robust surface design strategy to obtain pre-defined, and sometimes otherwise unreachable, frictional properties?

I propose to create rough surfaces by placing individual asperities one by one, each with a well-defined location, shape, material and altitude. Doing so, one will control the exact way the area of true contact grows with the weight, through the involvement of more and more of those asperities. Such a control is perfectly reachable using the current knowledge about how single micro-asperities with simple shapes (spherical for instance) deform under load. By changing the way rough surfaces are usually organised (see figure), we will be able to access new frictional behaviours, much richer than the mere proportionalities Nature can offer.

Despite its simplicity, such a design strategy actually represents a change in paradigm in how we study friction. So far, research in the field of friction has been mainly descriptive. Although this is still the right strategy to tackle important issues about natural systems (earthquakes for instance), our approach to manufactured systems is ready to become more active and creative. We can now start from the desired behaviour and then create the specific meta-surface that will produce it.

One major advantage of this new paradigm is that, technologically speaking, it is not limited to a single length scale. It can be applied using any means of surface manufacturing available, from micro-milling at (sub-) millimetre scales, to lithography techniques (those used for instance in the micro-electronics industry) at micrometre scales, through 3D printing. Producing surfaces with pre-defined frictional properties is very well. But it would be great to switch between different such properties during the lifetime of a given object. And it would be even greater to be able to actually control the friction level in real time, for instance just using a remote control! Analogous programming or tuning capabilities are currently achieved in the growing field of smart materials, for instance with shapechanging airplane wings, by introducing actuators in their structure. So, why wait to import those advances into the field of friction?

In the country of frictional metasurfaces, imagination is in power!



Julien Scheibert Researcher CNRS/Ecole Centrale de Lyon Tel: +33 (0)4 2 18 62 26 julien.scheibert@ec-lyon.fr www.ec-lyon.fr/contacts/julien-scheibert



Investigating how to make more robust the farmed fish immunity

Dr. María Ángeles Esteban's group is searching for new biomarkers involved in fish immunity and welfare in farmed environments

he Fish Immune System Group is a research group that belongs to the University of Murcia. The group leader is Dr Esteban. They investigate the immune system of fish in species of interest for Mediterranean aquaculture. Farmed fish species are teleosts, a group that includes more than 40% of vertebrates, and shows remarkable diversity in immune system structure and function.

Aquaculture is an important source of food, nutrition (special interest is in the fish proteins and micronutrients), income and livelihoods for hundreds of millions of people around the world. At present, aquaculture provides half of all fish for human consumption.

"At present, the use of natural substances and innocuous compounds to improve farmed fish immune system has potential in aquaculture as an alternative to antibiotics and immunoprophylactics."

Aquaculture consists in farming finfish, shellfish and aquatic plants and it is one of the world's fastest growing food sectors. In Europe, aquaculture directly employs more than 85,000 people, mainly in SMEs or micro-enterprises in coastal and rural areas. Furthermore,



A micrograph of European sea bass blood leucocytes phagocytised bacterium

in the EU aquaculture is renowned for its high quality, sustainability and consumer protection standards.



Faculty of Biology. Campus de Espinardo

According to the FAO, it is expected that aquaculture needs to increase 40% in the next 10 years reaching a production of around 30 million of tonnes of products in 2015. To be able of continuing increasing at the expected levels it is important to improve some aspects related to the aquaculture production practices developed at present. Among them are of special interest to control the pollution of the farms to avoid undesired negative impacts (such as environmental impacts, use of chemicals) or to diminish the levels of harmful substances in the aquatic products.

In other words, soon this important activity must be sustainable and has the necessity of the adoption of fish welfare-oriented therapeutic and prophylactic strategies. In this sense the Dr. Esteban group focuses on the study of the fish immune system since different points of view.

Techniques

Firstly, the team is always tuning tech-



Different by-products of breweries tested in fish feed

niques or developing new experimental approaches to expand existing knowledge about the immune system of these animals, with concern in the identification of new biomarkers of disease diagnostic. Fish are considered to be a key model in comparative immunology studies, because it is a representative population of lower vertebrates considered as an essential link to early vertebrate evolution. Furthermore, fish immune system is adapted to the aquatic environment and to the fact that fish are coldblooded vertebrates.

"According to the FAO, it is expected that aquaculture needs to increase 40% in the next 10 years reaching a production of around 30 million of tonnes of products in 2015. To be able of continuing increasing at the expected levels it is important to improve some aspects related to the aquaculture production practices developed at present."

Secondly, of special interest is the fact of working on the selection of varied natural products (such as microalgae, yeasts, medicinal plants or extracts of plants, by-products from different food companies) which, when administered in diet to fish, either as ingredients or simply as additives, can exert beneficial effects on them. In this research, we focus our interest in the stimulation of fish immune status but most of the times, other beneficial effects for example growth promotion, antioxidant activity, improved disease resistance are also found.

At present, the use of natural substances and innocuous compounds to improve farmed fish immune system has potential in aquaculture as an alternative to antibiotics and immunoprophylactics. Moreover, these natural immunostimulants are more environmentally friendly since they are more biodegradable than synthetic molecules and they do not produce drug resistance.

> UNIVERSIDAD DE MURCIA



María Ángeles Esteban

Fish Immune System Group Department of Cell Biology & Histology Faculty of Biology University of Murcia aesteban@um.es http://www.um.es/

The future of additive manufacturing

Jan Torgersen, Brecht Van Hooreweder and Filippo Berto from the Norwegian University of Science and Technology discuss oil and additive manufacturing

ith the increase of the oil price since July 2017, the Norwegian industry seems to recover from previous shortfalls in the revenue from this sector that is most important to the Norwegian economy. Although this is a fortunate development, it also shows how vulnerable the Norwegian market has become from revenues on oil. A reduction in the profitability of its exploration immediately results in a decline of investment projects and a decline of the job market. In the upcoming years, it will be therefore indispensable to diversify industry and explore other sectors while focusing on core technical competences developed over the years of thriving oil production and additive manufacturing.

This core competence lies in the operation of complex components in ever increasing demanding and remote locations that are subject to high corrosion and wear. Safeguarding the compliance of materials to installation and operational conditions is therefore the driver of innovation that led to achievements for which Norwegian companies and research institutions received worldwide recognition.

Industries and research institutions are known for their ability to use of materials cost-effectively, safe and reliable in harsh environments. This involves deep knowledge in materials science that brought up widely used simulation tools, standards and guidelines.



Figure 1. Complex shapes that can be manufactured with AM processes

Preparing for the future

In the event of future losses related to oil sales, the utilisation of this knowledge in other fields will be key. The current developments within the 4th industrial revolution, spearheaded by central European countries, might provide such an opportunity. The aim for completely autonomous production paired with the need for parts that challenge today's production constraints necessitate the use of enabling technologies such as additive manufacturing (AM).

These technologies allow the direct conversion of digital designs into physical products within one production step and completely autonomous avoiding setup time and the use of tools. However, this digital workflow prompts structural property prediction routines that allow safeguarding reliable use of designed components, minimising physical testing by utilising advanced simulation based methods for both fatigue and fracture prediction. This goal is very ambitious since material properties of parts fabricated with respective technologies is challenging.

Material science

There is a clear knowledge gap between material properties, process parameters and design. AM material degradation mechanisms are even less explored, let alone the interaction between material properties and degradation mechanisms. Here, the world-leading knowledge Norwegian institutions can be of outmost importance to advance the field. Yet, Norwegian companies and research institutions had only sparse investments in AM technologies.

The material scientists Prof. Berto and Assoc. Prof Torgersen from the Department of Mechanical and Industrial Engineering at the Norwegian University of Science and Technology recognise this unused potential. They aim to quickly develop leading knowledge on this emerging technology. In this undertaking, they are collaborating



Figure 2. Top surface of an SLM Ti6Al4V sample before (AB) and after (CE) chemical etching

closely with Prof. Brecht van Hooreweder, a world-leading expert in powder-fusion based AM from the Department of Mechanical Engineering at the "Catholic University of Leuven" (KU Leuven).

Prof. Van Hooreweder was recently appointed professor, taking over from Prof. Jean-Pierre Krutch whose group pioneered in a process called selective laser melting (SLM), a process in which successive layers of powder are selectively melted by the interaction of a high energy density laser beam. Molten and re-solidified material forms parts, while non-melted powder remains in place to support the structure. This layer-wise production technique offers some advantages over conventional manufacturing techniques such as high geometrical freedom (see figure 1), short design and manufacturing cycle time and made-to-order components.

Changing processes

Layer-wise production techniques have evolved rapidly in the last 10 years and SLM has changed from a rapid prototyping to an additive manufacturing technique. Consequently, the static and dynamic material properties must be sufficient to meet in service loading and operational requirements. It is well known that the SLM process is characterised by high temperature gradients leading to rapidly solidified, non-equilibrium microstructures. High localised thermal gradients and very short interaction times, which leads to rapid volume changes, causes substantial residual stress development.

Furthermore, the option of changing the process parameters can have a strong influence on the microstructure, density and surface quality. As a result, the mechanical properties of SLM parts can differ substantially from one another and from those produced by conventional techniques. In this respect, it is recognised that the advantages of SLM can only be realised when the mechanical behaviour of the final products is at least able to be matched to conventionally produced components of the same material.

To achieve this, the ability to accurately assess the fatigue life of these advanced geometric complex components will allow for exploring the ultimate design freedom while safeguarding compliance against fracture and fatigue in harsh environments.

Together, the groups of Berto, Torgersen and van Hooreweder aim to combine abilities in AM technologies and structural integrity evaluation, a collaboration that is also supported by one of the leading labs in fatigue design from the University of Sheffield. The partners have established a technical committee has been initiated inside European Structural Integrity Society (ESIS). The popularity of this Technical Committee 15 (TC 15) on the Structural Integrity of Additive Manufactured Components (In-TEAM TC 15) is ever increasing now involving many prestigious university and research centers around the world.

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FBERTO GROUP Mechanical Engineering

Filippo Berto

Chair of mechanics Norwegian University of Science and Technology Tel: +47 73593831 filippo.berto@ntnu.no www.fbertogroup.org

Denmark in Horizon 2020 – size, shape and substance

Niels C. Beier, Deputy Director of the Danish Agency for Science and Higher Education explains Denmark in Horizon 2020 and the framework programme

The world's biggest research and innovation programme is European. Research and innovation are fundamental parts of the European project and identity, and represent a policy area of very wide political and public consensus.

As in a classic fairy tale, the 1950's research endeavours were quite modest in the beginning, but since 1984, Europe has financed almost €200 billion for its everexpanding R&I framework programmes. The current one, Horizon 2020, has a budget of €75 billion, which makes it the largest framework programme to date and in the world. The (at first glance at least) simple 3 pillar structure, combined with massive simplification measures, appears to have been successful in light of the ever-growing number of applicants. Four years in, more than 100,000 applications have been submitted.

Two concepts act as fundamental building blocks for the programme: EXCELLENCE and COLLABORATION. Grants are awarded to the very best projects, and 75 % of all funding goes to projects executed across national boundaries.

"OPEN TO THE WORLD" is the third Horizon 2020 mantra, meaning researchers and innovators from all over the world can take part, and as of now, more than 130 countries can boast about their participation in Horizon 2020. Hopefully, this number will be even larger when we reach the end of 2020.

Small country, bigger participation

"The Kingdom of Denmark has, despite its relatively small size, punched above its weight internationally", so argues the BBC in its country profile. And indeed, 1,282 Danish R&I stakeholders have received €555 million from – or about 2,5 % of – the Horizon 2020 budget,



which thus exceeds Denmark's financial contribution to EU budget.

In line with EU-levels, Danish universities thoroughly dominate the picture and receive 63 % of the EU funding, while the private sector accounts for 27 %.

But one thing is financing. More important are the less tangible benefits: Participants from Denmark in EU funded projects build new, valuable networks across Europe, acquire access to new knowledge, and citation rates are almost 75 % higher than the international

average. In short: The EU framework programme improves Danish R&I.

Keys to success?

Quite obviously, excellent R&I performers are the starting point for successful participation in Horizon 2020. As are effective and ambitious national R&I systems and budgets.

But other ingredients are also required: Counselling for both pre- and post-award stages is free and readily available across Denmark. The Danish National Contact Point, "EuroCenter", employs a team of dedicated specialists to answer questions and arrange information events and materials. And with input from thematic reference groups of R&I representatives, EuroCenter contributes actively to the Danish policy formulation and the promotion of DK viewpoints in the EU.

Potential applicants also enjoy the free services of locally based advisors from the EU-DK Support Network, that work to advise and provide an overview of the sometimes overwhelming EU R&I landscape.

Tying together these and a number of other efforts together, EuroCenter is in the midst of a massive mapping exercise that will pave way for a national strategy on how best to consolidate Danish participation in the framework programmes.

Expectations for the future

Although only midway in Horizon 2020, excitement is already palpable in terms of preparing its successor, the 9th framework programme 2021-2027. And indeed, R&I are expected to be key priorities in a modernised EU budget.

No matter the final figure, Denmark remains adamant that a strong framework programme is essential for the EU to maintain and strengthen its global position and for tackling societal challenges. Maximising impact, supporting the EU's political objectives, maintaining the principle of excellence, boosting innovation, taking simplification to the next level, and ensuring openness and inclusiveness are among Denmark's key priorities.

Another pivotal policy objective is the Danish emphasis on strengthening the coherence between research, innovation and higher education:

Robust links between the three spheres is one of the most – if not the most powerful means of disseminating knowledge to fuel R&I productivity and competitiveness – and vital for the quality of higher education and graduate employability. Knowledge exchange and transfer activities such as education, training and innovation activities for graduate and doctoral students can significantly raise the impact of publicly funded R&I.

Simply put, better coherence is vital to ensure the next generation of excellent researchers, innovators and graduates, and the effective circulation of knowledge for the sake of impact.

In conclusion: Research and innovation remain the keys to Europe's further development as a robust knowledge economy and to solving the grand challenges that we face. At the same time, European collaboration remains a vital contribution of added value to national R&I performance. Denmark will continue to take part and contribute actively to our common efforts in preparing Europe for the future.

Niels C. Beier Deputy Director General

Danish Agency for Science and Higher Education Tel: +45 3544 6200 sfu@ufm.dk https://ufm.dk/en/the-minister-and-the-ministry/organisation/danishagency-for-science-and-higher-education

Research equipment and facilities at Dublin City University are open to the world

Dublin City University is creating an environment where research equipment and state-of-the-art facilities are available for open use

ccess to top quality and state of the art research equipment and facilities is essential to enable scientists to perform unique research at the forefront of knowledge. Research facilities, equipment and instrumentation must also be supported by experienced technical support staff that ensures proper operation, provides user training and guarantees the maintenance of high functioning standards.

Dublin City University has gone a step further by creating a management scaffold around the research facilities that enables campus wide, straight forward access to research equipment and instrumentation, not only by internal users but also by other academic colleagues outside the university, as well as by industry customers and collaborators. This facility ensures that public investment in this regard is maximised, supporting the university in achieving a sustainable financial model for its infrastructure and promoting national and international academic, as well as industry engagement and collaborations.

A comprehensive database currently encompassing more than 80 instruments and steadily growing is currently available via the <u>DCU website</u>. The equipment is distributed mainly across the Glasnevin campus, with high density located in the <u>Nano Research</u> <u>Facility</u> (NRF) and the <u>National Institute</u> <u>of Cellular Biotechnology</u> (NICB). The NRF is a purpose built 3000m² advanced core facility, which allows DCU to integrate and connect current technical capability and equipment within DCU with scientific expertise to offer advanced capabilities in Nanosynthesis, Nanometrology, Micro and Nanofabrication, NanoBioPhotonics, as well as Analytical Characterisation.

"DCU mechanisms for access to the research equipment and infrastructure are transparent and straightforward. For external users, there are several engagement modalities including service provision, collaboration or direct access prior authorised training."

Equally, the facilities available at the NICB offer advance capabilities in proteomics, bioinformatics and mass spectrometry for biological and biopharmaceutical applications.

Available facilities

The NRF comprises modern customdesigned laboratories, a range of specialist support units and equipment, and dedicated technical and administrative staff enabling DCU researchers, visiting research teams and industry to collaborate, enhancing the process of bringing research from concept through to final prototyping and ultimately commercialisation. This facility is key to supporting many long established DCU research centres, such as the <u>National Centre for Sensor</u> <u>Research</u> and the <u>National Centre for</u> <u>Plasma Science and Technology</u>.

This facility is also key for the success of newly emerging centres such as the Fraunhofer Project Centre, the first of its kind in Ireland, which will focus on the development and manufacture of microfluidic "lab-on-a-chip" technologies to enable immediate point of use testing of liquid samples for a wide range of applications, including healthcare and environmental monitoring among many others.

Also, I-Form, another Science Foundation Ireland funded research Centre, will also draw on this infrastructure. The centre will focus on the production of highly advanced and customised 3D printed components for a wide variety of users, from devices for medical applications to the aerospace sector.

The facilities have been consolidated into <u>four large core competencies and</u> <u>include several enhanced specification</u> <u>laboratories</u>:

• Microscopy and Spectroscopy Core Facility;



- · Materials and Surfaces Analysis Core Facility;
- · Material Processing Core Facility and;
- Biological Research Core Facility.

"This facility is also key for the success of newly emerging centres such as the Fraunhofer Project Centre, the first of its kind in Ireland, which will focus on the development and manufacture of microfluidic "labon-a-chip" technologies to enable immediate point of use testing of liquid samples for a wide range of applications, including healthcare and environmental monitoring among many others."

The university also hosts a fully accredited bio resource unit, including SPF capabilities that enables the use of animals for research in a highly controlled and properly regulated

environment. We are also in the process of obtaining accreditation from the relevant Irish authority (HPRA) for a good manufacturing practice (GMP) laboratory, to produce small batches of GMP standard therapeutics. The latest additions to the DCU infrastructure network include 5 state-of-the-art pieces of equipment, which have been acquired with funding from Science foundation Ireland.

DCU mechanisms for access to the research equipment and infrastructure are transparent and straightforward. For external users, there are several engagement modalities including service provision, collaboration or direct access prior authorised training. Many companies have already avail of our facilities, some of them located in the DCU Alpha Campus. Co-located with Dublin City University, DCU ALPHA is a commercial innovation campus that promotes the growth of researchintensive businesses that are creating the technologies and services of tomorrow.

For enquiries or further information please contact: Robbie Sinnot, Manager of DCU Research Infrastructure Unit. Phone: 01 700 6320. Email: robbie.sinnott@dcu.ie



Dr Ana M Terres **Director of Research Support** Dublin City University Tel: +353 700 7011 ana.terres@dcu.ie www.dcu.ie/research/index.shtml www.twitter.com/anamterres

The organisation of the German Research Foundation

The inner workings of the German Research Foundation (DFG) are placed under the spotlight by Open Access Government in this insightful article

The German Research Foundation (DFG) is the selfgoverning organisation for science and research in Germany and serves all branches of science and humanities, along with interdisciplinary research across widespread areas of science. From the very beginning, it has focussed on these areas, ensuring excellence, diversity, and success in research and innovation.

Since then, it has come a long way and currently maintains its primary focus, while enjoying a high degree of both national and international recognition. DFG's membership consists of German research universities, non-research institutions, scientific associations and the Academies of Science and Humanities. The current president of the DFG, Professor Dr. Peter Strohschneider, heads the executive board, and below him exists departments Z, I, II, III, and the executive level.

Their collective main task essentially consists of selecting and considering the best projects submitted by individual researchers at universities and research institutions - on a competitive basis and to then finance these projects. This can become a competitive field as DFG funding guarantees quality-based differentiation in the German research system, while simultaneously giving researchers the means and freedom necessary for successful research. The DFG is thus a cornerstone of Germany's strength as a research location and helps to shape the European Research Area. Furthermore, early career researchers are a high priority for the DFG, providing young researchers throughout their careers with the appropriate support, therefore helping them achieve early independence and successful results so that they can hit the ground running.

Annual meeting

In the same vein, but more recently, a joint press release was supplied by the Alexander von Humboldt Foundation, the German Academic Exchange Service and the German Research Foundation on August 15th, 2017 stating that, "Germany woos young academics working in North America." Germany's academic system offers excellent career prospects for young academics who are currently working abroad in either the US and Canada, and following this, the 17th annual meeting of the German Academic International Network (GAIN) was held in San Francisco during August 2017.

"The German Research Foundation (DFG) is the self-governing organisation for science and research in Germany and serves all branches of science and humanities, along with interdisciplinary research across widespread areas of science."

This is the largest annual conference event outside Europe for academic careers in Germany, and gave over 300 researchers the opportunity to network with around 150 high-ranking German representatives from academia, politics and industry, enabling them to establish contacts and further their career prospects for the future. This goes to show that the presidents of these organisations who hosted the event (including Prof. Strohschneider), truly put into place their ideas as promised, thus pushing boundaries within the research sector.

The meeting aimed to focus on many recent developments in academic policy in Germany, one of which is The Excellence Strategy. Based on the administrative agreement reached by the federal and state governments on 16 June 2016, the DFG and the German Council of Science and Humanities will implement the Excellence Strategy in two funding lines:

 Clusters of Excellence for project-based funding in internationally competitive fields of research at universities or university consortia and;



 Universities of Excellence to strengthen universities as individual institutions or as university consortia in the long-term and further develop their leading international role – based on successful Clusters of Excellence.

In September 2017, the international committee of experts selected 88 draft proposals/full proposals from 195 due by February 21st as clusters of excellence to proceed to the final stage. The proposals will then be reviewed by the DFG in the Spring of 2018, and then reviewed internationally once more in the September 2018. Funding for this will begin on January 1st 2019. Clusters will be funded for 7 years, and even more so; a second 7-year funding period may also be granted providing successful proposal submission and review. This just provides more evidence describing the excellence and widespread opportunities offered by Germany and the DFG itself.

The DFG actively encourages international research cooperation: all its programmes promote cooperation between scientists and academics in Germany with their colleagues abroad. By offering many different opportunities to enable international partners to submit proposals at any time, or any topic, if they satisfy the funding principles, is an amazing opportunity and not one that many other countries would offer.

It places special emphasis on scientific collaboration within the European Research Area which is more important now than ever, in a world where technology is ever growing and cooperation is vital for furthering innovation. There are also specific partner organisations offered in partnership with foreign partner organisations.

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Bacterial Cell Biology

Prof. Dr. Marc Bramkamp explains how the latest science allow for increased understanding of the subcellular organisation of a bacterial cell

hen we think about bacteria, we have small round or rod-shape organisms in mind that dwell as individual, planktonic bacterical cell without any sophisticated internal organisation. This common view was shaped by the fact that research on bacteria was focussing mainly on bacteria studied in test tubes during the last century. Since many biochemical pathways were discovered and analysed in bacteria, or more precisely in isolated bacterial extracts, the subtle feeling manifested that these organisms are nothing more than encapsulated reaction vessels in which biochemical reactions are spatially and temporally not well organised and driven merely by diffusion. However, we are currently in the middle of a revolution that changes the way we see (and understand) bacteria.

Bacteria are not individualists, but actively work together

We have learned that bacteria are by no means individualists, but able to act in concert, actively shape their environment (which in fact is also us), they communicate chemically and they share and distribute labour.

Thus, it is maybe less surprising that these activities are going hand-in-hand with cellular differentiation. This differentiation can occur at a metabolic, or biochemical, level and even on a morphological level. Bacteria might develop into a biofilm full of cell chains or cells may transform in dormant stages, such as spores that lie idle until favourable conditions occur.



Figure 1. Localisation of a polar scaffold protein (DivIVA) in Corynebacterium glutamicum. Captured is a C. glutamicum cell, in which the DivIVA protein has been synthesised as fusion protein with pa-mCherry. Shown are an epi-fluorescence image (left) and a PALM image (right). The scale bar is 1 µm. The cell outline is shown as broken white line. Note the high degree of spatial organisation of DivIVA to cell poles and a midcell position were the cell will divide.

How are nanometre sized proteins organising micrometre sized cells?

For a long time, it was unclear how micrometre sized organisation such as the cell morphology was achieved by action of nanometre scale protein machineries. Better insights were prevented by lack of high resolution imaging techniques. The main bottleneck was the resolution limit of visible light, as used in conventional wide field microscopes. This physical limit allows the precise determination of objects only down to about 200-300 nm. The prototypical bacterial cell is less than 1000 nm in width.

Therefore, spatial information is limited when subcellular localisations of biomolecules, such as protein or nucleic acids are addressed. Furthermore, it needs fluorescent dyes to label individual molecules (proteins or nucleic acids) to allow their visualisation within the dense mixture of material in a cell.

New microscopy techniques are available now

The last two decades have given us new tools that allow microscopic imaging of subcellular structures in bacterial cells. A variety of different fluorescent proteins have been developed that can be used for translational fusions to identify protein localisation. Sophisticated dyes such as photo-switchable proteins can be used elegantly to track protein dynamics in living (bacterial) cells.

New microscopic techniques that circumvent the resolution limit of light also greatly helped in gaining deeper insights into the organisation of cells. My laboratory uses photo-activated localisation microscopy (PALM), a technique that allows unrivalled precision in protein localisation down to 20 nm in cells (Figure 1). We develop and optimise dual colour PALM imaging by combining various fluorophores such as mNeonGreen and photo-activatable-mCherry.

The bacterial plasma membrane is spatially organised in domains

With these modern techniques in the toolbox, my research team tries to answer several central questions in bacterial cell biology. A main topic is the organisation of the bacterial plasma membrane. This phospholipid and protein made cellular envelope is highly dynamic, but we start to appreciate that certain proteins and lipids cluster in defined regions in which they function optimally. Cells have evolved proteins that help to create membrane heterogeneity, to allow the existence of distinct reaction areas in which transport or signalling events are enhanced. Proteins involved in the formation or maintenance of the membrane domains are so-called flotillins, a class of proteins that is conserved from bacteria to man. PALM images show how that the flotillins indeed form distinct cluster in the membrane.

We are further interested how the cell keeps its membrane intact. This is an important aspect since the cell membrane is a classical target of many antimicrobial compounds. We identified a bacterial dynamin that acts in membrane surveillance. Upon membrane rupture, caused by antimicrobial compounds or phages, the bacterial dynamin clusters at the damaged sites and seals the membrane via lipid fusion. These are just two examples were bacteria use proteins that were long thought to be evolutionary achievements of eukaryotic cells.

Bacterial cell wall synthesis is spatially highly organised

Bacterial morphogenesis and cytokinesis is accomplished by highly complex protein machineries that catalyse the synthesis of the bacterial cell wall. The peptidoglycan (or murein) is a unique structure to bacterial cells and therefore a prime target of many potent antibiotics. Although most bacteria have a reasonable simple morphology in being round (cocci) or rods (bacilli), we observe a remarkable difference in the spatial organisation of the cell wall synthesis machineries. Many rod-shaped bacteria position their cell wall synthetic complexes along the lateral axis of the cell. This is true for Gram negative bacteria such as *Escherichia coli*, but also for the Gram-positive organism *Bacillus subtilis*.

Interestingly, actinobacteria, among them the rod-shaped Corynebacteria and Mycobacteria have polar localised cell wall synthesis complexes. Therefore, these species grow from their ends. We have chosen *Corynebacterium glutamicum* as a model organism to understand the spatio-temporal organisation in these cells for some simple reasons. *C. glutamicum* is an important organism in biotechnology and is used to produce amino acids, and other fine chemicals.

Furthermore, C. glutamicum shares its complex, multi-layered cell envelope with known pathogens such as Mycobacterium tuberculosis, the causative agent of TB. Our work revealed that apical cell growth is governed by cytoskeletal hub proteins that couple cell elongation and chromosome organisation. This close interaction between chromosome organisation and elongation growth may be an Achilles heel that hints to new antibiotic targets to combat drug resistant Mycobacteria.

These research topics give a glimpse into how basic research subcellular organisation in bacteria may lead to applied research. There is increasing effort worldwide and within Germany to address the subcellular compartmentalisation of bacterial cells.

Therefore, we are grateful that our

work on spatiotemporal organisation of bacteria is supported by grands from the German Federal Ministry of Education and Research (BMBF BMBF: 031A302 e:Bio-Modul II: 0.6 plus) and the Deutsche Forschungsgemeinschaft (DFG TRR174 & BR2915/6-1).

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LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Prof. Dr. Marc Bramkamp

Ludwig-Maximilians-Universität München, Fakultät Biologie Großhaderner Straße 2-4 82152 Planegg-Martinsried, Germany Tel: +49 (0)89 2180 74611 Fax: +49 (0)89 2180 74621 marc.bramkamp@lmu.de www.bacteriology.bio.lmu.de/ www.twitter.com/BramkampLab

Adaptivity and Digitalisation Enables Learner Centred Learning

A couple of seasoned experts from TU Chemnitz explore digitalisation and individual learning progress, in this informative profile

Digitalisation speeds up all kind of processes and enables new fields of business. To deal with this emerging challenges computer experts are needed. Thereby hardware, software, interface, network as well as process experts have to be educated in short time. A huge variety of education and expertise backgrounds as well as individual learning progress can be managed if the teaching focus is withdrawn from teaching books and drawn to the learner's need. This is called learner centred learning (LCL).

During the last decade e-learning platforms have been introduced to manage the education process for a variety of students, i.e. learners. Technical problems as providing access, secure data and course organisation are implemented pretty well. Thus, actual learning process include direct teaching, blended learning and elearning approaches. Additive instruments introduce collaborated learning approaches and video based tutoring.

However, in many cases the learner uses the e-learning platform as he is used by paper based learning driven by the course teacher. This is due to the simple fact that an e-learning platform by itself does not change the learning process at all.

In our research we developed new evaluation tools for tracking the stakeholder's interest as well as teacher's interests and learner's success. Several e-learning platforms have been evaluated by the SURE evaluation model. Results show clearly that learning progress and the stakeholder's and teacher's interests can be monitored.

Today, evaluation data is collected only once in a longer period of time, e.g. every two study years or less. With our SURE based evaluation, data can be collected as ongoing process. This allows us to use evaluation data to direct and support the learner ongoing and individual. This introduce LCL into modern learning processes.

Furthermore, it has been found that in many cases e-learning platforms are much stronger than the learner's progress. Very often, the learner is not using all available platform features. This is due to lack of information or motivation and some usability issues. LCL has to overcome this problem as well.

Our actual research therefore develops new methods to adapt the learning process to the learners needs. This is based on two ideas:

• **Decoupling:** The actual fact that many students joint one classroom with one teacher at the same time is eliminated. So, students are provided with access to learning information, exercises and tutoring individually. Within such a decoupled environment, the learner works on his own. Learning progress, repetition as well as applications can be managed individually. This eliminates many limits which restricts the learning process unnecessarily. Today, many students have to wait for the next course or exam.

"In our research we developed new evaluation tools for tracking the stakeholder's interest as well as teacher's interests and learner's success. Several e-learning platforms have been evaluated by the SURE evaluation model."

• Adaptation: Adaptation will be reached by combining all data from learners, the learning progress and the learning habits. Based on artificial intelligence methods a tutoring system can be built to guide the learner individually. In particular, we have a proactive tutoring in mind, in order to motivate and activate the learner with respect to his learning progress. The learning platform will automatically adapt the learning material to the individual skills and the personal progress of the learner, for example, additional exercises can be offered or well-structured tests with correct solutions are provided. In most platforms, the learning material is already available, the material is divided into small and feasible portions and exercises are implemented interactively. Adaptation will use this and adds an intelligent, automatically computed combination of learning steps for the learner.



This adaptive LCL approach will be applicable to a huge variety of courses and learners, especially for education in technical areas as digitalisation. Adaptive LCL offers new chances for the learner.

Challenges

• By introducing decoupling and adaptation into the LCL learning process, new challenges come up. Decoupling will lead to new learning processes at universities and schools. Comparable to online academies exam organization will change, e.g. actual group exams will become individual exams. Also, a mixture is possible. In this case, four or six exams are offered per study year instead of one or two. In addition, the business models of universities will have to change also. As long as the number of registered students is the basis for budgets - decoupled learning processes are difficult to handle. Also the import or export of learning modules to learners of other courses or institutes is restricted by such business models. The number of offered modules and participating learners will drive new models.



• Adaptation is also bearing non-technical challenges. Besides building up data bases with knowledge of study programmes and exam options, the individual learning approach must be captured. This will require a new quality of co-operation between the learner and the learning platform. For example, the reason for small non-learning periods can be very important for adequate adaptation. The lack of interest, missing theoretical basic knowledge or just a lack of time will lead to different adaptations. For explorations of this background-information, the learner's cooperation is needed. However, adapted LCL supports typical learning patterns, detected by automatic evaluations of learning processes. Our work on adapted LCL process uses ongoing evaluation information to adapt learning modules, as well as the communication between learner and platform. First case studies show encouraging results overcoming the restrictions pointed out.

By now, it can be stated that decoupling and adaptation can be intro-

duced to LCL. It leads to new learning strategies, which are suitable for the individual learner. Thus, the different individual needs can be covered by automatic adaptation based on ongoing evaluation.

"A huge variety of education and expertise backgrounds as well as individual learning progress can be managed if the teaching focus is withdrawn from teaching books and drawn to the learner's need. This is called learner centred learning (LCL)."

In addition, automatically provided individual coaching supports all kinds of learners with respect to their knowledge, language skills and social background. Application of adapted LCL methods will lead to huge innovation in terms of reduction of study time and study costs and increase the learners' motivation.



Prof. Dr. W. Hardt

Professor Technische Informatik

Dr. habil. Uranchimeg Tudevdagva Assistant Prof. TU Chemnitz Tel: +49 371 531 25550 hardt@cs.tu-chemnitz.de www.tu-chemnitz.de/informatik/index.php.en www.twitter.com/WolframHardt

Challenging the stereotypes in science

Chief Executive of the British Science Association Katherine Mathieson provides a compelling insight into how we can challenge stereotypes in science

Science needs to be taken out of its cultural ghetto. Currently, it's seen as the realm of professionals and experts. But other parts of society – business, politics, art, or sport – are perceived as being there for anyone to own and engage in. But how can we re-examine stereotypes in science?

Like science, these parts of society have experts and professionals. Unlike science, they have a wider community that feels a sense of identity and ownership within them.

These are the people who pick up their paintbrush, guitar or camera at a weekend, or simply enjoy a kickabout. They're the people who vote in elections, bet on big sporting events or invest in stocks and shares.

Generally, we don't have these people in science. There are a growing number of exceptions – campaigners,

pop-science fans – but science is still seen as "that thing that scientists do". I recently spoke to someone with a PhD in physics, who worked as physicist for 20 years but has now moved into what he calls "sociology". Remarkably, he no longer considers himself a scientist. Imagine then the relationship a person without a science background may, or more likely, may not have with science.

The result is that it's under-valued in our culture. When it's not something people feel a part of, science is overlooked in decision-making. Communities keep it at arm's length and don't feel like their voices will be heard, even when it directly affects them. Politicians and business leaders often push it to the side or leave it as a second thought.

Society's biggest challenges and opportunities – pandemics, climate change, cyber-security, food security,



Katherine Mathieson, Chief Executive of British Science Association

healthcare – are all-too-often seen as scientific issues, there to be debated and decided upon by scientists.

The truth is that science belongs to a wider community. Each of these issues requires a partnership with the rest of society – whether that's entrepreneurs, artists, civic leaders, nurses, farmers, policymakers, or the general public.

At the British Science Association, we want to rebrand science. We want it to be seen by all people as something that is a fundamental and inclusive part of our society. Our mission is to support, grow and diversify the community of people who are interested and involved in it; and to strengthen their influence over its direction and place in society.

We continually work with the public, government and business to develop campaigns and initiatives to help us achieve this goal. Our longest standing project is the British Science Festival, which has visited a different city across the country since 1831. The festival is completely free and encompasses science in the broadest sense to ensure there is something for everyone. From theatre performances to brewing our own festival beer, from firework displays to art installations, we show that science spreads through the fabric of society.

We also organise British Science Week, a ten-day celebration of science, technology, engineering the maths. This is more of a grassroots initiative, with events happening all over the UK. These are usually funded by grants and organised entirely by local communities, giving them complete ownership over science, delivering it to the people and communities they know the best.

Run the Solar System

As part of British Science Week, we developed an initiative called Run the Solar System. This is a virtual race from the Sun to Neptune via a free running app, where the solar system is scaled down to a 10 km distance. The app tracks your position using GPS and as you reach the position of each planet, broadcaster and space enthusiast Dallas Campbell commentates a beautiful narrative about the planets, interspersed with original recordings from planetary missions.

This was a hugely successful initiative, engaging a wonderful mixture of people from all corners of the globe, many of whom had never heard of or interacted with the British Science Association before.

The success of Run the Solar System was down to tapping into something that people love: sport, and engaging them in a fun, relaxed way, sparking their imaginations and our human nature to explore and hear stories.

Mixing the physical with the mental meant that astronomical distances of billions of miles, which can seem abstract and untouchable, were felt by the runners. You race past the first 4 planets in a couple of kilometres, but the distance between Saturn and Uranus is a full third of the 10 km distance. Astronomical distances will never be looked at in the same way again by those who took part.

This is the essence of what we want to achieve at the British Science Association. We want people to engage in science and feel a part of it, without fear or alienation. We want it to be fun and fascinating, to be something that people can feel ownership of. It affects all our lives in huge ways, impacting our health, wellbeing, families and the world we live in. We, as an entire global population, deserve to claim science as our own.

Katherine Mathieson Chief Executive

British Science Association Tel: +44 (0)20 7019 4935 katherine.mathieson@britishscienceassociation.org www.britishscienceassociation.org www.twitter.com/BritSciAssoc

Dutch government policy and its social impact

The Netherlands Institute for Social Research (SCP), unveil their fascinating research into the social impact of government policy

he Netherlands Institute for Social Research (SCP), is a Dutch interdepartmental scientific institute and a government agency. SCP carries out independent research and issues recommendations based on that research, both on request and on its own initiative.

SCP also publishes these recommendations in advisory reports aimed at the government, parliament and the heads of government departments. SCP's research reports are also an important source of information and advice for leading professionals and civil servants in the public sector, as well as for scientists and journalists. In addition, SCP staff contribute to the public and scientific debate through articles, lectures and interviews.

During the 1960s, politicians in the Netherlands began to take an increasing interest in the welfare of the population. This heightened interest also created an increased need for information: facts and figures on how people lived, on social trends, and the changes taking place in society.

This development coincided with the increasingly prevalent ideas at that time, about the need to base policy decisions on sound scientific knowledge, and it was from this basis that the Netherlands Institute for Social Research (Sociaal en Cultureel Planbureau, SCP) was founded by Royal Decree on 31 March 1973. The Decree lists the tasks of SCP as being:

- To describe the social and cultural situation in the Netherlands and to map out likely future developments;
- To contribute to the responsible selection of social and cultural policy objectives and resources, and to formulate appropriate alternatives and;

• To evaluate past and current policy, interdepartmental policy.

SCP is one of three policy research institutes in the Netherlands, which began life as 'planning offices'. The oldest, the Netherlands Bureau for Economic Policy Analysis (CPB), focuses on economic trends. The Netherlands Environmental Assessment Agency (PBL) is concerned primarily with spatial development in the Netherlands, as well as the sustainability and quality of the living environment.

The studies and reports for which SCP is responsible cover the policy fields of the following ministries:

- General Affairs (Prime Ministry's Office);
- Foreign Affairs;
- Security and Justice;
- Interior and Kingdom Relations;
- Education, Culture and Science;
- Economic Affairs;
- Infrastructure and the Environment;
- Social Affairs and Employment and;
- Health, Welfare and Sport.

As a scientific institute, the Netherlands Institute for Social Research SCP supplies central government with independent scientific information on the Dutch welfare state. For over 40 years, SCP has been charting developments in the daily lives of the Dutch population:
work, income, health, education, social security, housing, culture, how they spend their time and their opinions on a whole range of subjects. The SCP also shows how government policy does or could influence these aspects.

The institute SCP falls under the formal responsibility of the Minister of Health, Welfare and Sport. Various government departments are involved in the formulation of the Research Programme, and there is also liaison with the fellow research institutes CPB and PBL. SCP also cooperates closely with Statistics Netherlands (CBS).

SCP employs more than 100 staff, most of them scientific researchers (sociologists, political scientists and economists). SCP is led by a board, comprising Professor Kim Putters (general director) and Dr Rob Bijl (deputy director).

Scope of activities

SCP reports regularly in a variety of publications on the living situation of the Dutch population. Among the aspects covered are the health status, education level, labour market participation rate, housing situation, disposable income and leisure time utilisation of various sections of the population such as older people, young people, women, the disabled and members of ethnic minorities. The reports also look at the take-up of government provisions by these groups, and the effects of various government measures on that.

Social and cultural trends

The opinions of the Dutch population on social, ideological and political topics are monitored through SCP's surveys. SCP also monitors the behaviour patterns of the population, by carrying out studies of how the Dutch spend their leisure time, plus their use of amenities and take-up of provisions.

Based on these studies, SCP publishes reports on a wide variety of social themes, such as the division of tasks between men and women, social cohesion, participation in cultural life, safety and information technology.

Public sector

The bulk of government spending in the social and cultural field goes on provisions for education, health care and welfare, social security, the police and judicial apparatus, cultural affairs, training and recreation. SCP carries out important inter-sectoral and comparative research, into the use and costs of this sector.

Policy evaluations

SCP possesses large databases spanning many years. This makes it possible to track both current and longterm trends accurately, and to study their interrelationships. This is of importance for the identification and evaluation of intended and unintended effects of government policy.

"During the 1960s, politicians in the Netherlands began to take an increasing interest in the welfare of the population. This heightened interest also created an increased need for information: facts and figures on how people lived, on social trends, and on the changes taking place in society."

International comparisons

International comparisons form an important part of many SCP-reports. For these comparisons, SCP uses international databases. Most of these reports are made on behalf of the Dutch government or the European Committee. SCP also participates in international research projects on many different subjects. Apart from that, SCP published a comparative analysis of western welfare states, as well as studies on different social security systems in the European Union.

Publications

All SCP research results are in the public domain. All SCP publications, whether research reports or digital publications, such as 'card stacks', are posted on our website <u>www.scp.nl</u>. The website also contains information on SCP itself, as well as on its databases and research questionnaires. Publications may be downloaded there free of charge.

The Netherlands Institute for Social Research (SCP) PO Box 16164 2500 BD The Hague The Netherlands Tel: +31 (0)88 9846 300 info@scp.nl www.scp.nl

Demountable construction enables structural diversity

University of Luxembourg's Prof. Dr.-Ing. Danièle Waldmann-Diederich explains how demountable construction responds to changing structural demands

Buildings are often demolished due to a needed conversion or change of the architectural design, although the supporting structure remains completely undamaged and fully intact. This leads to huge quantities of waste which need to be discharged on mining tips. Thus, the building sector is generating a large amount of CO_2 emissions, resource consumption and waste production. Given the high resource-intensity and CO_2 emissions of the sector, new ecoconstruction approaches are needed.

Demountable construction

Demountable building constructions are defined as structures which allow destruction-free dis- and re-assembly responding to changing structural demands, revitalisation or removal. This could only be reached by designing modular, flexible, adaptable and upgradable structural components with detachable connections. But it is not sufficient to consider only the erection phase of the elements, they must be optimised in terms of materials ageing and energy consumption in an integrated situation within an overall building concept. The idea of developing construction systems which are demountable is not new. Although, many precast structures have been erected in the meantime, the reuse of complete structural elements is still not practiced. The advantages of reuse, with a saving of energy consumption, raw material and CO₂ emissions are obvious.

Furthermore, no waste is produced which is needed to be discharged on building rubble dump. So the question rises why the idea of demountable construction could not been pushed forward until now.

"The current research of INCEEN is driven by the aim to reduce energy and resource use throughout the entire life-cycle of buildings and their components."

The raisons are manifold. One major reason is certainly that this kind of construction needs a change in philosophy: first of all, the architect is limited in his design as he has to align to a given grid. So the development of architectural typologies and adapted constructive principles are necessary to permit the reutilisation of whole elements after one life cycle. Furthermore, these architectural principles should also allow a reuse of the building in case of conversion. Then new deconstruction methods have to be developed: e.g. renders, insulation, floor covers, screeds are fixed to the structure so that an easy disassembly is not anymore possible. Here, new techniques have to be developed which allow after the first live cycle of the building an easy disassembly and cleaning. Another major reason is certainly that after the first life cycle of a building often the information about the load bearing structure and other performance criteria is not any more available. Retracing the information about one single load bearing element with its reinforcement position, grade, diameters, concrete cover and concrete class etc. is difficult. Often the documents of the statics and the structural design are not anymore available.

Furthermore, a condition assessment of these elements must also take place to assess the remaining load bearing capacity. Another major aspect is that no circular economy market is yet installed which would provide schemes and solutions for the deconstruction, transport, condition assessments, temporary storage and reuse of whole structural elements. Thus, the systematic integration of large quantities of elements in new buildings needs new concepts on different levels and a change in the building process without forgetting the client who must accept to invest in a new building which load bearing structure is a conglomerate of old structural elements.

All these aspects are currently addressed in research projects of the Institute of Civil Engineering and Environment (INCEEN), a sub-structure regrouping the civil engineers of the research unit of engineering sciences at the University of Luxembourg. The overarching mission of INCEEN is to solve scientific questions and to develop new scientific and technical methods for sustainable buildings. By doing so, it aims to advance the level of scientific understanding in key-



domains relevant to the next building generation, including modular construction, applying principles of the circular economy. Further INCEEN aims to catalyse interdisciplinary research collaborations in the areas of structural engineering and the environment, as well as contributing to solving sustainability challenges of the built environment sector responsible for a large amount of CO₂ emissions and resource consumption. INCEEN has strong research experience in the design of reinforced/prestressed concrete, steel and composite structures and structural health monitoring.

The current research of INCEEN is driven by the aim to reduce energy and resource use throughout the entire life-cycle of buildings and their components. By showing how buildings can be used as material and component banks, the research projects of INCEEN seeks to trigger a paradigm shift in the construction sector. The research also analyses the possibility of business models based on loaning materials and components to customers. Therefore the applicability of monitoring systems in structural components by internal electronic chips (RFID) which are readable from outside guaranteeing a provision of all relevant information for a reconstruction or reutilisation in future reuses will be developed and tested.

To sum up, the concepts to be developed are based on the investigation of a wide spectrum of factors, taking into account different (often competing) technical, ecological and economic constraints imposed by planning, design, pre-fabrication, on-site operations, in-use consumption and emissions, as well as requirements for refurbishment and demolition/recycling at the end of a building's life-cycle. Understanding sustainable construction as an important component towards the reduction of the total resources-related footprint of a building, it is evident that only an integrated and inter-disciplinary approach to such a multi-objective constrained optimisation problem can be successful.



Prof. Dr.-Ing. Danièle Waldmann-Diederich Head of the Institute of Civil Engineering and Environment

Head of the Laboratory of Solid Structures Faculty of Sciences, Technology and Communication at the University of Luxembourg Tel: +352 46 66 44 5279 daniele.waldmann@uni.lu www.uni.lu

The outermost frontiers of knowledge and scientific progress

The National Science Foundation (NSF) is an agency created in 1950 to further scientific progress, as Open Access Government reveals

The National Science Foundation (NSF) is an independent federal agency created by Congress in 1950 "to promote scientific progress; to advance the national health, prosperity, and welfare; to secure the national defence" according to the organisations website².

The National Science Foundation (NSF) has an annual budget of \$7.5 billion (FY 2017), NSF are the funding source for approximately 24% of all federally supported basic research conducted by America's colleges and universities. In many fields such as computer science, mathematics and the social sciences, NSF is the major source of federal backing.

NSF fulfils their mission chiefly by issuing limited-term grants – currently consisting of about 12,000 new awards each year, with an average duration of three years - to fund specific research proposals that have been judged the most promising by an objective and rigorous merit-review system. Most of these awards go to individuals or small groups of investigators, while others provide funding for research centres, instruments and facilities that allow scientists, engineers and students to work at the outermost frontiers of knowledge.

NSF's goals of discovery, learning, research infrastructure and stewardship all provide an integrated strategy that advances the frontiers of knowledge, cultivates a world-class, broadly inclusive science and engineering workforce and expands the scientific literacy of all citizens, as well as building the nation's research capability through investments in advanced instrumentation and facilities. NSF also strongly supports excellence in science and engineering research and likes to say that they are "where discoveries begin." have won some 223 Nobel Prizes as well as other honours too numerous to list here. These pioneers have included the scientists or teams that have discovered many of the fundamental particles of matter, analysed the cosmic microwaves left over from the earliest epoch of the universe, developed carbon-14 dating of ancient artefacts, decoded the genetics of viruses, and created an entirely new state of matter called a Bose-Einstein condensate for example.

NSF also funds equipment required by scientists and engineers, but is often too expensive for any one group or researcher to afford. Examples of such major research equipment include Antarctic research sites, giant optical and radio telescopes, high-end computer facilities and ultra-high-speed connections, sensitive detectors of very subtle physical phenomena and gravitational wave observatories plus ships for ocean research.

Another crucial element in NSF's mission is support for science and engineering education. The research NSF funds is thoroughly integrated with education, to make sure there will always be plenty of skilled people available to work in new and emerging scientific, engineering and technological fields, as well as sufficient capable teachers to educate the next generation.

No single factor is more important to the economic and intellectual progress of society, and to the enhanced well-being of its citizens, than the continuous acquisition of new knowledge NSF believes and as such, they are proud to be a key player in that process.

Research areas

NSF is divided into the seven directorates that support science and engineering research and education:

During the past few decades, NSF-funded researchers

1. Biological sciences;

- 2. Computer and information science and engineering;
- 3. Engineering;
- 4. Geosciences;
- 5. Mathematical and physical sciences;
- 6. Social, behavioural and economic sciences and;
- 7. Education and human resources.

Every section named above is headed up by an assistant director and each is further subdivided into divisions, such as materials research, ocean sciences as well as behavioural and cognitive sciences. Within NSF's Office of the Director, the Office of Integrative Activities also supports research and researchers and other sections of NSF are committed to activities such as award processing and monitoring, financial management, award processing and monitoring, legal affairs and outreach.

The main research areas of the NSF are summarised below:

Biological Sciences (BIO)

- Biological Infrastructure (DBI);
- Environmental Biology (DEB);
- Emerging Frontiers (EF);
- Integrative Organismal Systems (IOS);
- Molecular and Cellular Biosciences (MCB).

Computer and Information Science and Engineering (CISE)

- Office of Advanced Cyberinfrastructure (OAC);
- · Computing and Communication Foundations (CCF);
- Computer and Network Systems (CNS);
- Information and Intelligent Systems (IIS).

Education and Human Resources (EHR)

• Graduate Education (DGE);

- Research on Learning in Formal and Informal Settings (DRL);
- Undergraduate Education (DUE);
- Human Resource Development (HRD).

Engineering (ENG)

- Chemical, Bioengineering, Environmental and Transport Systems (CBET);
- Civil, Mechanical and Manufacturing Innovation (CMMI);
- Electrical, Communications and Cyber Systems (ECCS);
- Engineering Education and Centers (EEC);
- Emerging Frontiers and Multidisciplinary Activities (EFMA);
- Industrial Innovation and Partnerships (IIP).

Environmental Research and Education (ERE) Geosciences (GEO)

- Atmospheric and Geospace Sciences (AGS);
- Earth Sciences (EAR);
- Ocean Sciences (OCE);
- Office of Polar Programs (OPP).

Integrative Activities (OIA)

International Science and Engineering (OISE)

Mathematical and Physical Sciences (MPS)

- Astronomical Sciences (AST);
- Chemistry (CHE);
- Materials Research (DMR);
- Mathematical Sciences (DMS);
- Physics (PHY);
- Office of Multidisciplinary Activities (OMA).

Social, Behavioural and Economic Sciences (SBE)

- Behavioural and Cognitive Sciences (BCS);
- National Center for Science and Engineering Statistics (NCSES);
- Social and Economic Sciences (SES);
- SBE Office of Multidisciplinary Activities (SMA).

Chemistry (CHE) focus

One of the above areas is explored here, as we take a closer look at the Chemistry (CHE) division, within Mathematical & Physical Sciences (MPS). This section of the NSF envisions:

- Being a global leader in transforming chemical innovation and discovery, whilst also advancing chemistry education, literacy plus America's competitive edge.
- Encouraging chemists to lead multi-disciplinary efforts that expand humanity's knowledge and address both short- and long-term societal problems;
- To be a major voice in the communication of the value of chemistry to the public and;
- Being comprised of outstanding staff, all of whom are dedicated to the vitality of the chemistry field.

In addition, the Division of Chemistry (CHE) strongly supports innovative research in chemical sciences, integrated with education, through strategic investment in developing a globally engaged U.S. chemistry workforce that reflects America's diversity.

Reflecting NSF's values, CHE believes in:

- The importance of fundamental scientific research for society's benefit;
- · Empowering future generations in science;
- Maintaining the highest standards of both integrity and ethical behaviour;
- Fairness, openness and clear communication as well as;

 The diversity of America's scientific workforce and broadening participation in all CHE activities, at every level.

Biological Sciences (BIO)

Another division of the NSF worth looking at is the Directorate for Biological Sciences (BIO), which sets out to enable discoveries for understanding life. BIO-supported research advances the frontiers of biological knowledge, increases understanding of complex systems, and provides a theoretical basis for original research in many other disciplines of science.

The Directorate supports research to advance understanding of the principles and mechanisms governing life. Their research extends across systems that encompass biological molecules, cells, tissues, organisms, organs, populations, communities, and ecosystems up to and including the global biosphere.

On NSF's website, we learn more about the Directorate's important work. "Comprehensive concepts that bridge and unify the diverse areas of biology include complexity, robustness, communication, resilience, adaptability and cooperation. Achieving a coherent understanding of the complex biological web of interactions that is life is a major challenge of the future.

"This challenge will require that knowledge about the structure and dynamics of individual biological units, networks, sub-systems and systems be compiled and connected from the molecular to the global level and across scales of time and space. Integral to all activities across the directorate is a commitment to integrate research and education, broaden participation, and promote international partnerships"¹.

The Directorate of Biological Sciences is organised into a number of divisions, which you can learn more about at: <u>https://www.nsf.gov/dir/index.jsp?org=BIO</u>, but they are listed in summary below:

- The Division of Biological Infrastructure (DBI);
- The Division of Environmental Biology (DEB);
- The Division of Integrative Organismal Systems (IOS);
- The Division of Molecular and Cellular Biosciences (MCB) and;

• The Emerging Frontiers (EF) Division.

In recent news, we discover that NSF funds the future of materials science, as evidenced in news that eight new 2017 Materials Research Science and Engineering Centre (MRSEC) awards will drive cutting-edge science and engineering in the future. Totalling a staggering \$145 million, these six-year grants aim to support innovative work in materials science and help train the next generation of materials researchers.

"These awards are representative of the incredibly broad, highly multidisciplinary research portfolio spanning all Division of Materials Research priority areas," Linda Sapochak, director of the NSF Division of Materials Research (DMR) says. "These centres will forge new research frontiers through team-based development of novel materials that are relevant to future high-tech applications" she adds.

The centres address a national priority: fostering collaboration among universities, national laboratories, industry and international scientific organisations to address complex fundamental research challenges. Such challenges include extreme miniaturisation, atomically thin "paper" materials that self-fold into functional structures, and control over the assembly and reconfiguration of nano particles connected at the molecular scale.

We read that the MRSEC awards will have far-reaching impact on fields ranging from telecommunications and clean energy, to quantum information sciences. "Research outcomes from these awards could revolutionise computer memory and wearable medical devices," Sean L. Jones, DMR's deputy division director comments.

"The MRSEC centres provide leadership for the country concerning new materials and new materials phenomena addressing national needs, including sustainability and innovation," Sapochak says. "We are especially excited about the international, industrial and national laboratories' collaborations that will give junior researchers in the centres experiences valuable to their lives as scientists and engineers, and the incredibly diverse and highly skilled personnel participation."

Of the eight awards, three are for new centres: The University of Texas at Austin, the University of Illinois

Urbana-Champaign plus the University of Washington. The other five awards support centres that have stood out for successful, collaborative and ongoing research. You can read more about the 2017 MRSEC awards at: <u>https://www.nsf.gov/news/news_summ.jsp?cntn_id=24</u> <u>3377&org=NSF&from=news</u>

Funding

One final point to highlight is that when it comes to the all-important subject of funding, it is certainly true to say that NSF funds research and education in most of science and engineering fields. It does this diligently through grants, and cooperative agreements to no less than 2,000 colleges, universities, K-12 school systems, businesses and other research organisations all over America. NSF accounts for about one-fourth of federal support to academic institutions concerning basic research needs.

According to NSF's website, NSF receives around 40,000 proposals each year for research, education and training projects, of which approximately 11,000 are funded. In addition, NSF also receives several thousand applications for graduate and postdoctoral fellowships.

In addition, it is well worth noting in closing that the agency operates no laboratories itself, but does fully support national research centres, user facilities, certain oceanographic vessels and Antarctic research stations. NSF also supports co-operative research between universities and industry, as well as US participation in international scientific and engineering efforts, plus educational activities at every academic level.

1 https://nsf.gov/about/

2 https://www.nsf.gov/dir/index.jsp?org=BIO

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Extreme muscle plasticity or novel myogenic precursors in skeletal muscle

Graciela A. Unguez, Professor of Biology at New Mexico State University sheds light on skeletal muscle in vertebrate animals

Skeletal muscle is one of the most abundant tissues in vertebrate animals. Skeletal muscle is also very diverse, as it is comprised of muscle cell types that differ in their biochemical, morphological and functional properties. Skeletal muscle heterogeneity is further emphasised by the variable sensitivity of distinct muscle cell phenotypes to exercise, nerve-dependent electrical activation patterns, denervation, regenerative capacity following injury or disease and aging.

In the last four decades, studies have also elucidated that muscle heterogeneity is manifested during embryonic development when distinct classes of myogenic stem cells, or satellite cells, associated with different muscle groups are involved in muscular patterning, growth and regeneration. Moreover, postnatal muscle cells demonstrate a great ability to respond to changes in environmental signals, by altering their gene expression and adapt to new physiological demands. Here, the robust heterogeneity of vertebrate skeletal muscle cells and their plasticity is examined from the perspective of some teleosts species that possess highly specialised non-contractile myogenic tissues.

Intermittent muscle contractility exchanged for continuous electrogenesis

In electric fishes from South America (Gymnotiforms) and Africa (Mormyrids),

some skeletal muscle fibers exhibit an extreme phenotypicplasticity by losing their contractility during normal development to give rise to electrocytes, the specialised cells that generate electricity and make up the electric organ (EO) (Bennett, 1971). The cells that make the EOs are not only novel in their morphology, gene expression, and functional specialisation but also unique in that they retain some phenotypic properties of their mature muscle precursors.

Currently, it is thought that one key event in evolution of electric fish was the origin of the EO from the complete transformation of striated muscle during development wherein partly or fully differentiated muscle fibers disassemble their contractile apparatus, undergo striking changes in shape and size, and become innervated by a separate population of spinal motoneurons known as electromotoneurons (Bennett, 1971).

Whether electrocytes arise from a population of embryonic cells separate from that of muscle is not known. Histological data from an ontogenetic study by Kirschbaum and Schwassman (2008) suggested the presence of a germinative zone located below the hypaxial muscle region that contains electrogenic precursor for electrocytes. These electrogenic precursors appeared to differentiate without going through a true muscle fiber stage. The authors interpreted these findings to support the existence of unique electrocyte precursors, they referred to as "electroblasts".

A presumed electroblast-dependent origin of electrocytes during early postnatal development is not fully recapitulated during regeneration in adult *Sternopygus. macrurus* (Weber et al., 2013). Specifically, following tail amputation, Pax-7 positive satellite cells associated with both intact electrocytes and muscle fibers proximal to the cut site begin to replicate and contribute to the formation of fully striated muscle fibers.

The muscle fibers located most centrally and expressing fast myosin heavy chain (MHC) differentiate into myotubes, that contain fully mature sarcomeres, fuse and then proceed to disassemble the striated complexes while also downregulating many of the sarcomeric genes to give rise to the non-contractile electrocytes (Unguez and Zakon, 1998a).

Hence, the cellular processes of electrocyte regeneration in the adult cannot be fully compared with those observed during postnatal development. Firstly, although distinct populations of Pax-7 positive cells are associated with mature muscle fibers and electrocytes in adult tails (Weber et al., 2013), Pax-7 immunolabeling was not carried out in the postnatal developmental study. Future studies should determine whether "electrob-

lasts" in early postnatal electric fish express Pax-7, fuse to generate the multinucleated electrocytes (Unguez and Zakon, 1998a; Weber et al., 2013), and transiently express fast-MHC. These data would be first in demonstrating the existence of Pax-7 positive stem cells that contribute to the development and regeneration of a highly specialised non-contractile myogenic cell type in vertebrates.

Although much about the origin of the electric organ from muscle remains unknown, such understanding is a reachable goal in the near future. Recognising and elucidating the cellular and molecular programs that give rise to the non-contractile current-producing cells of the electric organ will not only expand the breadth of the known heterogeneity and plasticity of striated muscle, but will be key to unravelling the evolution of myogenic electric organs.

Intermittent muscle contractility exchanged for thermogenesis

Additional cases of fish skeletal muscles being modified for non-muscular functions also include those in some groups of oceanic fish, commonly known as billfish. In billfish, extraocular muscles (EOMs) transform into a heat-generating organ located beneath the brain and close to the eyes (Block, 1986). This thermogenic organ is composed of modified EOM cells (heater cells) that are structurally distinct from all other types of skeletal muscle.

In the superior rectus muscle of billfish, myofibrils and contractile filaments are virtually absent, multiple nuclei are centrally located, and the cell is packed with mitochondria and smooth membranes (Block, 1986). That thermogenic cells derive from striated muscle precursors is evident by the presence of isolated patches of disarrayed myofilaments. Heater cells of the adult organs also express contractile proteins associated with fasttwitch fibers (Block, 1986; Tullis and Block, 1997).

For example, two key SR proteins associated with calcium transport, the SR Ca2 – ATPase and the SR Ca2 release channel link heater cells to fast-twitch muscle fibers (Block et al., 1994; Tullis and Block, 1991). The high degree of similarity between heater cells and fast-twitch muscle fibers would favour development from myoblasts that give rise to fast-twitch fibers. Together, data from characterisation of electrocytes in S. macrurus and heater cells from billfish demonstrate that muscle tissue has a high degree of functional plasticity. Interestingly, the incidence of a higher degree of plasticity among fast muscle fibers phenotypes may be an inherent characteristic maintained across species.

It is not known how or when the heater phenotype develops in the extraocular muscles. Heater cells could develop directly from myoblasts without first passing through a contractile stage. Alternatively, mature contractile muscle fibers could be directly transformed into heater cells. Unfortunately, for both electric fish and billfish, breeding in captivity is extremely challenging, and it is difficult to obtain larval and juvenile animals, which precludes direct examination of the developmental trajectory of muscle fibers into electric organ and heater cells.

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Graciela A. Unguez, PhD Professor of Biology New Mexico State University Tel: (575) 646 7963 gunguez@nmsu.edu

Sexual selection theory and research

Dr Mollie Manier from the Department of Biological Sciences at The George Washington University lifts the lid on the arena of sexual selection theory

harles Darwin developed sexual selection theory to explain why the peacock should possess such splendid tail feathers, despite what must be a disadvantage against predators. He proposed that the male's showy display defies its evolutionary disadvantage in the arena of natural selection by winning in the arena of sexual selection, where success is defined not by survival of the fittest but by acquiring the most mates. Here, females find the largest and showiest male ornaments the most attractive, and these males leave sexy sons with the best features. However, female preference is insatiable; males evolve larger and showier ornaments to satisfy the demanding female taste, leading to tail feathers disproportionate to the poor male that must carry them.

What Darwin did not discuss is that sexual selection continues after mating has occurred, in the form of sperm competition and cryptic female choice. Here, the arena of sexual selection becomes the female reproductive tract, and males evolve complex sperm that battle each other for fertilisations, assisted by seminal fluid proteins that modify female behaviour, morphology, and physiology to favour the male that carried them. However, the female here is not simply a passive vessel for ejaculates. She provides an environment that can nurture as well as kill.



Darwin proposed that the male peacock's showy display defies its evolutionary disadvantage in the arena of natural selection by winning in the arena of sexual selection. Here success is defined not by survival of the fittest but by acquiring the most mates

Within the female reproductive tract of the diminutive *Drosophila* fruit fly, an epic battle unfolds whose evolutionary outcome has produced the longest sperm known to science – the 5.8cm long sperm of *D. bifurca*. Evidence from a distant relative, *D. melanogaster*, suggests that these giant sperm are selected for by the equally impressive female sperm storage organ, the seminal receptacle (SR), which can reach 8cm in *D. bifurca*. In *D. melanogaster*, which itself sports sperm a mere 1.8mm long, the female's SR selects for longer sperm, but only when the SR itself is longer. Scientists believe this dynamic may have led to the coevolution of SR length and sperm length across the Drosophila lineage, in which species whose males have longer sperm also have females with longer sperm storage organs.

This coevolutionary dynamic may have also been fuelled by a genetic correlation between sperm length and SR length, an evolutionary requirement of the Fisherian runaway process thought to drive evolution of extreme male ornaments like the peacock's tail. The extreme nature of sperm length as well as its genetic correlation with the female's post-mating "preference" for longer sperm (in the form of extremely long sperm storage organs), suggests to scientists that a similar runaway process drove the evolution of giant sperm and sperm storage organs in the tiny fly.

Improving reproductive ability

But how do longer sperm do better? And how does the female reproductive tract facilitate this advantage? Genetic tools have allowed us to transform ordinary flies into ones that express a jellyfish green fluorescent protein (GFP) or a coral red fluorescent protein (RFP) in sperm heads, allowing us to precisely track and count sperm from different males within the female reproductive tract. Females mated first to a GFP male and later to an RFP male (or vice versa) can be frozen at different time points after mating, and sperm can be counted in all regions of the reproductive tract, providing snap shots in time of sperm displacement and cryptic female choice.

In *D. melanogaster*, approximately 1200-1600 sperm are ejaculated into the main chamber of the female reproductive tract, called the bursa or uterus. From there, sperm immediately begin to enter one of three sperm storage organs: the SR or paired mushroom-shaped spermathecae. Within the spermathecae, sperm stored from a previous male get to stay where they are, and the stores

are simply topped off with sperm from the second male. In the SR, however, the first male's sperm are physically displaced into the bursa by incoming sperm from the second male. This process continues until the proportion of first-male and second-male sperm in the SR is equal to that in the bursa, at which point an equilibrium has been reached. The displaced first-male sperm and unstored second-male sperm in the bursa are then ejected by the female, ending the displacement process.

The sperm remaining in the SR and spermathecae now constitute the "fertilisation set", the pool of sperm now available for fertilisation. When females begin laying eggs, they will use sperm from one of their three sperm storage organs and can bias fertilisation to favour the first or second male's sperm in either the SR or spermathecae.

She can also bias sperm use to favour one type of sperm storage organ over the other. Because fertilisation in insects is very difficult to observe directly, we estimate sperm use bias using mathematical models based on numbers of first- and second-male sperm remaining in the different sperm storage organs and paternity success in offspring.

We have applied this approach to discover that some species favour the SR for fertilisations, while others use both the SR and spermathecae equally. Moreover, sperm use bias may favour the first or second male depending on the sperm storage organ. This pattern of bias across the female reproductive tract allows females to favour one male over another by switching the sperm storage organ from which she draws sperm for fertilisation.

The female reproductive tract of Drosophila represents the greatest morphological diversity yet documented within an evolutionary lineage, with SR lengths varying by a factor of 200, from 400 µm in *D. pseudoobscura* to 80,000 µm in D. bifurca. The species richness of Drosophila (approximately 2500 species) and its genetic resources (approximately 25 species with sequenced genomes) adds to the power of this modest fly to help us understand how form affects function, to test models of male-female coevolution, and to explore the relationship between microevolutionary process and macroevolutionary pattern in traits that vary in the simplest way possible, along only a single dimension.



Dr Mollie Manier

Department of Biological Sciences, The George Washington University Tel: +1 202 994 0126 manier@gwu.edu

The natural world – Why field studies matter

Thomas L. Fleischner, Ph. D, Executive Director of the Natural History Institute discusses the critical importance of direct engagement with the natural world

ost major leaps in understanding the complex workings of the natural world have been discerned by naturalists, in the field, engaged in careful observation of plants, animals, and their interactions in natural settings. Experimental manipulations, laboratory-based inquiries, and theoretical models often yield exciting and important information. But frequently, such studies represent attempts to sharpen insights that came initially from the direct observation and description at the core of natural history - "the practice of intentional, focused attentiveness to the morethan-human world, guided by honesty and accuracy."

The unifying theory of modern biological science - evolution through natural selection – was famously developed independently by two astute field naturalists, Charles Darwin and Alfred Russel Wallace. Only direct field study of real organisms in real landscapes offered a clear enough view into the phenomena of nature for this unifying theory to be revealed. As the renowned ecologist Paul Dayton has noted: "There is simply no substitute for actually experiencing nature, to see, smell, and listen to the integrated pattern that nature offers an open mind."

Today, in the grip of climate change and the sixth mass extinction, our need for understanding how nature



works is more urgent than ever. But the startling fact is that fewer and fewer biologists have the opportunity to develop the skills of field biology and natural history. Over the past few decades, academic field studies have diminished on both sides of the Atlantic, as institutions and funding agencies have privileged theory over empirical field studies.

The American conservationist Aldo Leopold lamented the loss of field studies in biology education more than 70 years ago – and the situation has only grown more critical. Biologists with the skills to identify plants and animals have become the exception rather than the rule. How can we recognise human impacts on biodiversity if we can't recognise the species that comprise it?

I've had the honour of directing a

working group – representing a broad diversity of academic institutions and other NGOs – focused on the decline of field studies in biology education. This project was supported by the U.S. National Science Foundation, and coordinated through the Natural History Institute.

The benefits of study

The value of field study is vast: field experiences not only contribute to better science, but also create better scientists, citizens, and people, thereby substantially affecting the human-nature relationships that form the basis for sustainability.

Observing nature is the touchstone for understanding how life works, and thus field studies serve quite literally as the grounding for the biological sciences. At the same time, field experiences often force observers to

question and to re-evaluate their assumptions about how the natural world operates.

Accordingly, field observations can lead to re-calibration of research strategies for exploring biological phenomena, explanations for which are often subsequently tested using information collected by observational approaches in the field. Field observations reveal patterns, and these often lead to development of formal hypotheses. Theoretical models are only as solid as the field natural history foundations on which they rest.

Field-based education is particularly critical to the biological sciences, providing fundamental training for key disciplines such as behaviour, ecology, evolution, systematics, and conservation science. Field studies underlie the conceptual and technical bases for these disciplines and are required to ensure their healthy growth.

Now, as society struggles to respond appropriately to losses of biodiversity, range shifts due to climate change, and emergence of new human pathogens, the decline in opportunities for field study means that subsequent generations of biologists will be increasingly divorced from the primary setting – the natural environment – in which the phenomena that they study occur.

As the capacity to modify biological systems expands – from genomes to ecosystems to global cycles – it is imperative that scientists and the broader public can critically evaluate the outcomes of these changes in the context of complex natural settings. Within academia, this need also applies to the educators charged with training future generations of problem solvers. Field studies are an essential component of every scientist's training.

Field education also promotes development of place-based understanding. Students who engage in field experiences have greater opportunity to cultivate the critical connections to real places that transform abstract concepts into tangible realities. This outcome extends to the cultural, social, and political settings in which field studies occur. A sense of place can be a powerful motivator for learning and stewardship and thus individuals who become strongly connected to a specific setting, tend to become more effective advocates for all elements of that environment.

On an individual level, field studies often spark a "sense of wonder" that can launch students on a path of discovery-based science, resulting in life-long commitment to careers in natural, environmental, and medical science. Field experiences - in particular residential and other immersive experiences - also provide unparalleled opportunities for development of intra- and inter-personal skills that are critical to effective leadership. There is also empirical evidence that field courses contribute to improved academic performance and cognitive learning in undergraduate biology students.

Challenges to study

Higher education has changed dramatically since Aldo Leopold wrote about the importance of field studies in the 1930s. Institutional challenges to field studies include decreasing financial resources and increasing regulatory concerns. Institutions, presuming high costs, fearing legal liability issues, too often construct administrative obstacles to faculty offering field experiences for students.

Accommodating study

Collectively, these factors contribute to a significant decline in field study opportunities for students and lack of pedagogical guidance for instructors interested in conducting field courses. At many institutions, instructors interested in providing field experiences must negotiate a complex suite of financial, logistical, legal, and attitudinal hurdles.

Sometimes, something as simple as the lack of a vehicle for transporting students is what denies them field study opportunities. Over time, these hurdles may sap the energy and morale of even the most dedicated instructors, thereby reinforcing the cycle of decline for courses that include a field component.

More than ever, the world needs the passion, insight, and wisdom that come from field studies. Academic institutions must recognise that field experiences are more crucial, not less, in the 21st century, and work to encourage, rather than obstruct, field education. Funding agencies have an important role to play by supporting this critical foundation of learning how nature works.



Thomas L. Fleischner, Ph. D Executive Director Natural History Institute 126 N. Marina St. Prescott, Arizona 86301 USA (Faculty Emeritus, Prescott College) tom@naturalhistoryinstitute.org www.naturalhistoryinstitute.org

The Champion of Regenerative medicine – the Axolotl

Professor Malcom Maden of the Department of Biology & UF Genetics Institute unveils his thoughts on the fascinating world of regenerative medicine

he fundamental goal of regenerative medicine is to be able to regenerate complex tissues of the human body that have been damaged by trauma or chronic disease. How amazing it would be if we could regenerate cardiomyocytes in the heart that have died because of a heart attack, or replace neurons that have died after a stroke.

The discovery of stem cells in many tissue in the body provided great hope for regenerative medicine because it became possible to isolate them, increase their number in the culture dish and then graft them back to a site of damage. The hope was that they would engraft and differentiate into the damage tissue and thus repair the damage. However, this strategy has had very little success because it turns out that the number of cells that successfully engraft is vanishingly low.

Another contemporary approach to regenerative medicine is to create biological scaffolds, which mimic the composition and biophysical properties of the extracellular matrix in the hope that this might encourage endogenous stem cells to migrate into the scaffold and differentiate there. This is an approach which has particularly been used in attempts to regenerate severely damaged muscle, but again with very little success.

The third strategy is to study those organisms which can already regenerate organs and complex tissues and



Figure 1. An axolotl

discover how they do it. This knowledge can then be used for stimulating endogenous regenerative processes in humans. Lower vertebrates, notably fish such as zebrafish and newts and salamanders, such as the axolotl have prodigious powers of regeneration. Axolotls and newts can regenerate virtually everything – forebrain, midbrain, peripheral nerves, spinal cord, heart, lower jaw, retina, lens, gut, tail, skin and whole limbs to mention but a few. This is one model organism that we study in my lab.

Regrowing limbs

The regenerating limb has been a subject of fascination since 1769 when the first treatise was published on limb

and tail regeneration by Spallanzani. Today we are still trying to find out how this remarkable process occurs. We know that after amputation of the limb the epidermal cells rapidly migrate over the cut surface to heal the wound and then pile up to form a structure called an apical cap which becomes a signalling centre (fig. 2, centre panel). The mesodermal cells of the tissue which have been cut through by amputation undergo a process known as dedifferentiation whereby they lose their differentiated genetic programme, e.g. the synthesis of actin and myosin in muscle cells or collagens in the cartilage and instead become embryonic-like - the nuclei enlarge and cell division begins.



Figure 2. An axolotl limb amputated through the middle of the lower arm (dotted line on left panel) generates a blastema consisting of a mass of proliferating cells (centre panel), which grows and perfectly replaces all the amputated structures (right panel).

There are also some stem cells which contribute to this process e.g. the satellite cells of the muscle and together they create a mass of proliferating cells at the amputation site called a blastema (fig. 2). The blastema proliferates and elongates under the influence of the nerve supply and under the control of the apical cap and gradually the lost tissue re differentiates in a proximal to distal sequence, to replace perfectly all the amputated structures. (fig. 2).

In collaboration with a colleague, Dr James Monaghan at Northeastern University in Boston, we are identifying the signalling pathways that the apical cap uses to guide the regeneration of the blastema. Does regeneration use the same signalling pathways that the limb used to develop in the first place? Typical limb developmental pathways include the sonic hedgehog pathway, the Wnt pathway, the retinoic acid pathway and in a recently performed microarray experiment we have identified a new pathway involving insulinlike growth factor.

"The third strategy is to study those organisms which can already regenerate organs and complex tissues and discover how they do it."

In our joint National Science Foundation project grant, we are concentrating on the IGF and the RA pathways. With regards to RA, several years ago I found that if the regenerating limb is treated with RA (this is the active form of vitamin A) then instead of regenerating exactly what was removed as happens normally (e.g. fig. 2) extra limb segments are regenerated (fig. 3). This shows the regeneration of a complete limb from an amputation plane through the hand. The cellular property which is being altered here is known as positional information and this normally ensures that the regenerated limb is perfectly in harmony with the stump. Being able to generate extra tissue on the limb at will with RA allows us to investigate the molecular nature of positional information. We know that after RA treatment there are several hundreds of genes that are up- and down-regulated and identifying which are the ones involved in positional information is the crucial question.

To help cut down on the number of targets we are using so called retinoic acid receptor selective agonists which are synthetic compounds which activate only a sub-set of the genes that RA does. In this way, we will home in on the positional controlling genes which are thought to be cell surface molecules. The identification of cell



Figure 3. An axolotl limb amputated through the hand will normally regenerate the hand (left panel) but if treated with RA (right panel) a complete limb will regenerate instead of just the hand.

surface targets of RA would be very exciting for our understanding of how cells measure and respond to local differences in position.

"AxolotIs and newts can regenerate virtually everything – forebrain, midbrain, peripheral nerves, spinal cord, heart, lower jaw, retina, lens, gut, tail, skin and whole limbs to mention but a few."

We are also studying a pathway which is unique to regeneration and not present in the developing limb. This is the neurotrophic pathway. It was discovered as long ago as 1823 by a British naval surgeon while in Naples harbour, that if the nerves supplying the limb are cut or crushed (the limb is denervated) then after amputation the limb does not regenerate. It was proposed by Marcus Singer in the 1940's that the nerves supplied a neurotropic factor which permitted the cells of the regenerate to proliferate, but since that time the nature of the neurotrophic factor has remained

elusive although there have been several candidate factors proposed.

James Monaghan has now identified neuregulin as the neurotrophic factor since it is present in the nerves supplying the limb, it disappears after denervation and the denervated limb can be rescued from failed regeneration by being supplied with neuregulin on an implanted bead. Further work is being conducted on the role of the cells which surround the nerves, namely Schwann cells, in transmitting the neuregulin signal from the nerve to the blastemal cells and well as the nature of the interaction between neuregulin and the apical cap.

There are many features of the regenerating limb we are studying which will vital for the extrapolation these findings from axolotls to mammals. Firstly, the blastema is a crucial structure for regeneration which allows a complex tissue such as a limb consisting of many different tissue types to regenerate as a coordinated whole. The production of a blastema will be an important first step in the induction of mammalian tissues and organs.

Secondly, mammals will not be able to regenerate complex tissues unless they can measure and assess positional information and identifying the molecular basis of this phenomenon will provide a leap forward in inducing regenerative processes.

Thirdly, it is very possible that mammals cannot regenerate complex structures, because they cannot proliferate in a controlled manner (too much proliferation leads to tumour formation) in response to damage and understanding how neuregulin acts and whether there are insufficient levels in mammalian tissues will also make great inroads into our ability to induce human tissue and organ regeneration. If this turns out to ultimately be successful then we will have the lowly axolotl to thank for many significant insights.



Malcom Maden Professor Department of Biology & UF Genetics Institute Tel: +1 352 273 7875 malcmaden@ufl.edu



Looking forward to the future of chemistry

Angela K. Wilson and Carol A. Bessel from the Division of Chemistry (CHE) at the National Science Foundation (NSF) provide a fascinating insight into the future of chemistry

The National Science Foundation (NSF) <u>Division of</u> <u>Chemistry</u> (CHE) is essentially concerned with fundamental chemistry. CHE funds everything from fundamental research related to the development of instrumentation to making and understanding chemical reactions; areas of research include catalysis, synthesis, and the study of life processes, the environment, and nanomaterials, reveals Division Director Angela K. Wilson as the interview kicks off. She then says more about CHE's work in her own words, including their annual budget and the kind of activities they are involved in.

"Our annual budget is approximately \$240 million per year, and we are broken up into Individual Investigator Award (IIA) Programs, of which there are 8. Within these programs, individuals and teams can submit their proposals. In addition to these core programs, we also have a Centers for Chemical Innovation (CCI) Program – which funds much larger teams working on very complex problems. These center awards are for \$4 million per year – for up to 10 years (\$40 million total).

"The CHE Division also takes part in the Research Experiences for Undergraduates (REU) Program. Here, undergraduates can learn how to do research over the summer months and this helps to develop our scientific workforce. CHE also participates in the Major Research Instrumentation (MRI) Program. This program supports major instrumentation such as nuclear magnetic resonance (NMR) spectrometers, electron microscopes, and other instruments used by the chemistry community, so that people can do their work."

NSF's Ten Big Ideas

In summary, NSF's Ten Big Ideas includes the following research and process ideas:

Research ideas:

- 1. Harnessing Data for 21st Century Science and Engineering;
- 2. Work at the Human-Technology Frontier: Shaping the Future;
- 3. Windows on the Universe: The Era of Multi-Messenger Astrophysics;
- 4. The Quantum Leap: Leading the Next Quantum Revolution;
- 5. Understanding the Rules of Life: Predicting Phenotype;
- 6. Navigating the New Arctic.

Process ideas:

- 7. Mid-Scale Research Infrastructure;
- 8. NSF 2050;
- 9. Enhancing STEM Through Diversity and Inclusion and;
- 10. Growing Convergent Research at NSF.

On the importance of fundamental scientific research to benefit society, much of CHE's work leans heavily towards this. For example, fundamental discoveries take place within the CHE's Catalysis Program and Chemical Synthesis Program – these groups focus on designing and making new molecules – and often these molecules end up being a part of the wider industry such as agriculture, pharmaceuticals, plastics, and materials for energy capture and conversion.

New materials

The NSF-funded Center for Sustainable Polymers (CSP) is concerned with designing and developing a much more biodegradable type of polymer. Wilson adds that it's not easy to recycle plastics, such as plastic grocery bags or soda bottles, so CSP are coming up with much better materials for these industries. Deputy Division Director, Carol A. Bessel then joins in the conversation, to tell us about sustainable chemistry, which is a vital aspect of the CHE's work.

Concerning the <u>Ten Big Ideas</u> for Future NSF Investments, research agendas that identify areas for future investment at the frontiers of science and engineering, Bessel points out the Quantum Leap: Leading the Next Quantum Revolution idea, where investigators work in areas such as materials chemistry and computing. She says that building a new type of computer could help solve many of today's encryption problems and this is critically important to providing security in areas such as banking, medical records, and national security Bessel explains. She then expands on this interesting point further.

"The aim in CHE is to develop new products and technologies for the future. CHE wants to get people ready to be a part of the discoveries in the future."

"Such quantum computing only exist today as very simplistic models, but we are currently developing materials and computer methods to make the next generation of computer. New quantum materials would be passed on to computer scientists and engineers for further development and commercialisation. Nearly every division at NSF could have a role in quantum computing, for example, we need investigators in the social, behavioural, and economic sciences to understand how such devices could impact society."

Wilson is keen to tell us about the important area of harnessing data, which is another of NSF's Big Ideas, and is also very important to the wider chemistry community. In terms of data in laboratories, Wilson believes that we need to come up with better ways to harness data – that is, data visualisation, data mining, machine learning and other data analytics that can be used in the domain sciences such as chemical catalysis.

"There are many possible catalysts that would be useful to manufacturers. Chemists have only explored a very small number of catalysts because it is labour-intensive to make them, characterise them, and then study their reactivity with other molecules. If we had better ways to explore our current data, then perhaps we could identify new types of catalysts in a faster way. It's like the drug discovery processes, where a lot of modelling

is done to design and select the best pharmaceutical molecules before the experimental work is begun in the laboratory or in the clinic."

Biological processes

Bessel then tells us that one of the areas CHE plays a significant role in is around biological processes that are controlled by chemical reactions. That could be anything from the use of glucose to make your muscles work – to the neuron that control how your brain gets and stores information. Bessel then stresses that CHE seeks out to understand the fundamental processes that are controlling life and as such, they are focussed on the Understand the Rules of Life – another Big Idea. NSF's role in examining the rules of life is different than that of the National Institutes of Health (NIH) in the US. NSF generally examines the how chemical and biological structures influence biological function, while NIH examines the malfunction of fundamental life processes that lead to disease and death.

In closing, I asked Wilson and Bessel what their vision is for the future of the NSF's Division of Chemistry (CHE). Wilson begins by revealing that there has been much emphasis on the Materials Genome Initiative (MGI), which concerns exploring space in terms of the discovery of new materials and developing these materials from modelling and experimental perspectives. Such efforts make it is easier to make materials with specifically desired properties.

"In the same way, we need to do more of this in the field of chemistry, by harnessing data. We started this initiative in 2016, but there is much more work to be done in this area, and we want to use this to really push forward chemical discovery."

Bessel adds her thoughts on the matter, by highlighting the logistics in terms of making things happen and to move communities forward, so that they can explore the interactions with other fields, such as materials, computing, biology and physics.

"In this vein, we want to grow new fields where the workforce of the future will be employed. CHE wants to

be a leader in new industries that will make life better. We are trying very hard to develop new networks for our communities, so they can work not only with chemists, but also with mathematicians and computer scientists, as well as those in engineering or the economic and social sciences.

"The aim in CHE is to develop new products and technologies for the future. CHE wants to get people ready to be a part of the discoveries in the future."

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In closing, Wilson adds that along the above lines, CHE has held many workshops which aim to bring those from diverse communities together, to talk about emerging areas in chemistry.

Angela K. Wilson Division Director

Carol A. Bessel Deputy Division Director

Division of Chemistry (CHE), National Science Foundation (NSF) Tel: +1 703 292 5111 info@nsf.gov https://www.nsf.gov/div/index.jsp?div=CHE www.twitter.com/NSF

In silico chemistry: Pursuit of chemical accuracy

Kirk A. Peterson from the Department of Chemistry, Washington State University discusses the fundamentals of *in silico* chemistry

n silico chemistry simply refers to carrying out investigations of chemical processes entirely by computational methods. Over the last few decades, computational chemistry has been an invaluable tool in understanding chemical reactivity, structure, and thermodynamics. This is particularly true for short-lived species such as free radicals and reaction intermediates, as well as novel species that have yet to be observed by experiment. Computer modelling can also provide for the study of a chemical system in a pristine, welldefined environment without some of the additional complexities occurring in an experiment that might complicate the interpretation of a fundamental process.

With the increasing power of modern computing resources, *in silico* chemistry has seen significant success in the prediction of thermochemical properties of molecules in the gas phase, e.g., bond enthalpies, heats of formation, ionization potentials, etc. The benchmark standard has long been the so-called "chemical accuracy" threshold, loosely defined as an accuracy of 1 kcal/mol (~4 kJ/mol).

For molecules consisting solely of atoms ranging from hydrogen to chlorine, this threshold can now almost routinely be met, and for relatively small molecules (perhaps not more than 5 non-hydrogen atoms) accuracies on the order of 0.25 kcal/mol



(1 kJ/mol) are possible. The latter certainly then becomes competitive with or even exceeds the accuracy attainable with many experimental approaches to these quantities.

However, as the numbers of electrons increase and the electronic structure of the elements become more complicated, e.g., transition metals and heavy elements such as lanthanides and actinides, achieving 1 kcal/mol accuracy becomes much more difficult for purely first principle or ab initio methods. It does seem clear from current research, however, that accuracies of ~3 kcal/mol are possible even in these instances. So, what exactly is required to attain such a high level of accuracy that is reliable enough to perhaps even replace experiment in some cases?

Schrödinger's equation

Just as in calculating the physics of everyday macroscopic particles where

Newton's equation, F=ma, must be solved, the relevant equation of quantum mechanics that describes the properties of atoms, electrons, and hence molecules, is the Schrödinger equation (SE), $H\Psi=E\Psi$. This modestlooking equation yields the possible energy states (E) of the system, as well as the wavefunction (Ψ), which is related to the probability of finding the quantum mechanical particles at some location in space.

For a given molecule (or collection of molecules), this equation describes the motion of the individual nuclei together with all their associated electrons, which, unfortunately except for the very simplest of molecules, makes this equation impossible to exactly solve, and intractable to even obtain approximate solutions.

Fortunately, the Born-Oppenheimer approximation, which recognises that nuclei and the much lighter electrons

move at very different speeds, allows their motion to be separated. This leads to two separate Schrödinger equations, one for the nuclei and one for the electrons moving in the presence of the nuclei fixed in space. One then solves the latter electronic SE at different positions of the nuclei (bond lengths, angles, etc.) and the resulting potential energy function is used in the nuclear SE to obtain energies of molecular rotation, vibration, etc.

Relevant to the present discussion, thermodynamic properties can also be extracted from these calculations with the main limitation to the final accuracy coming from solutions of the electronic SE. Unfortunately, even this cannot be exactly solved for any molecule larger than H_2^+ , and approximate solutions yielding the desired accuracy can be very computationally demanding. In particular, this cost very steeply increases with the size of the chemical system, in terms of both the number of electrons and nuclei.

The way forward for accurate *ab initio* thermochemistry is via so-called composite methods^{1, 2}. In these calculations, the results of a series of smaller, tractable calculations are combined to approximate the results of a single large target calculation that would presumably be impossible or impractical to carry out. In order to achieve chemical or sub-chemical accuracy, all appreciable sources of error in a calculation must be accounted for in a systematic way. The two central ones are related to how the wavefunction Ψ is approximated in the solution of the SE, and they are strongly coupled: (a) how is Ψ represented in terms of the underlying atomic orbitals and (b) how are these orbitals numerically represented.

The first is generally referred to as the quantum mechanical method, while the second refers to what is called the basis set, generally consisting of Gaussian-type functions. A major breakthrough for quantitative in silico chemistry was made more than 25 years ago when Dunning³ introduced the family of correlation consistent Gaussian basis sets, which had the unique property of providing systematic convergence towards the complete basis set (CBS) limit, i.e., a limiting result that corresponds to the exact solution of the chosen quantum mechanical method. This effectively eliminates one of the major sources of error in a very systematic way. With contributions from our research group at Washington State University, correlation consistent families of basis sets are now available for nearly the entire periodic table^{4, 5}.

Hence a composite thermochemistry calculation with a goal of chemical accuracy begins with the use of an accurate, but not exact, quantum mechanical method with a sequence of correlation consistent basis sets of increasing size. These individual solutions to the electronic SE are then extrapolated to the CBS limit to remove basis set errors. Smaller contributions are then accounted for which may be chosen based on their appropriateness for the chemical system under study. Generally, these always include the effects of special relativity and molecular vibrational effects, but could also involve more esoteric contributions such as Born-Oppenheimer breakdown terms (when hydrogen atoms are involved) or quantum electrodynamics (QED). The resulting accuracy is then nearly completely dictated by the initial choice of quantum mechanical method. Coupled

cluster methods are often the best choice since they can in principle be extended towards the exact solution, albeit with high computational cost.

The key to chemically accurate *ab initio* thermochemistry is clear – a systematic approach that in principle leads towards the exact solution of a relativistic SE is mandatory, and fortuitous error compensation must be avoided at all costs. This is what leads to truly predictive *in silico* chemistry.

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Kirk A Peterson Edward R Meyer Professor of Chemistry Department of Chemistry Washington State University Tel: +1 509 335 7867 kipeters@wsu.edu https://chem.wsu.edu/faculty/peterson-kirk/ http://tyrO.chem.wsu.edu/~kipeters

Maintaining international collaboration: Chemistry has no nationality

Royal Society of Chemistry President Professor Sir John Holman reflects on the importance of maintaining international collaboration following Brexit

was recently with the German Chemical Society (GDCh), to help them celebrate their 150th anniversary. The Royal Society of Chemistry maintains international collaboration of the GDCh, and we were given a prominent position in the programme. It was a fantastic event, held in the Berlin Concert House, and brilliantly well organised.

I gave a short talk about our joint origins, and I made the point that chemistry has no nationality. It is an international subject with an international language, and chemists collaborate outside of borders.

In fact, when the GDCh had their 25th anniversary, the then-president of the Royal Society of Chemistry – or the Chemical Society as it was then – sent his greetings to the president of the GDCh, and he made this same point, that chemistry has no nationality.

What he said then is just as true today. With Brexit, we need to emphasise it more than ever now, because chemistry, like any science, depends on scientists crossing borders, and if they can't cross borders they can't get to work with each other. You might wonder why that matters now that we have the internet, but it does, because we're human, and humans work best when they can interact personally.

So, the one transcending theme that I find whenever I go overseas is this theme that chemistry has no nationality, and that scientists must be free to cross borders, to interact and exchange ideas.

The other thing that I'm struck by is that the Royal Society of Chemistry is held in very high regard internationally. Not only because we are a very long-established organisation – one of the longest-established chemical societies in the world – but also because of what we do now. We run a highly successful international publishing business, and we have conferences, and journals, and ways of interacting with people all around the world. We've got members across the globe – in 124 countries at the latest count. The feeling of warmth and respect towards the Royal Society of Chemistry – whether I'm in the USA, Brazil, India, Germany or wherever – is very striking.

"Our job is to make sure that the needs of science are made very clear, and are emphasised again and again and again. Because I really believe that strong science in this country benefits everyone. And it's not just scientists who benefit, because a country that's got a strong base in science will have a strong base in technology and will have a strong knowledge economy."

When you travel, you keep learning. You meet new people and you learn about the different things they do. But you also realise there are an awful lot of similarities in the way that science is practised and the things that motivate scientists – the need to pursue one's career, the respect that young researchers have for the older researchers that they've learned from, and the lifelong bonds that form through that relationship. These are consistent in any country.

In visiting other countries, I also learn how lucky we are, in many ways, in having such a strong UK university system, which without any doubt is world-class. You see what a long way some countries still must go in the development of their research, but also how fast some of them are moving, particularly in countries like India and Brazil.

Doubt surrounding Brexit

Now Brexit is causing a lot of uncertainty. I think chemists around the world are disappointed, and



Professor Sir John Holman

worried that we aren't going to interact with them in the way that we have done in the past. I am determined that everything we do demonstrates that we will be open to cooperation, and it's great that the EuCheMS conference is coming to Liverpool next year and that we will be able to show, in person, the truth of our desire to continue collaborating strongly with our European partners.

As far as the Royal Society of Chemistry is concerned we are throwing the doors open even wider – we're not closing them. Whether the eventual settlement that the government comes up with will help us do that, we'll have to see. We can only hope, and we can only advise, and tell government that this isn't just about funding, it's about people. It's about the easy movement of people, and as part of the UK science minister's high-level group on Brexit I'm fortunate to have an opportunity to emphasise that. I think he understands it, but he is one minister amongst many and they have competing demands – there are all sorts of tensions pulling in different directions as we negotiate Brexit.

"The one transcending theme that I find whenever I go overseas is this theme that chemistry has no nationality, and that scientists must be free to cross borders, to interact and exchange ideas."

Our job is to make sure that the needs of science are made very clear, and are emphasised again and again and again. Because I really believe that strong science in this country benefits everyone. And it's not just scientists who benefit, because a country that's got a strong base in science will have a strong base in technology and will have a strong knowledge economy.

It's very important that we send out a clear single message. This is a very complex situation, and scientists are very good at understanding complexity, not necessarily so good at simplifying it down to clear messages. That's what we've got to do now – gather a consensus for a clear single message.

Professor Sir John Holman President

Royal Society of Chemistry Tel: +44 (0)1223 420 066 www.rsc.org www.twitter.com/RoySocChem

Understanding the characterisation of sustainable materials

Moniek Tromp, Van t Hoff Institute for Molecular Sciences, Sustainable Materials Characterisation sheds light on sustainable materials and their benefits

A n integrated expertise characterisation centre providing a full set of advanced characterisation methods, some of which unique to the world, will enable sustainable materials scientists to characterise their materials and processes in all detail; using all eyes and ears to make pictures and movies of molecules and materials in action. This allows the rational design of novel materials and processes, which meet today's societal challenges, i.e. clean, requiring limited energy and using cheap and abundant resources.

Important ace of sustainability

Sustainability is important to accommodate the growth of the world's population and its future demand of resources for water, food and energy at a higher average standard of life. This requires a significant change of today's practice, including the minimisation of the manufacturing footprint of a material, but also the sustainable gains of its use during the life cycle and clever reuse of the material or its components. Integral sustainability must become a driver for new energy technologies, to produce durable systems to convert, produce and store clean energy.

Resources for energy (fossil origin) and raw materials (rare elements) are depleting and this requires a transition to sustainable energy production as well as the reduction, replacement, or recycling of rare elements and the



Overview of the facility, including embedding with full laboratory and computational facilities as well as data processing and analysis. Morever, a commercial service for data acquisition and analysis will be set-up (XSpect)

further development of bio-based materials. The transition to a sustainable society will likely have a tremendous impact. While initial efforts are aimed at reducing the footprint by making existing technologies more efficient, the final goal is a (circular) society based on truly sustainable resources for energy and materials. In this transition to a sustainable society, advanced materials will play a crucial role; a sustainable society cannot be realised without the corresponding materials that enable it. These materials will have in common: less nonrenewable energy use and less greenhouse gas emission during the synthesis, construction, processing, packaging, transportation usage, recycling, and reuse.

Materials science

Materials Science is the discipline that engages with the design, synthesis, structure, dynamics and performance of materials. It is a multidisciplinary field that includes physics, chemistry, biology, and engineering, and studies materials in a broad range of length scales from the atomic scale, through

nano and micro, all the way up to the macro scale. In order to replace scare raw materials, the functionality of materials needs to be understood much better, i.e. at all levels and in all its details. Further development and increased availability of the characterisation toolbox for this is a prerequisite in this domain.

Proper understanding not only means characterisation of the geometrical structure, from atomic to molecule and agglomerate /particle scale, but also the electronic structure. The latter determines, for a large part, the properties and reactivity of materials, but is also typically difficult to pinpoint, requiring a multitude of different and non-standard characterisation techniques. A radically different approach towards materials characterisation is thus required.

Most laboratories active in a specific materials research area specialise and invest in one characterisation technique only, which is most important or best available to them, and have experts in that one technique only. The problem with most techniques is that they only provide partial characterisation of the material under investigation. Combining several measurements of the same sample, under identical conditions, often leads to much more information than just the sum of individual data. Current challenges in sustainable materials, as described above, require detailed characterisation on multiple levels which can only be achieved with multiple techniques, i.e. 'all the eyes and ears one can have'. Groups or laboratories generally do not have the possibilities (staff, finances and expertise) to offer, develop and/or

execute all of these well. In addition to that, important X-ray techniques, allowing characterisation from atomic (Angstroms) up to inter-molecular information (micrometer) are typically performed at synchrotrons, with high oversubscription rates, severely limiting the accessibility. A radically different approach to materials characterisation is therefore crucial to ensure one can meet the materials science challenges we are facing today.

"Sustainability is important to accommodate the growth of the world's population and its future demand of resources for water, food and energy at a higher average standard of life."

National Characterisation Centre for Sustainable Materials

To unravel the novel chemistry displayed by these feedstocks and materials as well as their differing reactivity requires multiple advanced techniques, in an integrated approach. We are therefore in the process of setting up a National Characterisation Centre for Sustainable Materials (NC2SM) in which we bring important non-standard techniques together in one place, as well as develop novel and combined ones, by making x-ray absorption, emission, and scattering techniques available in the laboratory. Having access to all techniques in one place, thus making it possible to collect all necessary data in an unequivocal manner on the same sample under identical (operando) conditions, is key to fundamental materials understanding and subsequent rational design and development.

The suite of techniques will give detailed structural as well as electronic

information on the broad range of materials, at different time and length scales, from all different parts of the material/molecule. All techniques have their individual strengths and limitations, and only a combination of all can provide a full picture and movie of the sample and its reactivity. Moreover, the integrated centre will therefore not just act as a place to obtain data, but also as a sounding board and discussion platform for materials scientists, spectroscopists and theoreticians, which will catalyse novel and exciting science and advances in all fields.





Prof. Dr. Moniek Tromp Professor University of Amsterdam Van t Hoff Institute for Molecular Sciences, Sustainable Materials Characterisation Tel: +31 20 525 6994 m.tromp@uva.nl www.suschem.uva.nl www.twitter.com/moniek_tromp

Swedish research and education is at the forefront of change

The work of Swedish Minister for Research and Education, Helene Hellmark Knutsson, is profiled by Open Access Government in this compelling article

nowledge is the foundation of positive societal change and our primary means of competing internationally. Sweden must compete on the basis of knowledge and skills – not low wages."¹

In the above quote, Swedish Minister for Research and Education, Helene Hellmark Knutsson, voices her opinion and that of the whole Ministry of Research and Education loud and clear. Education should not be a luxury, it should be a necessity. It is clear to see Sweden's viewpoint on education and it is that of a positive one. All girls, boys, women and men should have the opportunity to test and develop their abilities and skills to achieve their full potential.

A good education provides any given person solid foundations for finding a job, multi-interdisciplinary skills, a thirst for knowledge in a global and complex world, and lays the foundations for a well-functioning society in which no one is discriminated against or excluded. This notion strives for a school that gives its pupils the support they need, where teachers enjoy their work, and are offered the opportunity to develop professionally and personally, giving all children a fair chance of succeeding in life.

Thus, it is one of Sweden's priorities to utilise and develop the skills of the whole population, fairly and slowly. The ministry is very aware that with Ms Knutsson leading it, that to create, live in, and sustain a successful democratic society, it is important to better yourself through a life in education.

Now, Sweden is a leading knowledge nation, but to maintain this, an equal education system and international competitiveness through world-class research will help this country to thrive even more. However, there are many challenges to tackle regarding society



Helene Hellmark Knutsson, Swedish Minister for Research and Education

itself and socio-economic issues, and Sweden points to education as a means of battling this. "We therefore need to invest in heavily in Education and Research".²

International collaboration

Another priority of the ministry is international cooperation, and the amazing benefits that it can bring. For example, Tuesday 4th April marked the meeting of the Minister of Education and Higher Education of Qatar, Dr. Mohammed Bin Abdul Wahid Al-Hammadi, and the Swedish Minister for Higher Education and Research, Ms Knutsson. During the meeting, mobility of



researchers and students as well as other types of cooperation within higher education and research were discussed – two very current topics. The ministers also discussed the issue of gender equality within higher education and research – an issue that Ms Knutsson has previously been very vocal about and expressed her concern.

More recently, Ms Knutsson has confirmed international ties with China, signing a cooperation agreement as the end of August, during a meeting that she hosted with Wan Gang, Chinese member of Science and Technology. It is apparent that Sweden is a very popular place for students from China to come and study abroad, meaning the link between the two countries has been considerable for several years, and it is only getting stronger.

In areas such as technology and renewable energy, and furthermore, Swedish-Chinese research cooperation will only increase with the signing of the cooperation agreement between the Swedish agency for innovation, and the Chinese Ministry of Science and Technology. This agreement will confirm cooperation between the two countries on areas such as: traffic safety, life sciences, ageing and climate change. All these areas will further interest in education, knowledge and collaborative research and innovation. The overarching objective of the Education and Research Policy is for Sweden to be a prominent knowledge and research nation, characterised by high standards. Excellence in research, higher education and innovation will lead to social development, prosperity and business competitiveness, and respond to the ever-changing economy and society overall. It is at the upmost importance to allow people to thrive under education, nationally and internationally, and it is more than obvious that the Ministry of Research and Education in Sweden, is being proactive in doing so.

1 http://www.government.se/government-of-sweden/ministry-of-education-and-research/helene-hellmark-knutsson/

2 http://www.government.se/4ad0ba/contentassets/1b098730913a 430aa4150f448831602d/towards-an-outstanding-knowledge-nationwith-equal-education-and-world-class-research.pdf

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Protein plastics for a future sustainable society

Mikael Hedenqvist, Professor at KTH Royal Institute of Technology provides a fascinating glimpse into research on the development of protein plastics

The polymeric materials division at the Royal Institute of Technology, has been doing research and development of protein plastics since the late 1990's, often together with the group headed by Professor Eva Johansson at the Swedish Agricultural University, Department of Plant Breeding. There is an ever-growing need for plastics from renewable resources rather than oil, to reduce the amount of green-house gases produced, leading to global warming.

"...we have shown that there are many possible applications for protein-based plastics and even though they are moisture sensitive, for more demanding environments (high moist conditions), they can be prepared with antimicrobial agents (in the same way as wood is for certain applications)."

Using a renewable feedstock will minimise the "pollution". Protein plastics are an interesting alternative, not the least since it is often a side-stream product (co-product or by-product) from an existing industrial process. By making plastic products (added-value products), especially from a by-product improves the effectiveness by which we use the natural resources and leads to a more sustainable society.

The sustainability improves even further if the additives put into the plastic are from a renewable resource. When it comes to renewable resources, proteins for plastics can be obtained from "food" plants (e.g. from soy, wheat, corn, oat, potato, pea) but also from non-edible sources (e.g. cotton and oil plants like Crambe Abyssinica and Brassica Carinata). Animal-based proteins are also alternatives for plastic production, refer to e.g. proteins from milk (casein and whey), connective tissues (collagen and casein), feathers and wool (keratin) and silk (fibroin).

Available proteins

Figure 1a shows some of the protein plastics we are or have worked with. Wheat gluten is among the proteins that forms the most cohesive material. Therefore, it has been used to improve the cohesion of other protein materials (Fig. 1a).¹ Wheat gluten plastics can be made into many different types of products, including flexible films, foams and rigid solid 3D items. It can be coloured in all kinds of colours and made opaque or translucent. Proteins plastics are stiff and to obtain flexible products, these have to be plasticised with e.g. a natural sugar (keeping the whole product bio based).

The plasticisation will also make the material tougher. Glycerol is a large by-product from biodiesel fuel production and therefore available in large amounts. There are alternatives to glycerol (e.g. sorbitol) but it is hard to beat glycerol in terms of its effectiveness as a plasticiser.² The rapeseed protein (rape seed meal/cake) is also available as a by-product from biodiesel production.³ Mixing it with wheat gluten and plasticiser leads to material that resembles PVC flooring (flexible but inelastic/dull). Crambe Abyssinica is a plant with oil seeds which is, based on its toxicity, inedible for both humans and animals.

We have shown that it is possible to extrude Crambe into films when it is combined with wheat gluten and plasticiser.¹ Whey protein (by-product milk protein from the cheese production) is a protein that with plasticiser forms flexible films with good cohesion.⁴ If it is a high protein purity grade (whey protein isolate) the films are fully transparent. To reduce the price films can be made with lower protein purity, but the films will be less transparent. For the lower purity grades, there is also a distinct smell of cheese.

Wheat gluten with its high cohesion is perfect for foaming (refer to breadmaking). Hence foams are easily obtained with this protein.5 Our freeze-dried foams have both closed and open cells and can be either rigid or flexible (with plasticiser). With different additives, the strength can be increased (e.g. with bacterial cellulose nanofibers), the foams can be conductive (using nano-sized carbon black or carbon nanotubes).⁶ Soft conductive foams can be used e.g. to provide protection for static sensitive devices. The foams can also act as sponges (absorbents) with a large uptake of both polar and non-polar liquids.⁷



Figure 1a. The dark-brown plate is made of a mixture of wheat gluten and a rapeseed protein-based material. The green material is a caramel-coloured wheat gluten film and the cube is a wheat-gluten foam, obtained from freeze-drying an aqueous protein dispersion. The transparent film is a whey protein-isolate sample and the light grey film is based on proteins from Crambe Abyssinica and wheat gluten. All samples except the foam is plasticised with a sugar (glycerol).

Figure 1b. Two plasticised wheat gluten films with (in the front) and without a flax fibre weave.

The research in the field of bio based composites is extensive. To preserve a fully bio based material both the matrix and the reinforcement should be obtained from a renewable resource. We have shown that it is possible to obtain flexible films with improved strength and fracture resistance by combining a plasticised protein plastic (wheat gluten) with a flax fibre weave (Figure 1b).⁸

To conclude, there are many possible applications for protein-based plastics and even though they are moisture sensitive, for more demanding environments (high moist conditions), they can be prepared with antimicrobial agents (in the same way as wood is for certain applications).

To preserve rigidity in e.g. water, the proteins can be crosslinked. The protein plastics constitute in several ways a material group by itself, it is not a classical thermoplastic since the properties change somewhat after each thermal treatment, with plasticiser it resembles an elastomer or a duller material, similar to plasticised PVC, at high protein aggregation/polymerisation the protein turns into a thermoset.

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Mikael Hedenqvist Professor

KTH Royal Institute of Technology Dept. of Fibre and Polymer Technology School of Chemical Science and Engineering Tel: +46 706 507 645 mikaelhe@kth.se kth.se/en/che/divisions/polymeric-materials



Environmental toxicology in the regulation of chemicals

A group of experts at the Society of Environmental Toxicology and Chemistry-Europe shed light on the environmental risk assessment of chemicals

epending on the regulatory context, chemicals including pharmaceuticals, pesticides, biocides, metals but also any other substance that may be released into the environment, are assessed for their potential risks for the environment. This environmental risk assessment involves the estimation or measurement of environmental concentrations of the individual chemical, which may be done for each relevant environmental compartment.

The risk is then assessed by comparing these estimated or measured environmental concentrations, with the concentrations that are considered to cause no effects in organisms or functions of the respective environmental compartment. Environmental toxicology supports risk assessment by informing about exposure concentrations inducing adverse effects at different biological levels.

The Ecosystem

These effects may be determined at the ecosystem level (in situ or field studies), community, population, individual, cellular or molecular level, based on the regulatory context or problem formulation. Thus, it englobes ecotoxicology that describes the study of effects in organisms and functions used in an environmental risk assessment. The risk assessment is a tiered approach which requires refinements at both the environmental fate and effect sides but it starts with rather simple models and standard tests in the laboratory.

Identifying suitable test species, relevant measurement endpoints and test designs, requires the involvement of different scientific skills and stakeholders. Academics can provide information about environmental chemistry, ecologically relevant species and measurement endpoints as well as their handling. Governmental



scientists and regulators inform about the need for a certain test guideline and its acceptance in a regulatory context. Industry scientists implement those guidelines routinely, give feedback from others on the practical feasibility and learn from the data generated in the long term.

"Environmental toxicology supports risk assessment by informing about exposure concentrations inducing adverse effects at different biological levels."

By following its credo "Environmental Quality Through Science" ©, the Society of Environmental Toxicology and Chemistry (SETAC) provides a unique platform fostering this exchange. SETAC is the world largest professional non-for-profit organisation bringing together experts from all the three sectors – this tripartite principle is reflected throughout all parts of SETAC.

The Society's members are dedicated to the study, analysis and solution of environmental problems, the management and regulation of natural resources, research and development, and environmental education. SETAC is divided into five geographic units: Africa, Asia-Pacific, Europe, Latin America and North America. Each of them harbors various regional branches or chapters.

The annual or bi-annual meetings of each geographic unit became a focal point of exchange regarding specific and local, but also general and global environmental problems. Questions, challenges and tasks are often discussed in further detail in SETAC's over 30 "special interest groups" focusing on topics such as nanotechnology or sustainability.

Based on the input of these special interest groups or SETAC members, workshops are regularly organised to tackle current aspects of environmental concern and to develop the environmental risk assessment of chemicals. As a consequence of these efforts, in combination with the tripartite paradigm, the workshop recommendation (published via various outlets, including books and scientific articles) are often accepted among the three sectors.

Anne Alix

Dow AgroSciences, UK

Mirco Bundschuh

Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences, Sweden & Institute for Environmental Sciences, University of Koblenz-Landau, Landau Campus, Germany

Karel De Schamphelaere

Ghent University – Environmental Toxicology unit (GhEnToxLab), Belgium

José Julio Ortega-Calvo

Instituto de recursos Naturales y Agrobiologia de Sevilla, Consejo Superior de Investigaciones Científicas, Spain

Society of Environmental Toxicology and Chemistry-Europe Tel: +32 2 772 72 81 setaceu@setac.org www.setac.org www.facebook.com/setacworld www.twitter.com/SETAC_world

Environmental chemicals: factors for neurodevelopmental disorders?

Pamela Lein, University of California, looks at whether environmental chemicals influence individual risk for the diagnosis of neurodevelopmental disorders

eurodevelopmental disorders (NDDs) are a group of clinically heterogeneous conditions characterised by impaired growth and development of the brain. These include autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), schizophrenia, learning and intellectual disabilities, and sensory impairments. The current prevalence of ASD is estimated to be at least 1.5% of children in developed countries; the worldwide prevalence of ADHD is estimated to be 5.3% of children and adolescents; and learning and intellectual disabilities are more common than ASD and ADHD combined. Considered in the context of the tremendous costs these conditions exact on the affected individual. their families and society, these statistics underscore the urgent need to identify factors that confer risk for NDDs.

Until recently, research on the aetiology of NDDs has focused largely on genetic causes. However, this research has clearly shown that even for ASD, which is considered one of the most heritable of the complex NDDs, single genetic anomalies can account for only a small proportion of cases and, overall, genetic factors seem to account for at most 30-40% of all NDD cases. Such observations have contributed to a paradigm shift such that many NDDs are now largely thought to result from complex gene-environment interactions.

Why do we think environmental factors influence NDD risk?

Compelling evidence in support of an environmental contribution to NDD aetiology includes the rapid increase in the prevalence of ASD and ADHD over the past several decades. This is unlikely to have been caused by evolutionary shifts in the human genome. While some have guestioned whether this represents a true increase in the number of affected children, studies to address this question have uniformly concluded that the broadening of diagnostic criteria, increased awareness and improved detection can only partially account for the increased prevalence of NDDs.

Genetic studies also support a role for environmental factors in determining NDD risk. Incomplete monozygotic concordance is a consistent finding in twin studies of both ASD and ADHD, and even in genetic syndromes highly associated with ASD, a significant percentage of individuals carrying the ASD-linked gene do not express autistic phenotypes. More recently, a study of 192 mono- and dizygotic twin pairs, and another of 14,000 children with autism, independently concluded that 50% or more of cases could be attributed to environmental causes. Collectively, these studies are consistent with a model in which environmental factors modify genetic risk to significantly influence not only susceptibility to NDDs, but also the variable expression of phenotypic traits. This model

provides a biologically plausible explanation for both the dramatically increased prevalence and clinical heterogeneity that are characteristic of complex NDDs.

Environmental factors associated with increased NDD risk

Observations of a high incidence of autism associated with congenital rubella were among the first reports demonstrating that an environmental factor could influence NDD risk. Subsequently, prenatal infections were linked to an increased risk for other NDDs, particularly schizophrenia, and the range of non-genetic NDD risk factors was expanded to include intrauterine stresses, increased paternal age, maternal nutrition and metabolic status, and endocrine disruption. The first indication that chemical exposures may also influence NDD risk were reports that in utero exposure to valproic acid or thalidomide during critical periods of development was associated with increased expression of autism-related traits. Subsequent epidemiological studies reported increased NDD risk associated with maternal use of various medications and drugs of abuse, including alcohol, as well as prenatal or early postnatal exposure to diverse environmental chemicals. Environmental chemicals postulated to confer risk for NDDs include legacy chemicals known to be toxic to the developing human nervous system, such as lead, mercury and polychlorinated biphenyls (PCBs), as



well as more contemporary contaminants such as pesticides, including organophosphorus (OP) and organochlorine (OC) pesticides, neonicotinoids and pyrethroids, flame retardants including the polybrominated diphenyl ethers (PBDEs), plasticisers such as phthalates and bisphenol A, and complex environmental mixtures such as air pollution and cigarette smoke.

Current challenges in the field, and a potential path forward

Current epidemiological data support the hypothesis that chemicals in the human environment contribute significantly to NDD aetiology, but also highlight the difficulty of establishing causal links between environmental exposures and NDDs. Recent reviews have concluded that, with the possible exception of tobacco and alcohol, there are insufficient numbers of epidemiological studies and/or studies are too limited in scope to either infer causality or to rule out the possibility that specific environmental factors confer NDD risk. The challenges of using epidemiological approaches to identify environmental risk factors include obtaining accurate measures of exposure, particularly for chemicals with short half-lives such as some of the pesticides, phthalates and BPA, controlling for confounding factors, especially socioeconomic stressors that tend to co-vary with environmental exposures, and are known to influence neurodevelopment independent of chemical exposures, and dealing with

multiple exposures, a not insignificant issue in light of reports that 250 environmental chemicals were detected in biological samples from a 2013 representative sample of the United States in the National Health and Nutrition Examination Survey. Epidemiological approaches must also deal with the phenotypic heterogeneity and complex multigene aetiologies that are likely to create a range of sensitivities to environmental factors, which will further mask clear associations between exposure and diagnosis.

To overcome these challenges, it will be necessary to invest resources in basic mechanistic research using experimental models to understand how environmental factors modify genetic predispositions to influence individual susceptibility and/or severity for NDDs. While a number of mechanisms have been proposed to explain gene-environment interactions, one fundamental way in which heritable genetic vulnerabilities can amplify the adverse effects triggered by environmental exposures is if both factors (environmental and heritable) converge to dysregulate the same neurotransmitter, signalling system or neurodevelopmental process during a critical developmental window. Genetic studies have identified convergent molecular mechanisms for many NDDs, which provide a biological framework for developing cell and animal models to identify and study specific gene-environment interactions

that confer susceptibility. Such mechanistic insights can then be used to inform and focus epidemiological studies.

Clearly, research is urgently needed to better predict which combination of defective genes and environmental exposures pose the greatest risk for NDDs. The fact that environmental factors are modifiable risk factors, in contrast to currently irreversible genetic risks, suggests that identification of specific environmental risk factors may provide rational approaches for the primary prevention of NDDs, which provides a compelling reason to invest in this endeavour.



Pamela J. Lein Professor of Neurotoxicology

University of California, Davis/School of Veterinary Medicine Tel: +1 530 752 1970 pjlein@ucdavis.edu http://www.vetmed.ucdavis.edu/faculty/results.cfm?fid=19369 http://www.vetmed.ucdavis.edu/leinlab/index.cfm

Promoting Science: Step-by-step is a step in the right direction

Gustavo Carvalho and Emanuel Matias from the Youth Science Association's (AJC) discuss the importance of promoting science amongst young people in Portugal

anu Prakash, an Indian born bioengineering professor at Stanford and co-creator of the fascinating Foldscope – a paper foldable microscope produced with less than \$1 – stated at Intel ISEF 2017 Opening Ceremony: "Science is not a sprint, it's a marathon". "The only way to grasp a modern science-denying world is by assuming that some people didn't learn how to walk – in Associação Juvenil de Ciência (AJC), we help youngsters start that journey."

Science communication and promotion is, undoubtedly, more than simple advertisement: It is essential for the survival and progress of the human species. Imagine if we could get a glimpse of a world where would suddenly be no more scientists: How would you perceive, for instance, evolution? Years of worldwide stagnation in every sector would rule.

We have this inherent hunger to constantly perceive what surrounds us, to define, to create and gather knowledge, and Science allows us to fulfill that need: we are indeed natural-born scientists. This is the reason why we find any attempt to break Science promotion so unreasonable and irrational, and we believe in the priority of cherishing it among youngsters. It is impossible to win a race without preparation, but even so you may not succeed.

However, it is impossible to finish a marathon without persistence and tenacity: in Science, you always win. The hard and sometimes painstaking effort put into practice by anyone who dares to start this journey leads to personal success, to character and to an informed and active citizenship. But the true value behind Science is the empowerment given towards making us able to shield ourselves from attacks against unalienable realities, such as denying global warming or disclaiming the roundness of our planet, some of them shockingly endorsed by very well-known public figures. Again, some of them probably didn't had the help required to know how to walk. Isn't that right, President Trump?

We understand Science may seem bizarre and, occasionally, we may fear that some things it proclaims to be factual are just too good to be true. But as Neil deGrasse Tyson once said: "The good thing about Science is that it's true whether or not you believe in it". If we invoke science in the correct fashion, with the right purpose and for the right use, there's no way science fails the smell test.

"Sadly, the scientific panorama in Portugal is highly restricted by its lack of funding. Our country continues, nevertheless, to show great resilience as we have cemented our place as one of the greener countries in the world."

Portuguese Science

The Portuguese Youth Science Association (AJC) is a group of young people committed to promote Science among the youth. It was created in the 1980's and since then has been formed and managed by young people, being the only association of its kind in Portugal and one of the few in the world. Its early founders are some of the best Portuguese scientists and it currently counts with more than 1900 associates. AJC is also a member of the MILSET family.

Against all odds, this year we celebrated 30 years of existence. To be fair, it's 35. The truth is that Youth Science Association comes from Youth Science Meeting (Encontro Juvenil de Ciência – EJC), our national Science meeting. In its first edition, it had a remarkable attendance of around 100 participants. Four years later,



This year, the 35th YSM was held in the city of Oporto. Around 100 participants from 8 different countries attended this edition

after its fifth edition, an organising committee was created to plan the succeeding meetings and related affairs, which is currently known as the National Board of AJC.

"We have this inherent hunger to constantly perceive what surrounds us, to define, to create and gather knowledge, and Science allows us to fulfill that need: we are indeed natural-born scientists."

In 2014, the doors were opened for international participants, having Associação Juvenil de Ciência (AJC) and Encontro Juvenil de Ciência (EJC) adopted their respective international designations: Youth Science Association (YSA) and Youth Science Meeting (YSM).

Every year, around 100 participants from all around the world accept our challenge and effusively defend their own projects, while enjoying a full week in a different Portuguese city. They all leave culturally and scientifically enriched, collecting friendships for a lifetime. Yet, they're still competing for prizes, such as having the opportunity to participate in international scientific contests: e.g. ExpoScience. As a non-profit association we exclusively depend on the effort and passion of our active members, as well as on the national funding we receive every year. Unfortunately, it's becoming increasingly difficult to make the ends meet, as we intend to maintain the quality and attractiveness of our annual activities, while seeing many of the entities that endorse us reducing or even cutting their indispensable financial backing.

Sadly, the scientific panorama in Portugal is highly restricted by its lack of funding. Our country continues, nevertheless, to show great resilience as we have cemented our place as one of the greener countries in the world. In fact, in May of 2016 Portugal was able to survive four days by only using renewable energies to feed its own electricity.

This was obviously an astounding accomplishment, but it's too difficult to overlook the writing on the wall. Our educational system is defective in attracting students to science, and many scientific fields are left underprovided. Students are educated to accomplish a certain mandatory grade, with which they will apply to college.

Minister for Science, Technology and Higher Education – Manuel Heitor

The mission of the Portuguese Ministry for Science and Technology is to formulate, conduct, implement and evaluate national science, technology and higher education policy.

Their work includes science and technology based innovation, scientific computing, the dissemination of scientific and technological culture and international scientific and technological cooperation, particularly with the Portuguesespeaking countries.



The current Minister for Science, Technology and Higher Education is Manuel Heitor, who was born in Lisbon in 1958. Heitor holds a doctorate from Imperial College London in Mechanical Engineering (Experimental Combustion), gained in 1985, having completed postdoctoral studies at the University of California, San Diego, 1986.

He went on to pursue an academic career at Instituto Superior Técnico in Lisbon, where he started developing its research activity in the field of fluid mechanics and experimental combustion.

Between March 2005 and June 2011, he was Secretary of State for Science, Technology and Higher Education of the XVII and XVIII Government. During this time, he was actively involved in increasing public and private funding for science and technology activities and in the reform as well as the modernisation of higher education in Portugal.

It is also worth noting that he was particularly instrumental in the design and implementation of international consortia in advanced research and training between Portuguese and North American universities, involving thematic networks of science and technology.

During the 2011/12 school year, Heitor was a visiting professor at Harvard University in the USA. He served as deputy president of the Instituto Superior Técnico between 1993 and 1998.

Added to that, since the dawn of the 1990s, he has been studying science, technology and innovation policies, including policies and the management of higher education. Founded in 1998, IST's Center for Studies in Innovation, Technology and Policy for Development, was named in 2005 as one of the Top 50 global centers of research on the management of technology by the International Association for the Management of Technology (IAMOT).

Heitor has also launched and coordinated the series of international conferences on technology policy and innovation and is co-editor of the series of books on science and technology policy, edited by Purdue University Press. He was co-founder of the international network – "Gobelins – the global network for the economics of learning, innovation, and competence building systems", in 2002.

More recently, Heitor has been involved in the promotion of the European step4EU network, science, technology, education and policy for Europe and the establishment of the International Observatory on Global Policies for the Exploration of the Atlantic, OIPG. In July 2015 he promoted in Portugal the Manifesto "Knowledge as the Future" and, later, the international declaration, "Knowledge as Our Common Future."
RESEARCH & INNOVATION



One of the recurrent activities is GTA. The participants build their own rocket with daily materials

In fact, three years of high school are as valuable as a three-hour exam. Our educational system is not planned to teach students anymore, or to prepare them to College; School is being envisioned to get students into College.

In AJC we also face some problems. The world is now closed on social networks and it's more and more difficult to get youngsters out of their houses. For many of them, Science is not appealing anymore. Therefore, besides the financial effort, the world is gifting us with the challenge to revolutionise the way we promote and communicate Science. We happily and promptly accept this challenge, because we recognise that this is the reason why we are scientists and, above all, why we became members of Youth Science Association. With the world shifting its interests so fast, we all want to take part in the evolution of Science and the world, inspiring other youngsters to do the same by doing everything possible to set our association in the frontline of science promotion and by preserving and treasuring the spirit that our history carries.

"Science communication and promotion is, undoubtedly, more than simple advertisement: It is essential for the survival and progress of the human species. Imagine if we could get a glimpse of a world where would suddenly be no more scientists: How would you perceive, for instance, evolution? Years of worldwide stagnation in every sector would rule."

As stated in the message of our founders, in the beginnings of our association: "A AJC é a vontade de muitos 'jovens do EJC' em não deixar de o ser" – "YSA is the will of many 'youngsters from YSM' of not ceasing to be it." This is the perfect portrait of our vision for Science, in Portugal and worldwide: A Science that constantly educates, a Science that influences every social and political system, a Science that keeps calling. We need a Science that can teach us how to walk: this will reduce the entropy, this will constantly modernise the modern, this will keep trying to stay free, young and with good health – just like a marathonist should.

Gustavo Carvalho Emanuel Matias Members of the AJC National Board Portuguese Youth Science Association (AJC) ajc@ajc.pt http://ajc.pt/# www.facebook.com/Associacaojuvenildeciencia www.instagram.com/ajc_associacao_juvenil_ciencia www.twitter.com/AJCiencia

Challenges for European science and technology – thermosphysics of fluids and nanosystems

An expert from the Faculty of Sciences at the University of Lisbon reflects on the gap between European science research and industrial utilisation



La uropean science and technology face a new paradigm – to perform research with very welldefined targets to resolve problems of society and development, bounded by environmental and health restraints. Many new fields and materials have emerged in recent years, and to respond to current needs implies the use of solid competences but open minds. As James Dewar (1842-1923), "Minds are like parachutes. They only function when they are open". Society needs scientists (and entrepreneurs) that can absorb this new paradigm.

Thermophysics is the science and technology of some of the most important properties of materials. Thermophysical properties are all material properties affecting the transfer and storage of heat, that vary with the state variables temperature, pressure and composition, without altering the material's chemical identity. Thermophysical properties play



an important role in several processes in the chemical, extraction and manufacturing industries, especially in those involving simultaneous heat and mass transfer. Most of the problems that affect our society need values of these properties to design control and characterise new products and processes, to replace unacceptable processes and compounds and to optimise energy balances and efficiency.

Until the 1960s much of the experimental work on the thermophysical properties of fluids was devoted to the development of methods for the measurement of the properties of simple fluids under moderate conditions. By the end of the 1960s a few methods had emerged that had both a rigorous mathematical description of the experimental method and technical innovation to render measurements precise enough to rigorously test theories of fluids for both gas and liquid phases¹.

After those early successes, there has been a divergence of experimental effort from the earlier thrust and, in the future, there needs to be focus on in situ measurement of properties for process fluids. These arguments are based upon the balance between the uncertainty of the results and their utility and economic value as well as upon technical developments, which have provided reliable and robust sen-

sors of properties. Leading scientists (Kestin, Wakeham, Nagashima, Sengers, among others) paved the way to the actual state of thermophysics, namely in one areas of fundamental interest for the future – the thermophysical properties of nanosystems (nanomaterials and nanofluids).

What is the situation now?

To make good measurements of thermophysical properties is difficult and time consuming and it is not fashionable not economically attractive for industries and funding agencies. The need for accurate data on thermophysical properties of fluids has been replaced to a certain extent by alternative methods of properties calculation, mostly based on computer simulation or prediction/estimation methodologies (cheaper, but risky).

Reasons for this can be summarised in the following items:

- Change of needs From laboratory work to in-situ measurements;
- Change of paradigm Fit for purpose instead of best uncertainty;
- Change of financing priorities from state funding agencies – Priority to industry driven/sponsored research;
- Decrease for users in industry of the added-value of property data of good quality and;
- The use and misuse of commercial equipment, with methods of measurement not adequate to the object systems.

The new research trends in thermophysics are: 1) Materials for nuclear engineering; 2) Materials for thermal storage; 3) Planetary bodies (thermal properties and heat flux); 4) Molten salts for solar applications; 5) Thermal properties of reservoir rocks; 6) Soft materials (textiles, food products, body fluids); 7) Steel/alloy industry (casting products and special alloys); 8) Nanofluids and IoNanofluids (nonaqueous and high temperature);9) Chemical products conformal with REACH; 10) Thermophysical properties of seawater (surface and deep); New lubricants. International Cooperation is fundamental.

In line with the challenges that are outlined in Horizon 2020, EURAMET has identified that the main social and economic triggers driving the development of thermophysical measurements are energy, environment, advanced manufacturing and processing, safety, security, and health. Thereby metrology for thermophysical properties will contribute substantially to the six priorities "Societal Challenges" which are in the focus of Horizon 2020².

The Molecular Thermophysics and Fluid Technology Group of Centro de Química Estrutural is an international recognised group in thermophysics of fluids and materials, with a strong experience on experimental measurement, modelling and correlation of thermophysical properties, designing equipment and sensors for fundamental and industrial applications. In the recent years, most of this research was directed to cutting-edge research, which include ionic liquids, nanomaterials and IoNanofluids and new engineering fluids.

One of the main advantages of our know-how is the possibility of implement the cross fertilisation of these research fields to resolve delicate problems, not only at a molecular level, but also in the possible industrial applications. Some examples of this research, patented when applicable, are: New spectrally selective coatings for solar paints, will allow us to produce films at low cost; Development of new nano-based heat transfer fluids, making a solar collector and heat exchangers more energy efficient obeying to the environmental goals set by the World Energy Council; Measuring viscosity of new molten alloys for hightech applications; Measuring thermal conductivity of humid air for high pressure turbines; Developing metal-film sensors for high temperature in situ measurements in incinerators.

In summary, our experience paves the way to a strong collaboration with other research groups and industrial companies in the frame of Horizon 2020. The strength of European economy and the welfare of our society depend strongly on this approach. We are prepared to make Thermophysics to contribute to this effort, resolving problems of the public sector.

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Carlos A. Nieto de Castro Vice-President Centro de Química Estrutural Group Leader Molecular Thermophysics and Fluid Technology Departamento de Química e Bioquímica Faculdade de Ciências da Universidade de Lisboa Tel: +351 217 500 918 cacastro@ciencias.ulisboa.pt https://ciencias.ulisboa.pt/perfil/cacastro http://groups.ist.utl.pt/~cqe.daemon/members-contacts/research-groups-2/205-2/

Human sperm cells, the overlooked sentinel of our living environment

Luigi Montano of the Local Health Authority (ASL) Salerno and Alberto Mantovani from Istituto Superiore di Sanità explore the relationships between the environment and sperm cells

The containment of pollution-related adverse effects is an emerging public health priority at global level. The World Health Organization estimates that about 25% of the current disease burden occurring are caused by prolonged exposure to environmental risks factors, with air pollution featuring among the top ten risk factors associated with premature mortality. Pollution can also adversely affect human sperm cells.

Increasing evidence points out that exposure to airborne pollutants increases the risk for health disorders other than respiratory diseases, concerning human reproduction. Airborne toxicants can be absorbed from the lungs and can be also deposited on edible crops and pastures: thus, an air-to-food exposure path does often occur.

The diverse chemicals (metals, solvents, dioxins, polycyclic aromatic hydrocarbons, etc.) carried by airborne pollution may elicit different toxicity mechanisms: genetic and epigenetic alterations, hormonal imbalances, oxidative stress induction. All such mechanisms may impact on critical quality parameters of human semen, such as the production, motility and/or fertilising capacity of spermatozoa.

Spermatogenesis is also a process that goes on continuously, from adolescence through to aging; thus, the formation of new spermatozoa (and secretory fluids from accessory glands, such as prostate) continuously occurs. Spermatozoa are fragile cells that rely on number, rather strength, to carry out their task of perpetuating the species.

For instance, sperm cells are highly susceptible to the effects of oxidative damage because the little cytoplasmic volume limits the space for housing an appropriate armory of defensive enzymes, and the cell membrane lipids contain high amounts of polyunsaturated fatty acids. In its turn, oxidative stress-induced genetic and epigenetic damage may lead to trans-generational effects, with increased incidence of diseases in the next generation(s), due to such features, as well as to easy sampling, human semen must be considered as potential time- and cost-effective marker for environmental health.

Pollution is not always the same. Due to waste discharge, traffic, industrial activities, intensive pesticide use, etc., in some areas the environmental pressure is definitely: exposure to contaminants involves the food chains as well as the living environment and often coexists with lower than average socioeconomic status.

Evidence is growing that high environmental pressure is consistently associated with heavier public health problems in terms of cancer and other chronic diseases. Epidemiological studies deserve the important merit of pointing out populations at higher risk; on the other hand, epidemiology registers health problems when they have already occurred, often after a year-long latency time as for cancer.

In addition, epidemiology seldom allows definitive causal assessments. Biomonitoring looks more attractive from the standpoint of early detection (and prevention) of environmental risks. But what biomarkers, then? The measurement of the pollutant or its metabolites in biological fluids, or specific substance-related biological signals (e.g., cholinesterase for organophosphorus insecticides) biomarkers is appropriate when the environmental pressure is due to one or few identified agents, such as dioxins in the Seveso accident (Italy, 1974). No doubt, the direct measure of biomarkers in body fluids is more directly relevant to health risk

RESEARCH & INNOVATION

assessment than the collection of data on contaminants in soil, air, water and foods.

Reducing affects

But, what to do when many pollutants are involved, as in the majority of instances? Comprehensive biomarkers could flag peaks of the overall environmental hazard, as well as the impact of risk reduction measures such as lowering emissions or risk communication to citizens.

Several studies indicate that human semen quality is highly sensitive to pollutants, but normal parameters can be restored by an improved living environment. Moreover, recent research has shown that new biomarkers might be used in human semen as early sentinels, including the levels of essential trace elements (e.g., copper), antioxidant enzymes, sperm DNA fragmentation and telomere length in spermatozoa. Under this respect, men at fertile could become a population group important for estimating the amount and extent of the environmental exposure as well as its health relevance.

In fact, the main mechanisms that impact on semen quality (e.g. genotoxicity or endocrine disruption) are also highly relevant for other long-term adverse outcomes, such as cancer. Thus, a poor semen could be considered as a timely flag for environmental hazards getting to biologically active levels in the organism.

The optimal "environment-health" approach should be a "one-health" approach that integrates and exploits several data flows from environment (including food chain) and biomonitoring. It is also important to include dietary and non-dietary habits, as they play an important role in the environment-health framework and are related to socio-economic status: examples are the consumption of certain foods (e.g. fatty fishes as a source of dioxins) and lifestyles that may act in synergy with environmental toxicants, such as tobacco smoking.

Fertility and in general reproductive health is important for the future of communities, supporting the inclusion of a "time" dimension into the scientific and ethical aspects of health risk assessment/management. Indeed, a sustainable societal development should satisfy the needs of the present generation without jeopardising the future, including the health, of the next generation(s). There are several ongoing initiatives striving to develop an integrated "Environment-Health" assessment to be applied in practical situations. The network "EcoFood-Fertility" (<u>www.ecofoodfertility.it/</u>) has stemmed from the need for an evidence-based response toward the so-called "Land of Fires": a large and densely populated area of Southern Italy (2,5 million inhabitants), ill-famed for the concurrent presence of multiple pollution sources (waste disposal, traffic, intensive agriculture). EcoFoodFertility pivots on human semen biomonitoring as an early and reliable tool for assessing the environmental impact on health, not limited to reproduction.

Biomonitoring must be integrated with studies on life-style and diet, both as risk-modulating factors and as drivers for empowerment of pollutant-exposed people, to reduce their toxicant burden. The objective in progress is an international network of action: the groups involved investigate environmentally-challenged populations and intend to develop a sciencebased prevention framework, including novel, sensitive and robust panels of biomarkers.

Under this respect, andrology can provide major inputs. Andrology is enjoying an increasing role in the last decades, due to growing problems of male infertility and reproductive cancers (testis, prostate): pollutants such as endocrine disrupters (<u>http://www.iss.it/inte</u>) are considered as significant risk factors for male reproductive disorders.

This scenario calls for joined efforts by clinicians, toxicologists and environmental scientists to get practical goals. Thus, the research that must be carried out by EcoFoodFertility and other networks has to targeted on the priorities and needs of exposed communities and be carried out in a spirit of "translational prevention": from bench to risk analysis.

Luigi Montano

Local Health Authority (ASL) Salerno and EcoFoodFertility Project, Italy I.montano@asIsalerno.it http://www.asIsalerno.it/

Alberto Mantovani

Istituto Superiore di Sanità, Roma, Italy alberto.mantovani@iss.it http://www.iss.it/

Supporting world-class research in France

Open Access Government lifts the lid on the work of the French Minister of Higher Education, Research and Innovation and the National Center for Scientific Research (CNRS)

n the view of France's National Center for Scientific Research (CNRS), interdisciplinary research in France is of the upmost important in the country today. CNRS is a public research institution, under the French Ministry of Higher Education, Research and Innovation. With more no less than 15,000 researchers and nearly 17,000 engineers and technicians, CNRS strongly emphasises global research and the production of scientific papers.

CNRS covers all scientific disciplines, including the humanities and social sciences, biological sciences, nuclear and particle physics, information sciences, engineering and systems, physics, mathematical sciences, chemistry, Earth sciences and astronomy, ecology and the environment.

They have also defined 10 societal challenges, which include:

- (1) The management of resources and adaptation to climate change;
- (2) Clean, safe and efficient energy;
- (3) Industrial renewal;
- (4) Health and well-being;
- (5) Food security and demographic challenges;
- (6) Sustainable cities and transport;
- (7) Information and communication society;
- (8) Innovative, integrative and adaptive societies;(9) Space and;
- (10) Freedom and security of European territory, citizens and residents.

You can find out more about these by going to: <u>https://uk.ambafrance.org/The-French-National-Strat-egy-for-Research-is-out</u>

Interdisciplinary programmes

CNRS strongly supports innovative interdisciplinary projects, where its teams join forces across a varied array of scientific fields. The aim here – is to provide support for the most dynamic teams and the promising projects – to ensure the development of complementary research among different fields.

The main objectives of the programmes are:

- To support the emergence of new research themes at the interface of traditional fields;
- To provide answers to scientific and technological challenges, as well as socio-economic objectives or societal problems;
- To structure the scientific community, by supporting exchanges between researchers from different disciplines and by facilitating the installation as well as the use of common equipment and;
- To help build teams and projects for ANR and European calls.

Frédérique Vidal, Minister of Higher Education, Research and Innovation

We noted earlier that the CNRS is a public research institution, under the French Ministry of Higher Education, Research and Innovation. By way of background to the Ministry's work, it is worth mentioning that Frédérique Vidal currently heads up France's Ministry of Higher Education, Research and Innovation. Vidal's impressive background certainly befits her current role, some of which is worth a mention here.

RESEARCH & INNOVATION



Frédérique Vidal, Minister of Higher Education, Research and Innovation

Vidal was President of the University of Nice Sophia-Antipolis (UNS), before being named as the Minister of Higher Education, Research and Innovation. In terms of her qualifications, she holds a master's degree in biochemistry from the University of Nice Sophia-Antipolis, a DEA from the Institut Pasteur, and a doctorate from the University of Nice Sophia-Antipolis.

Going further back, since 2004 Frédérique Vidal was a university professor in biochemistry, molecular and cellular biology at the UNS. She has also been the deputy director of the Department of Life Sciences, from 2007 to 2009, and was appointed research associate to the Dean of the Faculty, then director of the department, from 2009. Vidal is also Knight of the Legion of Honor, an honour she has held since 2013.

Another highlight of her career is her work as an external member of Inserm's regional scientific council from 1999 to 2003, as well as being a member of the jury of the Master of Virology at UPMC-Paris Diderot-Institut Pasteur, since 2004. She was also co-head of the European project Tempus, which concerns the reform and modernisation of higher education systems in the Partner Countries of Eastern Europe, Central Asia, the Western Balkans and the Mediterranean region ¹.

In terms of recent developments within the Ministry of Higher Education, Research and Innovation, one worth looking at concerns future investments for 17 noteworthy projects. Frédérique Vidal and Louis Schweitzer, Commissioner General for Investment on 17th October announced the amount of the allocations allocated to the 17 winners of the first wave of the call for projects, New curricula at the University of PIA 3. The envelope of €250 million over 10 years that can be replenished, is for projects supported by IDEX or Isite, by the action, Supporting major universities Research Project 3. Ultimately, this announced funding will improve both student success and professional integration.

In another key development, in September this year, Vidal announced an increase in the budget of the Ministry. The minister's visit that month to the Pierre and Marie Curie University was an opportunity to detail several measures in favour of research. Since laboratories are places of excellence and that French research must be maintained at the best international level, the Minister heralded an increase of more than €25 million in basic operating budgets of laboratories in support of research.

The Minister also recalled the role of project-based funding, and as such she announced that the budget of the National Agency for Research will be increased by at least 5% for 2018, to restore as quickly as possible higher success rates.

For Frédérique Vidal, higher education institutions must have new freedoms, a point which she was keen to explain in her own words as we end this article on a note of optimism: "Everywhere in the territory, our universities must be able to assert their identity and their project, dare to experiment and exercise the fullness of their skills"². In addition to a network of ten to fifteen world-class research and training universities, internationalised and strongly linked with research organisations, Vidal stressed that it will be necessary to develop a network of universities that value their specific excellence in the fields of training and where they choose to invest, she went on to say.

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Understanding evolution, past and future

Dr Virginie Courtier-Orgogozo from CNRS details her work on fruit flies, which examines the intricate link between genes and visible traits of living creatures

ach individual presents a unique set of observable characteristics. Where do these traits come from? Through her work on fruit flies, Dr Virginie Courtier-Orgogozo aims to decipher the connections between genes and observable features of living creatures, in order to better understand our evolution.

Our attributes result from complicated biological mechanisms translating our genes into something we can actually see. Genes can determine differences whether we have brown or blond hair, whether we are tall or short and our similarities. Each species is characterised by a series of visible traits. For example, compared to our closest living species, the chimpanzee, we humans have no tail, shorter hairs on most of the body, soft nails and a sophisticated language. To understand what makes us what we are, as human beings or as individuals, it is important to explore the origin of our traits.

Dr Courtier-Orgogozo and her team, from CNRS and the Institut Jacques Monod in Paris, employ a cutting-edge multi-tool genetics approach, financed by an ERC Starting Grant, to explore the genetic causes of species-specific traits. They examine visible changes between closely related species of fruit flies and aim to reconstruct their evolutionary history, and the origin of their differences. For example, between humans and chimpanzees there is about a 1-5% difference in DNA.



Fig. 1. From the field to the bench. Top left: Fly samples are collected from the wild. Top Right: Observation under the microscope. Bottom left: the fruit fly Drosophila santomea, male and female. Bottom right: Developing organs inside the fruit fly stained with artificial colours

Among all these mutations, which ones are responsible for our human characteristics? Fruit flies are perfect organisms for genetic research because closely-related species can produce hybrids, a process in which pieces of DNA from one species are introduced in the genome of another species, thus allowing researchers to explore the consequences of genetic mix and the effect of particular genomic regions.

Dr Courtier-Orgogozo's team recently analyzed a species of fruit fly which lives on the volcanic Island Sao Tomé. This species is devoid of two particular sensory organs that are present in all related species. The insular species contains more than one million mutations in its DNA compared to its sister species. Among all these sequence changes, the team searched for the one responsible for the loss of sensory organs. Their discoveries uncovered two unexpected results. First, they found not just one mutation but three different ones. Introducing one mutation at a time has a small effect, and introducing the three together

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The Database of Genotype-Phenotype Relationships Search Gephebase for genes, phenotypes, taxa, mutations, articles

Fig. 2. Gephebase. an online database of the relationships between genes and visible characteristics in animals and plants. www.gephebase.org

has a much stronger effect. Thus, one mutation is not enough to obtain flies with no organ, and each mutation has been important during evolution. Second, they found that the three mutations are located within a tiny portion of the genome. In contrast, the millions of mutations that occurred during the evolution of the insular species are scattered all over the genome. It is like looking for three cell phones lost anywhere along the road between New-York and Boston (300km) and finding them all within one meter. The team is now investigating why all three mutations happened in such a limited region of the genome. Their work suggests that the roads for evolution are not as numerous as previously thought. For certain visible changes to occur, nature does not have multiple options. In fruit flies there is a gene whose manipulation can lead to additional sensory organs when it is expressed at higher levels, and fewer sensory organs when expressed at lower levels. The three mutations were found to decrease the expression of this gene, thus leading to fewer organs. To change sensory organ number, evolution seems to prefer to manipulate this gene.

Another ongoing project examines the mechanisms that stabilise biological systems. Traits characteristic of human beings or of any other species are fairly stable between individuals yet such traits have changed between species during evolution. The goal is to explain the mechanisms and genes that act together to produce robust characteristics. Experiments are undertaken to test whether the mutations that occur during evolution first produce new traits that are unstable and that get stabilised secondarily because of subsequent mutations or whether mutations directly create new robust outcomes.

A third line of research is the compilation of data from scientific literature about the genes and the mutations identified to be responsible for natural variation between populations or species in animals and plants. The dataset is accessible at www.gephebase.org. It shows that evolution often repeats itself and does not take as many paths as we might have thought. For example, adaptation to high altitude evolved independently in humans and birds through modification of the same genes. This result is reminiscent of the team's results on the evolution of sensory organs in fruit flies. It seems like there is a dictionary of correspondence between traits and genes, and Dr Courtier-Orgogozo aims to decipher this dictionary. The current state of knowledge of the connections between genes and traits is so advanced that, in some cases, researchers can now successfully predict which genes should be modified to achieve a specific visible modification. The new CRISPR-Cas9 genetic engineering technology allows researchers to put this knowledge into practice, and to rapidly modify domestic animals as they wish. The laboratory is sensitive to the potential ethical

problems posed by CRISPR-Cas-9 and tries to bring his expertise to societal issues related to CRISPR-Cas9.

Dr Courtier-Orgogozo's research tackles several central questions in evolutionary genetics and provides new, rigorous data to better understand our evolution, past and future.



• What is the connection between genes and visible traits?

- What makes two species different?
- How do species evolve?





Virginie Courtier-Orgogozo Directeur de recherche CNRS Institut Jacques Monod Université Paris Diderot Tel: +33 1 57 27 80 43 virginie.courtier@ijm.fr https://virginiecourtier.wordpress.com/ www.twitter.com/Biol4Ever

GaN on Si: An example of the links between academic research and innovation in France

GaN is a young semiconductor material full of promises for research and development, in the view of Director of Research at the CNRS, Fabrice Semond

Semiconductor material represents a market of more than \$350billion. It is largely dominated, in terms of market, by silicon. However, there are other semiconductor materials, called compound semiconductors, that have new properties which are of interest to many sectors of industry. Among these compound semiconductors, gallium nitride (GaN) with a market of about \$18billion, has had the highest increase over recent years.

Under the impetus of Japanese researchers and industries, in particular S. Nakamura (Nichia Corp.), I. Akasaki and H. Amano (University of Nagoya), remarkable progress was made towards the end of the 1980s in the synthesis of GaN. These rapid advances have stimulated an extraordinary effort around the world and led to the demonstration of Light Emitting Diodes (LEDs) emitting blue light with great efficiency, which paved the way for the manufacture of LED lamps emitting white light.

The Nobel Prize in Physics was awarded to these three Japanese researchers in 2014. In the space of 3 decades, these LED lamps have revolutionised the lighting industry because they consume very little electricity compared to traditional light sources. Knowing that lighting accounts for 20-25% of the world's electricity consumption, the replacement of current lamps with LEDs will result in significant energy savings across the globe (about 6-8% of the total electricity bill).

GaN has many other advantages, as its remarkable properties also make it particularly well suited for the manufacture of electronic components to convert electrical energy in one form or another. These components are currently made of silicon, but GaNbased components can convert electrical energy more efficiently than silicon components. GaN electronic components are also expected to play a decisive role in the deployment of future generations of mobile telecommunication.

However, massive adoption of GaN products will only be possible if their production cost is significantly reduced and this is exactly what GaNon-Si is about.

GaN-on-Si, towards a technological revolution

GaN-based components are manufactured from a wafer consisting of a thin layer of GaN (a few micrometers thick) deposited on a thick substrate (several hundred micrometers thick). The choice of the substrate is essential because it will affect the manufacturing process of the component as well as the cost of production. Sapphire is the substrate mostly used to manufacture GaN-based LEDs. LEDs grown on sapphire have reached an extremely high level of performance. However, sapphire substrates also present some limitations in terms of size, price, thermal conductivity, and manufacturability.

By replacing sapphire with silicon, the fabrication of GaN-based components becomes compatible with the existing production lines of the microelectronics industry. As a result, significantly reducing the cost of manufacturing.

Therefore, the transition to GaN-on-Si will accelerate the adoption of GaN. But today GaN-on-Si plays a minor role in the GaN market because growing GaN is more difficult on Si than on sapphire. Technological problems are identified and solutions exist, but they have to be implemented in industrial production environments. This is precisely what is taking place around the world, with the creation of numerous start-ups and the announcement of major investments to develop GaNon-Si-based components.

By promoting the adoption of GaN components and the related energy saving systems, GaN-on-Si is expected to deeply impact tomorrow's economy and life.

GaN-on-Si in France

France intends to play an important role in the deployment of GaN-on-Si. Several start-ups have been created and companies in the semiconductor





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sector have invested in this technology. There is still a long way to go before celebrating any French success in this domain, but we can already underline the strong impact of the French academic research on the development of GaN-on-Si.

The CRHEA, a CNRS laboratory, instantly realised the interest of GaNon-Si, was a pioneer, and quickly became one of the leaders on the subject. In collaboration with academic and industrial partners notably IEMN and Thales TRT, high performance devices have been produced demonstrating the relevance of GaNon-Si.

From the beginning of the 2000s, the know-how and a related patent developed at CRHEA were licensed to a French SME (Picogiga) who then produced GaN layers for radiofrequency applications.

In 2003, Picogiga joined the SOITEC group. In 2008, a consortium of French industries (STMicroelectronics, OMMIC, Picogiga/SOITEC) and academics (CRHEA, Greman) decided to assess GaN-on-Si for applications in the field of power electronics for the

manufacture of more efficient energy converters. Based on this experience, on the CRHEA patent and with the CEA-LETI support, the Exagan startup was created in 2014 to produce and commercialized GaN-on-Si based power converters. Another output of these technological developments was achieved recently with OMMIC announcing the launch of a production line for GaN-on-Si radiofrequency circuits for next 5G antennas.

Recently, also based on the know-how developed by CRHEA, the EasyGaN start-up was born, with the objective of providing an original and proprietary solution (an advanced silicon pseudo-substrate) that makes easier to grow GaN-on-Si, in fact as easy as growing GaN on GaN. This technological brick should definitely accelerate the adoption of this GaN-on-Si technology.

In addition, CEA-INAC and CEA-LETI have transferred their know-how in the field of nanowire LEDs to the Aledia start-up created in 2011. Aledia develops an original LED technology based on GaN-on-Si nanowires for applications in the lighting and display markets.

Thanks to insightful and pertinent academic research and to the existence of a semiconductor ecosystem, a diversified industrial activity around GaN-on-silicon is born in France. This promising start has also benefited from the support of the "Plan d'Investissement d'Avenir" with the creation of the GANEX labex. This network of excellence has since 2012 strengthened the positioning of French academic actors in terms of knowledge and visibility while bringing it closer to the industrial world.



Fabrice Semond Director of Research at the CNRS Centre de Recherche sur l'Hétéro-Epitaxie et ses Applications Tel: +33 493 95 78 19 fs@crhea.cnrs.fr www.crhea.cnrs.fr

The rise and future of Blockchain

In this article, the founder and co-founder of the Blockchain Federation provide insight into the future for a blockchain-based purpose-economy

uring the years following the rise of Bitcoin in 2008, Blockchain and related digital technologies have spiralled into a revolutionary phase of development, spearheaded by idealists, anarchists, and investors. This is why the authors Eddy Wagenaar and Irina S. Zimakova founded the Digital Embassy in 2016, the international umbrella organisation for 16 digital technology federations: 3D Printing Federation, Artificial Intelligence Federation, Augmented Reality Federation, Big Data Federation, Blockchain Federation, Cloud Computing Federation, Crpytocurrency Federation, Cybersecurity Federation, Drones Federation, FinTech Federation, ICO Federation, IoT Federation, Quantum Computing Federation, RegTech Federation, Robotics Federation, and Virtual Reality Federation.

With the Blockchain Federation as its flagship federation, the Digital Embassy aims to connect local governments, businesses, and educational institutes to digital technologies, anticipating future changes through agile-like discussions to ensure a hyper-intelligent and smooth transition into the digital era. It is putting together an international digital think tank of global thought leaders to address regulatory issues, expedite law-making and political shifting, and provide for social-economic architectures to effectively integrate digital tech into existing societies.

Blockchain has been explained many times over. For those still unable to understand, please think of Blockchain as if it were a 'digital database', roughly one hundred times safer than Google's infrastructure. It is basically Bitcoin's 'operating system', recording financial transactions peer-to-peer, cutting out the middleman (bank). The ability to record almost anything onto this digital distributed database, is probably the greatest invention since the Internet, which is why the Blockchain is often referred to as the Internet of Value.



In the very near future, anything and everything will be put 'on the Blockchain': passports, ID-cards, medical records, letters of credit, freight & customs documents, hotel & flight bookings, and so on and so forth.

Everything will become transparent and immutable. There will be no more room for error, no more room for corruption. Society will change into a blockchainbased purpose-economy, where people subscribe to global peer-to-peer networks to find divergent microjobs they like doing, paying them cryptocurrencies by

the minute. Work will feel like a hobby. Mutual ratings will ensure trustworthiness and reliability between client (employer) and contractor (employee). Smart (automated) contracts will allow for the right type of insurance and paperwork for the job, matching with contractor's fundamental criteria. Contractors will be paid instantly upon completion of the job, again via smart contract, which will show at their fee-less Blockchain smartphone.

"Society will change into a blockchain-based purpose-economy, where people subscribe to global peer-to-peer networks to find divergent micro-jobs they like doing, paying them cryptocurrencies by the minute."

Effect on jobs

All digital technologies combined are expected to automate up to 80% of all current business processes, resulting in many millions losing their jobs. The key issue is if digital technologies will be able to provide for enough new jobs in time for us all to survive. It is paramount digital technology is accommodated, facilitated, and utilised in an intelligent fashion. The genie is out of the bottle: slowing down the process due to loss of 'old power', would potentially be harmful to an economy's global market position. Keep up with these modern times, that is the message.

Stiff competition from major international players such as Dubai, Estonia, Singapore, and Switzerland is keeping everyone at the tip of their toes. Dubai is very much aware of its fossil fuels ending and is anticipating on its future by means of digital technologies. All its government documents will be on the blockchain before 2020 – that's within a little over 2 years from now.

Dubai also recently announced 'emCash', the first state issued Blockchain-based digital currency, enabling its citizens to pay for various items such as their daily coffee, children's school fees, utility charges, and money transfers. Their digital currency provides for faster processing, improved delivery time, less complexity and cost, peer-to-peer lending, and credit rating to name a few.

What's more, Microsoft recently unveiled 'CoCo': technology to speed up blockchain and address scalability issues. CoCo, short for Confidential Consortium, will be ready and made Open Source by 2018. It involves commitment of Intel, R3, and JP Morgan aiming to make blockchain roughly one hundred times faster, targeting to create the foundation for Blockchain for enterprises.

The future of Blockchain, Cryptocurrencies, and related digital technologies is not in the hands of governments though and can easily spiral into riots or even civil war if not guided or addressed properly. It is imperative to balance the interests of those involved so it seems only logical to join the Digital Embassy or one of its 16 federations.

Each federation has its own small group of C-level decision makers, operational staff, and technical staff. Also, each federation has several special interest groups, allowing for cross-federation and cross-market interaction. This enables for example a UK insurance company in the Blockchain Federation to learn from a Dutch contact-centre's experience with Chatbots in the AI Federation. Sharing knowledge and learning from each other is the peer-to-peer model how to move forward in the digital future.





Eddy Wagenaar Chairman, Digital Embassy founder, Blockchain Federation

Irina S. Zimakova President, Digital Embassy Co-founder, Blockchain Federation www.blockchainfederation.org

www.digitalembassy.org www.twitter.com/EUBlockchainFed

Blockchain for sensitive and personal data

Returning control over our personal data to us through the Blockchain – explored by experts from Swiss Re and IBM Research

- Restoring customer control, trust and transparency over the use of personal sensitive data.
- Easing the burden of data ownership for the insurance industry.
- A joint initiative by Swiss Re & the IBM Research Lab.

hate getting insurance. It's such an impossibly convoluted process. With all the personal data we put out there on the net, why can't we have a smart app on the mobile that tells us what we need and lets us buy cover the same way we buy train tickets or books on Amazon?

As an insurance IT professional, I know that dealing with personal sensitive data can be a colossal headache. As an industry, we put a lot into gathering and harmonising such things as policy and claims data – and as soon as we have it, we fret over protecting it from ourselves in accordance with ethical principles and multivariate, fast-evolving legislative frameworks. Tap into other sources like fitness trackers or buying behaviour to drive "Insurance made Simple"? Challenging. Social media? Unthinkable. Or is it?

Trust and transparency

Let's look at the underlying problem. It all comes down to trust and transparency. Data modellers know that when a model causes inordinate pain it is usually because it does not represent reality quite right. So, where is the flaw in how we deal with personal sensitive data? Well, insurers act as guardians of individuals' personal sensitive data. And they shouldn't. The power to decide on who can see my personal data should be with me. Is that possible?

Traditionally, the answer has always been no. There simply wasn't a way to ask consumers in real time, nor a way to analyse large amounts of highly distributed data. So, we have become accustomed to hoarding that data on our premises, and managing it as best we can. But with the advent of truly distributed technologies, that is changing. If Blockchain can distribute ledgers and even the execution of code snippets that power in-block calculations for smart contracts, why shouldn't it allow us to distribute decisions on access to distributed data? Even distribute its analytic processing?

Power to the people

With that idea, a small group of curious minds from Swiss Re's IT innovation teams and IBM's Rüschlikon research lab set out to prove or disprove the feasibility of a platform that cleanly separates regulating access to personal sensitive data from storing and analysing that data. A platform that places decision power on access to personal sensitive data in the hands of the individual that data is about, and ensures full transparency on what that data is used for, by whom, when, and under what specific consent. We call it "Blockchain for Sensitive Data", or "B4S".

Traditional implementations of this vision are likely to fall short when it comes to their security and privacy guarantees. Indeed, users might not feel comfortable to hand over their sensitive medical data to a single entity: they might (legitimately) feel that they have lost control of where, when and how their data is used, and that they cannot fully exercise their right to opt out or revoke data access. Fortunately, it's Blockchain to the rescue.

A Blockchain primer

Technically speaking, Blockchain is a distributed operating system that provides an environment to execute so-called smart contracts, and to maintain all the data structures they require (a.k.a. world state).

The novelty with respect to other, more traditional, solutions to the problem is that Blockchain maintains its properties even in presence of buggy/malicious computing nodes.

Let's use an analogy to understand what this means: we can equate a Blockchain environment to a set of players playing a board game. The board game welcomes more than one player (and so the system is distributed). The players are free to interact with each other (and so they can execute bilateral or multi-lateral transactions).

Each player only needs to look at the board and its pieces to understand the state of the game – who's winning, who's losing etc. (and so there is a commonly agreed-upon world state). Crucially, the game may be designed in such a way that the players are forced to behave honestly, or be caught cheating and banned from playing on. **Blockchain for Sensitive Data**



Why blockchain?

Among other things, Blockchain is great at the following scenario: a set of entities would benefit in doing business together but – because of security and trust concerns – one of two things happen: either they don't do any business, or they do it inefficiently. Blockchain creates the technical foundations so that mistrusting participants can do business together in a way that their actions are limited to what they have previously agreed.

This use case fits perfectly: today medical data isn't being shared as much as it could. Blockchain creates the technical foundations for this to happen in a way that is acceptable to all.

More specifically:

1) Blockchain helps us create a new virtual entity that is trusted to access medical data on behalf of end consumers; for instance, this entity is trusted to access private healthcare data stored on Dropbox and Fitbit.

Why a virtual entity? Because we have already established that there is no real one (person, people or company) who is trusted by all to centrally handle such data, and so we need one that is created by the Blockchain and whose actions are constrained by the rules of the smart contract.

2) Blockchain enforces this very simple, yet powerful rule: medical data can be accessed if and only if two entities agree: the requester (e.g. an insurer) and the owner (i.e. the consumer); otherwise the request is denied.

Next: Build a community

So, yes, it can be done quite nicely on Blockchain. Next, we need to think about how it can be owned and managed so that end customers and regulators can fully trust it, and we can leverage it to provide value-adding services. We are beginning to reach out into the insurance industry, with the intention of forming a consortium that can build and operate an open industry-wide platform. Later, a foundation or the like could be set up, sharing control with consumer protection experts and regulators.

Under the best of circumstances, this will take a while. By then, distributed analytics (sending the algorithm to the data instead of pulling the data to the algorithm), will have taken hold and we will be able to run analyses on whole risk portfolios, with specific consent by individual consumers, without having to own the data.

And what will all that mean for us?

We will be able to have a smart app on our mobiles that walks us through covering our insurance needs in ten minutes every January. And we will know what of our data powers it, that we allowed it, and that the data won't be (mis)used elsewhere.

And in my insurance job life, I can get on with my work without being afraid of stumbling into non-compliance because of a legal change somewhere that I just had the misfortune to miss. I might even get an easier time with regulators. Because, with full transparency and control for the consumer, they might just find they can relax a bit, too.





Daniel Thyssen Business Partner & Digital Transformation Lead, EMEA Swiss Re Life & Health

Alessandro Sorniotti Researcher in security and cryptography IBM Research – Zurich http://www.swissre.com/reinsurance/ insurers/life_health/ https://www.zurich.ibm.com/

Blockchain insurance set to change the industry

Open Access Government's Jonathan Miles explores the tremendous potential of Blockchain in the European insurance industry

n the view of the European Insurance and Occupational Pensions Authority (EIOPA), "all stages of the insurance value chain are being impacted by InsurTech and more broadly digitalisation. In a roundtable organised by EIOPA during April 2017, we find out that, "insurance products are increasingly capable of being purchased online, including through smartphones that allow such purchases at any time and from any place."

For example, we find out that Artificial Intelligence is a technology with tremendous potential in insurance, especially concerning the areas of fraud detection and claims management. In addition, we discover that Blockchain in the world of insurance is constantly growing and therefore also has much potential, particularly in commercial lines, the re-insurance business and around intra-group transactions.

"Blockchain is likely to be first implemented in commercial lines than in personal lines, since the former are not affected by privacy issues such as the right to be forgotten recognised in the GDPR, which is at odds with the immutability of Blockchain."

New technologies, including Peer-to-peer (P2P) insurance, have the potential to significantly reshape the insurance landscape in the future. As part of this roundtable, the second break-out session underlined both Blockchain and smart contracts. Blockchain is a type of distributed ledger technology we find out, that is "characterised as a digital, chronologically updated, distributed and cryptographically sealed ledger of transactions."

Financial services

We also learn that Blockchain technology could significantly disrupt the financial services sector (and other



sectors), as it might remove some "middle men", as well as by reducing data redundancy, given that all the data would be stored in a single distributed database. The session also detailed examples of new use cases for Blockchain, such as European insurance and reinsurance undertakings, as the extracts below explain.

"New use cases for Blockchains are constantly emerging, underlining the nascent state of this field. During the break-out sessions, other use cases discussed included examples around identity or document management, where Blockchain could enable the automation of complex verification processes allowing the precise identification of an entity, person or document in the Blockchain. Blockchain could also be used in the area of regulatory reporting (RegTech), as well as for improving the recognition of claims history statements (which are used to calculate no-claims bonuses). It may offer innovative ways to complement or replace paper-based workflows.

"Blockchain is likely to be first implemented in commercial lines than in personal lines, since the former



are not affected by privacy issues such as the right to be forgotten recognised in the GDPR, which is at odds with the immutability of Blockchain. Blockchain has also great potential in the re-insurance business and for risk transfers in intra-group transactions; this is the approach that is being tested by a private Blockchain consortium of large European insurance and reinsurance undertakings."¹

"Insurance products are increasingly capable of being purchased online, including through smartphones that allow such purchases at any time and from any place."

Finally, the session explored the role that regulatory authorities could play in the world Blockchain. "In public Blockchains, supervisors may need to focus on a range of different issues, such as the role of miners and nodes, or security and privacy challenges. Some participants also noted that regulatory authorities could also consider addressing some of the legislative barriers preventing the implementation of Blockchain" we find out. In conclusion, the key findings around Blockchain from the EIOPA InsurTech Roundtable were that its use in insurance is still limited, but is showing potential. It is likely that Blockchain will be implemented first of all in commercial lines, in the reinsurance business and for intra-group transactions.

1 https://eiopa.europa.eu/Publications/Reports/08.0_EIOPA-BoS17-165_EIOPA_InsurTech_Roundtable_summary.pdf

Jonathan Miles Editor

Open Access Government Tel: +44 (0)1270 502 874 www.openaccessgovernment.org www.twitter.com/OpenAccessGov

Linking consumption and production

James Lomax from the Economy Division at UN Environment offers his thoughts on the policy priorities for global food systems

The 10-year framework of 6 programmes on sustainable consumption and production patterns (10YFP) is a global framework of action to enhance international cooperation and to accelerate the shift towards sustainable consumption and production (SCP), in both developed and developing countries.

At the United Nations Conference on Sustainable Development (Rio+20) in 2012, heads of state adopted the 10-Year Framework of Programmes on sustainable consumption and production patterns (10YFP), a global framework for action to accelerate the shift towards SCP in both developed and developing countries.

One of the programmes within 10YFP is the sustainable food systems programme (SFS), for which James Lomax is a focal point, who starts the interview by revealing that this aspect of the UN's work was very much aimed at bringing these ideas into policy-making. He then tells us about the concrete activities of the SFS programme, in his own words. "The SFS programme is there to address the fact that current food and agriculture systems – from production to consumption are failing in many ways. For example, in some parts of the world they are leaving people hungry whereas in some places, obese and everything in between. At the same time, the food system causes much environmental degradation so within that brief, UN Environment is working on the activities within the SFS programme's 5 themes.

"The first theme is around getting people to eat better, which could be described as sustainable nutrition. But what does that mean? It means more balanced diets and with less animal protein, – how to encourage people to move away from consuming processed foods and also to choose sustainably grown foods. Together this would mean more sustainable diets that are good for people and for planet. The second point is around reducing food losses and waste, indeed as you know 30% of food produced it not eaten.

"The third point is about sustainable supply chains and value, so how can they be more efficient and how can we bring in more sustainable markets to farmers? The fourth theme which is linked to the third, is around agriculture and how can we make this sector more sustainable and encourage farmers to adopt more sustainable practices.

"The fifth is a more overarching theme, which concerns enabling conditions and how to make food and agriculture policy-making more integrated. How can we bring in health practitioners into discussions about food production? How do we make food sector governance better from a sustainability angle? While it is all-encompassing – if all these things are done in the right way – then we can create a more transformative agenda."

"The SFS programme is there to address the fact that current food and agriculture systems – from production to consumption are failing in many ways. For example, in some parts of the world they are leaving people hungry whereas in some places, obese and everything in between."

Agriculture

Elaborating on sustainability in terms of the process from farm to fork, Lomax explains that policy makers at local and national level are not thinking in a crosscutting way. For example, there is much silo thinking between agriculture and food policy makers, that prevent the development of holistic solutions and activities that positively impact agriculture, environment, business and human health.

Lomax then offers his thoughts on the need for multistakeholder action and feeding this into policy making by the public and private sectors. For example, how can farmers be brought into discussions, but also with the private sector and NGOs convened by governments?

Looking back to the five themes, Lomax then underlines that if consumers can demand more diverse and balanced food, then that will have an impact on the supply chain. He goes on tell us more about this.

"It will change the way retailers produce and market their food to consumers, so from the food waste point of view for example, retailers have a great influence on the way consumers value food and how it is consumed at home.

"Therefore, at UN Environment, we want there to be a positive influence from the food supply chain to consumers, so they understand that bad diets and food waste is bad for them, the planet and when it comes to food waste is bad for their pocket too."

In closing, the conversation moves towards the technology angle in global supply chains, indeed Lomax is keen to expand this interesting point.

"Technology can play a very positive role and when it comes to efficiencies and food waste, it's very important. However sometimes supply chains can be over complicated, and technology plays a part in that – the horsemeat scandal is a good example where the distance between the consumer and production became too far to be traceable."

"The connection between the way food is both consumed and produced therefore becomes too far removed. This make it difficult for people to understand the inherent value it has. I think if we address the values we have around food, then things would change dramatically.

"There are a lot of technologies out there which are very good when it comes to efficiencies and price, but I think we have to look at quality over quantity and if food is priced correctly."

James Lomax

Programme management officer (food systems and agriculture)

Cities Unit, Energy and Climate Branch Economy Division, UN Environment Tel: +33 1 44 37 14 37 James.Lomax@unep.org http://www.un.org/ www.twitter.com/10YFP

Ambrosus: Digitalising the Global Trade with Blockchain

Angel Versetti, CEO of Ambrosus discusses the world's first blockchain ecosystem for supply chains and global trade



B lockchain is the new internet. 2017 has been explosive for the blockchain sector, with the technology permeating every possible industry, with every country and every corporation talking about it. Cryptocurrencies have taken financial markets by storm, with no institutional investor without sharp feelings about them: some calling them the future, others a scam. With countless Initial Coin Offerings (ICO) bootstrapping start-ups, blockchains and protocols overtaking Venture Capital by a factor of 3 within only months of reaching its volume. The market capitalisation of the industry grew from \$16 to \$160 billion USD just this year alone. Following the explosive growth in the first half of 2017, the regulations started coming in from all parts of the world in the second half of 2017 to try and reign in the booming sector.

Being a victim of its own success, blockchain also attracted a large number of opportunists and fraudsters, who abuse the unregulated markets and the powerful technology, as a result leading to a lot of public and financial sector stakeholders taking a very careful approach when it comes to using the blockchain. Most of them simply united into large consortia to build their own private distributed databases, which they call blockchains. When it comes to community-driven, public blockchains, they have to constantly prove themselves to be legitimate stakeholders in order to interact with the established industrial and financial players.

Ambrosus: Pioneering legitimacy and rejecting tens of millions of dollars

In the flurry of Initial Coin Offerings in 2017, most of which were conducted with little else than a white paper and a flashy website, and many of which broke countless regulations and practices, Ambrosus was different from the very outset. Emerging from the two leading Swiss technology clusters, the Crypto Valley in Zug and EPFL Innovation Park in Lausanne, Ambrosus secured both the financial backing and operational support from the public-sector entities in Switzerland; it boasted an official partnership with the United Nations 10YFP, responsible for implementation of Sustainable Development Goals, and an endorsement from EIT Food.

The team includes the ex-Director of the biggest public sector R&D cluster on food and nutrition in Switzerland, a former project lead at the UN, an ex-Vice President at JP Morgan and





With such a line-up, partnerships and real technology, Ambrosus already differentiated itself from any other ICO or TGE in 2017. The way it conducted its Token Generation Event was also remarkable, with over €32 million collected at the time of writing. Ambrosus was the first major blockchain to introduce a comprehensive Know-Your-Customer (KYC) policy.

With anonymity being treasured by many parts of the community, many members did not pass the stringent requirements. Ambrosus had to reject over €35 million, something that was met with shock and disbelief in the crypto-industry, which wondered why would anyone raising funds, give up such a big amount just to stay compliant. This is the price Ambrosus was paying in order to stay compliant and signal to other players in the industry that this is the way the process would have to be done.

And soon enough, under the regulatory pressure, the compliant way to conduct ICOs, paved by Ambrosus, became the new norm in the industry, although implemented by many half-heartedly, to allow as much money as possible to pour in. The compliance and legitimacy of Ambrosus is what resulted in a big



outreach from various policymakers, both in Europe and in other regions to reach out and see how Ambrosus could help transform supply chains and trade in those regions. Witnessing the way Ambrosus stands by its values gave them confidence to choose Ambrosus as partner for their pilot projects.

Why connecting tiny sensors to blockchain is a huge deal

Ambrosus combines high-tech sensors, blockchain and distributed open-source software to build a universally verifiable, community-driven ecosystem to assure the quality, safety & origins of products. Located in Switzerland, the most innovative country in the world for 6 years running, Ambrosus innovates within the innovation space of blockchain. It introduced Amber, the world's first data-bonded token, to which sensor-generated readings are assigned through an immutable ledger. It created an architecture that permits compliance, quality control and audits to be automated by smart contracts, creating value for both the private sector and the governments.

If integrated in the supply chains, Ambrosus can monitor the flows of goods, payments and storage conditions, bringing transparency and accountability to the global commerce. It can also ensure that imports and exports do correspond to norms and regulations by serving as an independent verification mechanism.

The key to making this vision work is to turn sensors into oracles, the trusted source of information for the blockchain. Coupling the integrity of sensor-generated data with the blockchain consensus mechanism results in the ability to create the truthful digital reflection of the real world on the blockchain. The implications are significant for the economy, because to build distributed economy, blockchain alone will not be enough. Linking it to billions of Internet of things (IoT) devices and sensors producing quadrillions of readings will be key for any smart city or any economy that wants to run on the blockchain. Ambrosus already works on integration of various third-party sensors into its blockchain - through APIs and gateways and is applying all its collective brainpower to the ultimate quest for the scalability of its network and seamless integration into IoT protocols.

Applications and Use-Cases of Ambrosus ecosystem

Ambrosus is a general-purpose solution, providing a trusted backbone to link products to data. On top of this backbone various layers and protocols can be built, enabling functionalities derived from Ambrosus blockchain, such as data analytics, data visualisation, decentralised storage, payment settlements mechanisms, real-time audits and process management and traceability. By keeping the blockchain open-source, having various APIs and developer tools in place and leveraging



the digital token Amber, Ambrosus creates opportunities for developers to integrate existing software or build new one, instantly monetising the traction through a digital token, Amber, which serves as the unit of exchange and as fuel on Ambrosus blockchain. Amber enables participants to derive value from the early adoption of the network, given the fixed limited supply of Amber. The value of adoption of Ambrosus protocol is thus threefold: short-term marketing boost, mediumterm value from rising value from adoption of the network, long-term value from creating a public good, a universal repository of data for the global commerce and intelligent supply chains.

The initial applications that were launched in Ambrosus ecosystem, include a peer-to-peer marketplace for quality assured products, where any two parties can enter a commercial deal, with quality parameters for products stipulated within the selfexecutable contract. Another application has been the supply chain management software, where all the processes from sourcing to processing to distribution could be monitored and managed through smart contracts, permitting automation of the processes. We are currently working on commodities barter platform, where tokenised commodities with assured quality can be exchanged securely.

Early success and adoption of Ambrosus

Ambrosus has developed use-cases for a wide variety of markets: food & beverages, pharmaceuticals, commodities and luxury items. For each market, the supply chain will have unique features, which can be reflected in customised smart contracts and distributed software. We have published detailed reports on protecting labels of products, assuring quality and tracing origins. The sensor system can monitor external environment (e.g. temperature, humidity, pressure, location) and internal parameters (structure of tissue, composition, presence of foreign bodies, chemical analysis, DNA analysis).

Ambrosus has become the most popular blockchain in the supply chain domain, with participants in its Token Generating Event hailing from over 100 countries and contributing over €32 million. Worldwide community of developers, engineers, enthusiasts and supporters of Ambrosus exceeds 50 thousand people, creating a lively and dynamic ecosystem.

Ambrosus has been invited to over 30 top-tier events this year, including being selected by Pioneers Festival, Start Summit, Hello Tomorrow and many others; it has been featured in over 100 media articles including Nasdaq, Vice Media, Finance Magnates and Food Navigator. Ambrosus has over 25 existing partnerships and over 100 in negotiation, with the goal to create a multi-stakeholder consortium for its public blockchain for supply chains and global commerce.

We welcome any partners and collaborators in our quest to transform the global trade.



Angel Versetti CEO & Co-Founder Ambrosus Gotthardstrasse 26 J

Gotthardstrasse 26, 6300, Zug, Switzerland EPFL Innovaiton Park, Station 13, 1015, Lausanne, Switzerland info@ambrosus.com www.ambrosus.com

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CONTACT

Andy Jowett Editor ajowett@pbctoday.co.uk



www.pbctoday.co.uk



Blockchain: what is in it for the European economy?

Benoît Abeloos, Policy Officer at the European Commission gives a compelling glimpse into how virtual currency could affect the economy

The publication of the white paper, "Bitcoin: a peer to peer cash system"¹ in October 2008 by the mysterious Satoshi Nakamoto (a fake identity), will be seen in the history of technologies as a disruptive milestone. By combining technologies which were known for years, the author created the first virtual currency, and a technology – blockchain – which enabled exchange of e-money without the usual unavoidable intermediaries: banks.

Developers and entrepreneurs then saw numerous new opportunities in the financial sector, especially as new regulations opened new possibilities and business models: RegTech, peer to peer payments, peer to peer lending, exchange of securities, crowdfunding, initial coin offerings, debt trading, etc.

People soon realised that the broader family of tech-

nologies called 'distributed ledger technologies' (of which blockchains are a subset) could be used not only to build virtual currencies or offer new financial services, but by exploiting their characteristics, explore new possibilities in many different areas and industries, such as the Internet of Things, energy, health, identity management, taxation, e-government, management of intellectual property and copyright, smart homes and cities. These technologies provide immutability, security and privacy of the data through encryption, while offering their ubiquitous distribution to all nodes.

The European Research and Innovation community didn't wait long to propose, in the frame of the EU Horizon 2020² programme, blockchain based research projects. D-Cent³ (Decentralised Citizens ENgagement Technologies) project, which was the first of its kind, was established as early as October 2013. The aim was

to actively foster open source and distributed platforms to encourage direct democracy and economic empowerment.

In the same vein, Decode⁴ provides tools that put individuals in control of whether they keep their personal data private or share it for the public good. MyHealth-MyData⁵ explores the very important political objective to empower patients to manage their health data. Bloomen⁶ provides an innovative way for content creation, sharing, monetisation and copyrighting, and symbloTe⁷ a single mobile application to interact with different IoT platforms. The next Horizon 2020 framework programme will, from 2018 to 2020, provide more opportunities, through calls for proposals, to innovate with blockchain, for example, in e-government, FinTech, Next Generation Internet, IoT, Smart Homes or Media.

New policies

The Commission is also exploring the use of distributed ledger technologies in relation to its policies. The first investigations concern the possible creation of a financial transparency gateway, with a pilot being tested, to improve the efficiency of financial data reporting, or tax and customs data collection. Application of blockchain to the CO_2 emission trading system, or the circular economy, could also be considered.

In this new reality and a digital market where the stance 'the winner takes it all' has too often become a standard, it is important for the European Commission to put in place policies avoiding the emergence of de facto standards, which may limit competition and keep customers, (public and private) locked with single vendors. Moreover, it will be very difficult for service providers to develop applications and services which can seamlessly operate on different platforms if they are proprietary.

These are the reasons why the European Commission, as part of the Digital Single Market strategy, is active in fostering the development and the adoption of international standards. It has established a liaison with the ISO Technical Committee 307 on Blockchain and Distributed Ledger Technologies, which has been set up recently. The Commission organised a policy and standardisation workshop⁸ on 13 September 2017 with European stakeholders representing the industry, governments, standards development organisations, citizens, and NGOs. European Standardisation Organ

isations⁹ have been approached to take a leadership role to identify EU specificities with regards to Blockchain, and produce a white paper.

Is blockchain going to deliver on its promises? Is "blockchain going to help to end hunger" as I saw on a slide recently? Is it going to be the new internet? Is a bubble being formed, with the frenzy of ICOs reaching summits of capital raising? Aren't we on the top of a hype cycle where inflated expectations are culminating? Are we going to soon reach the trough of disillusion?

All these statements probably have their part of veracity. The truth is that we need to validate the pertinence of blockchain for every kind of use we can envisage, compared to existing technologies. New business models need to be validated by real businesses and pilot projects. Lawyers and policy makers need to carefully assess several legal questions. Is the apparent contradiction between blockchain immutability and the right to be forgotten a real issue? Is the solution technical or in the interpretation of law? Can smart contracts be legally enforced, stopped, or reversed without changing the laws and/or the technology? What is the appropriate governance for blockchain?

The Commission will launch a European Blockchain Observatory and Forum¹⁰ (early 2018) to help answer these questions and explore the unknowns of this fascinating domain. It will also prepare policy initiatives to help EU start-ups and established companies to seize the opportunities. And grow.

- 1 <u>https://bitcoin.org/bitcoin.pdf</u>
- 2 http://ec.europa.eu/programmes/horizon2020/
- 3 https://dcentproject.eu/
- 4 <u>https://www.decodeproject.eu/</u>
- 5 http://www.myhealthmydata.eu/
- 6 http://cordis.europa.eu/project/rcn/211092_en.html
- 7 https://www.symbiote-h2020.eu/
- 8 <u>https://ec.europa.eu/digital-single-market/en/news/blockchain-and-</u> distributed-ledger-technology-policy-and-standardisation-workshop
- 9 CEN, CENELEC and ETSI
- 10 <u>https://ec.europa.eu/digital-single-market/en/news/eu-blockchain-observatory-and-forum</u>

Benoît Abeloos Policy Officer, ICT Innovation

European Commission, Digital Single Market https://ec.europa.eu/digital-single-market/en/benoit-abeloos www.twitter.com/DSMeu



The outlook of the Finnish economy

Finland's Ministry of Finance lifts the lid on the current phase of rapid growth of the Finnish economy and their expectations for the same in 2018

The Finnish economy is in a phase of rapid growth. In 2017 the rate of economic growth will reach 3% after which the projected growth rate slows down. In 2018 and 2019 GDP is expected to grow 2.1% and 1.8% respectively, which are above the estimated potential growth rate. Economic growth based on a strong increase in labour productivity will keep the improvement in the employment moderate. Rapid growth increases tax revenues and strengthens public finances, which remains still in a deficit because of structural factors and general government debt to GDP ratio lowers but only temporary.

Over the next few years, economic activity will be driven by both domestic and foreign demand. The patterns differ clearly, however. Private consumption and to some extent investment demand growth will slow, but exports will pick up. Improving global demand and business cost competitiveness will boost growth prospects for exports.

Household consumption demand will be hampered by subdued purchasing power. Investment growth will be held back by a slowdown in housing construction growth but accelerated by major production-related investment projects.

Globalisation and specialisation have led to a fragmentation of value chains, which means that the manufacture of individual end products is distributed across several countries. Intermediates exports as a proportion of total exports have consequently increased. The globalisation of value chains is directly reflected in trade structures.

Project ReCon

Project ReCon is essentially a research project that concerns the implications and applications of (primarily) non-currency blockchain technologies, as well as raising awareness of the possibilities of blockchain technology, especially in Finland.

It started its life in September 2016, with a view to explore strange new technologies, to seek out new ideas and applications, and to explore where very few have gone before. The team consists of 4 researchers, 4 companies and the Ministry of Finance in Finland, the latter of which has set up a group of experts to enhance and monitor the conditions in which financial services technologies can evolve. The group's coordinator is ministerial adviser, Miki Kuusinen.

Back in December 2016, the Bank of Finland cooperated with the Ministry of Finance in Finland, a seminar to discuss the possibilities that blockchain and distributed ledger technologies in different sectors of society.

At this event, 10 projects were presented, with a view of developing applications to harness blockchain technology for the needs of public administration, the financial sector and the needs of industry. In his introductory remarks, Governor Erkki Liikanen highlighted the Bank of Finland's vital role as catalyst and overseer of payment and financial systems.

"Our task is to ensure the reliability and efficiency of the payment system and the overall financial system and to participate in their development. Research into, and support of, new innovations shaping the financial sector constitute part of this work, Liikanen said."

The aims of the project include demystifying the blockchain. Producing actionable, understandable knowledge about blockchain technologies and their applications for entrepreneurs, decision-makers and the public is a key aim of the project. It also aims to demonstrate how blockchain technologies might be fruitfully used both for the betterment of society, as well as business applications.

In addition, the project also aims to spark discussion, which includes raising public awareness concerning the impacts of new technologies and their development. The project also intends to educate, train and connect interested people and parties in Finland and further afield.

Finally, the project also emphasizes producing quality academic research to find out more about the implications of blockchain from organisational, business, management and societal perspectives.

Finnish exports consist predominantly of intermediates, which are processed into final products or integrated as part of larger installations in some other country. Intermediates exports account for around two-thirds of total Finnish exports. This is a common feature; intermediates are an important component of exports in other advanced economies, too.

The growth of foreign value added in exports is indicative of a more specialised and internationally more interconnected production structure. The increased share of foreign value added undermines the potential for export-driven GDP growth: not all streams of export revenue contribute to GDP growth in the same way.

In the medium term economic growth is projected to return to the level of potential output growth, that is, a little over 1%. The slowness of potential growth is due to structural factors in the economy. On the one hand, the shrinking of the working-age population and the persistence of relatively high structural unemployment maintain zero growth in labour input despite the more active participation of older age cohorts in particular in the labour market.



On the other hand, productivity growth has slowed as the output of high-productivity sectors has declined significantly and the overall structure of the economy has shifted towards services. In addition, the low investment rate that has continued for several years has slowed the generation of new productive capital.

"In 2018 and 2019 GDP is expected to grow 2.1% and 1.8% respectively, which are above the estimated potential growth rate. Economic growth based on a strong increase in labour productivity will keep the improvement in the employment moderate."

Growth and effects

The continuing reasonably rapid rate of GDP growth will have a positive effect on employment and at the same time the number of unemployed persons will decrease. The number of employed persons is projected to increase by average 0.7% p.a. and will bring the employment rate to 70.5% in 2019.

The activation of persons outside the labour force to

become jobseekers is likely to slow the decline in the unemployment rate. This indicates a rather high rate of unemployment throughout the forecast period, despite stronger economic growth. The unemployment rate is expected to fall to 7.8% in 2019.

The number of the long-term unemployed decreased rapidly in early 2017 across all age groups. Due to strengthening economic growth, the number of the long-term and the structurally unemployed can be expected to decrease further in the next few years, albeit more slowly than in recent months. The number of the structurally unemployed is still high, almost 200,000 persons according to the employment service statistics of the Ministry of Economic Affairs and Employment, which will contribute to slow the reduction in the unemployment rate in the next few years.

The economic growth outlook for the 2017–2019 is far more positive than in previous years, but the general conditions for economic growth and the structures determining these have not, however, changed to increase the economy's growth potential.



The long-awaited economic growth is also improving the state of general government finances. Tax revenue is increasing and the decline in unemployment is reducing unemployment expenditure. The economic rebound does not, however, eliminate the structural factors weakening general government finances, with the most important of these being population ageing, which increases growth in pension, care and nursing expenditure and therefore slows down improvements in general government finances.

Despite the economic recovery, general government expenditure clearly exceeds revenue. While robust GDP growth will set the debt ratio on a downward trajectory in the next few years, central government indebtedness will still continue in 2021.

To complement the debt objective, the target of the GDP-to-debt ratio levelling off by the end of the government term 2019 and living on debt coming to an end in 2021, the government has set specific targets for the general government budgetary position. For the targets to be reached, general government finances will need to be more or less in balance at the end of the government term.

To achieve the targets and to ensure the long-term stability of general government finances, it is important that the revenue generated by economic recovery be used to balance general government finances and reduce central government borrowing.

Marja Paavonen Head of public finances

Mikko Spolander Head of department

Jukka Railavo Head of macro forecasting Ministry of Finance, Finland Tel: +358 295 16001 jukka.railavo@vm.fi http://vm.fi/en/frontpage

www.twitter.com/VMuutiset

Human-centred approach to data leads the way to a smarter digital age

Markus Hautala and Antti Kettunen at Tieto reveal how Blockchain has rapidly emerged as one of the disrupting technologies of the digital age

rust in the digital age is broken. Can you remember the last time you got insurance or bought something from a private person from another EU country to yours? Or when was the last time you signed a contract or gave a power of attorney online? The chances are that you rarely have. Although our private and business lives have become increasingly digital, we still seem to lack mechanisms to conduct these common interactions online. The underlying reason of course is that the internet was not built with trusted interactions in mind. Online nobody can verify what you say or the information you share is true.

As the amount of data generated by people, organisations and devices continues to grow at an exponential pace - the IDC predicts a ten-fold increase in data generated from now to 2025 - it is becoming essential that we have practical means to manage and share our data. The regulators in Europe have also reacted to this need by launching regulatory initiatives such as Payment Services Directive (PSD2), General Data Protection Regulation (GDPR) and ePrivacy directive, which share the common ambition of empowering citizens to have access to their data as well as being able to control and share it. Through these initiatives, the EU aims to actively enforce data protection rules and create a fairer platform for data protection, that supports consumers and businesses whilst promoting innovation.

Data verifiability remains an issue in digital interactions

GDPR and PSD2 regulations are significant steps to the right direction of providing identity holders access and control over their data. Both focus on enabling data portability, with the goal of enabling new digital business innovations. As such, they will fuel disruption in the digital industry by opening existing data silos by allowing customers to migrate their data to a new service provider. As Erkki Poutiainen, chairman of the EBA Clearing Board mentions, PSD2 together with new technology can revolutionise the payment landscape and even banking as we know it.

While gaining access to data is a necessity for opening up competition, more is required. The key issue in data portability is not only that data is shareable, but also that the data retains its verifiability. Just imagine receiving a power of attorney digitally but not being able to prove its validity. Clearly verifiability is the crucial element that retains the value of data and as such is of critical importance.

Digital identities for people and organisations, as well as verifiable data are the fundamentals needed for digital trust interactions. Portable digital identity and data will enable us to create more equal and inclusive society by allowing anyone to participate in the new economy.

MyData and the new decentralised internet hold promise for solving the trust problem

Recently, a Nordic model for humancentred personal data management and processing called MyData has raised thoughts about how data could be managed with identity owner at the centre. MyData brings a fundamental change in how we view and use data. It is an ideology, driven by three main principles of:

1) Identity owner centric control and privacy;

2) Usable data. Data must be technically easy to access in a machine readable open format accessible via standardised interfaces and;

3) Open business environment. MyData proposes a new identity owner centric approach in exchanging data. In this concept the identity owner has a single hub for data management. Via the hub the identity owner can give services the authority to access and use data.

A key prerequisite for all the regulations and models to become truly effective – is that a new infrastructure paradigm for managing identities and sharing verifiable data is needed. Even if every person and organisation has an identity, we still fail to replicate this online. This is mainly due to identities being fragmented over various data

Identity owner centric approach to sharing data



silos. MyData and the regulations aim to remove the silos, but this is still not enough, since they don't provide the infrastructure which would foster true collaboration and competition, that are needed for the market to grow.

The rise of decentralised solutions, such as blockchain and other distributed ledger technologies (DLT), have given rise to new types of ecosystems where businesses, public organisations and individuals can form trust relationships without involving middlemen. These decentralised solutions hold also great promise for solving the identity and integrity issues prevalent in sharing and trusting on data.

Decentralised identity network can deliver the internet's missing identity layer

One of the most promising initiatives aiming to solve the challenge of being able to trust information exchanged online is Sovrin. Sovrin is a global, decentralised identity network that delivers the Internet's missing identity layer. Sovrin allows people and organisations to create portable, digital identities which they control.

In Sovrin, the identity holder forms secure digital connections with entities

(organisations, individuals or things) that can provide information about the identity holder. This information can literally be anything such as a personal identification number, home address, power of attorney or – in the context of GDPR and PSD2 – customers consent to a service provider. This information can then be shared forward by the identity holder to a party that requires these proofs. This provides for all kinds of rich digital interactions: Know-Your-Customer, contract and transaction signing (B2B, B2C, G2C), permits, asset ownership, and so on.

Towards a smarter society created with new technology

Blockchain has rapidly emerged as one of the disrupting technologies of the 21st century. We at Tieto believe that it will be one of the key ingredients of success for our customers' future business and that it can be harnessed to build more equal, inclusive and smarter societies. With this in mind, Tieto is working on various fronts to open up current data silos for the benefit of Nordic organisations and citizens.

• Tieto is currently looking into how to utilise blockchain technology within healthcare. Together with Californiabased company Gem, the company is working on how to link genetic data stored in biobanks, personal health records at hospitals and individual citizens to bring the benefit of <u>panomics</u> to diagnostics and treatment scenarios.

 Tieto and Evernym, the leading developer of self-sovereign identity technologies in October 2017 launched a Sovrin Pilot Program, aiming to introduce the Sovrin identity platform to Nordic customers. The helps businesses and public organisations better manage digital interactions, by increasing trust and reducing costs with the help of the distributed identity network. The multi-party initiative aims to rapidly validate and implement commercially viable solutions that leverage this global network.

By its design distributed ledger technology introduces a new trust model for ecosystem collaboration. To this end, Tieto is excited to explore new use cases utilising the technology in close collaboration with its customers and partners.

Read more about our thoughts on blockchain: <u>Self-sovereign identity delivers MyData in practice</u> <u>It's your data. Take it back. Unlocking your health data with</u> <u>blockchain</u>



Markus Hautala Head of Blockchain solutions

Antti Kettunen Solution consultant Tieto www.tieto.com www.twitter.com/TietoCorp

The future of blockchain: Learning from things yet to happen

Disruption, pivot, 10X change – these words describe current strategic interest in everything new, but how do we decide the future of blockchain?

n a forward-looking research project at Aalto University's Business School in Helsinki, together with partner companies and public organisations such as the Finance Ministry of Finland, we are studying one of the future change drivers, blockchain technology. While high on the hypecurve, the business and societal implications are not yet visible despite a lot of ongoing experimentation ranging from health care, finance, and logistics.

The members of the ReCon research project, or "Blockchain: Disruption of Business Systems and Reconfiguration of Trust" are particularly interested in questions such as how distributed, open technologies may transform the ways in which people interact. Socially constituted, comparative trust scores are familiar from internet sites ranging from amazon.com to the dark net. We rely on our fellow people's evaluations. Historically, or before the Internet, we relied on institutional sources of trust – the government license to operate or the family network. Or we took the risk.

Trust in cryptocurrency

A cryptocurrency like a bitcoin requires no trust: confidential buying and selling is possible without knowing the other parties at all. This is the unique characteristic behind the blockchain technology – it is a way of operating an economic system without the necessity to have trust among the parties, something that has been considered essential for all economic activity. A



lack of trust adds substantially to the transaction costs. Therein lies the blockchain revolution.

The Economist magazine called it "the trust machine", yet the writers were also concerned about the large societal implications: "The idea of making trust a matter of coding, rather than of democratic politics, legitimacy and accountability, is not necessarily an appealing or empowering one." (October 31, 2015, p. 24).

When states, governments, central banks become irrelevant, what happens to societies and their foundational legitimacy? Any political vacuum is likely filled with other interests. Prof. Lawrence Lessig from Harvard Law School in Code and the Commons, 1999, p.10, has warned: "To push the anti-government button is not to teleport us to Eden. When the interests of government are gone, other interests take their place. Do we know what those interests are? And are we so certain they are anything better?" So blockchain could have some significant societal implications, all the way down to the foundations of our societies that we need to think through.

Nevertheless, blockchain has very useful applications. Trusting blockchain with our health data has its advantages: In the era of data breaches, blockchain appears secure but also transparent in terms who has accessed the data. And of course, there is no need to carry documents from one health care provider to another by hand (as has happened to this author several times)! No wonder many think

that it is better to have the data on a blockchain, rather than in a national health institution's (hackable) servers.

Similarly, blockchain applications could save mountains of documents and hundreds of hours required to process the transport logistics of shipping companies. The origins of sensitive goods, such as diamonds can be recorded on a blockchain, and the integrity of the supply chains, for example whether food has been stored properly, can be shown.

And blockchain could save significant costs in financial transactions. According to a McKinsey&Company (see International Monetary Fund, The Internet of Trust, Finance & Development, June 2016, 53:2), banks extract an astonishing \$1.7 trillion a year, 40% of their revenue, from global payment services. Banks and financial institutions are currently developing their own blockchain applications.

However, many issues remain to be worked on. Here are some we at the ReCon research project are thinking about.

1. The problem of interference:

Establish the linkage between a digital trade and its value is what blockchain is very good at. However, when the non-digital world intrudes there is the human touch with the messiness of the physical world around us. Someone records a value at a particular time. Perhaps a sensor will report it. How can we trust that the person, or the sensoring device, has the right measurement and is honest, or accurate, about reporting it? Can we be sure there are no vested interests interfering with the recording?

2. Blockchain applications ('use cases'):

We are surrounded by technologies that perform adequately or even superbly solving business and life problems. When is blockchain at its strongest? What boundary conditions are there for using the technology purposefully and effectively?

"A cryptocurrency like a bitcoin requires no trust: confidential buying and selling is possible without knowing the other parties at all. This is the unique characteristic behind the blockchain technology – it is a way of operating an economic system without the necessity to have trust among the parties, something that has been considered essential for all economic activity."

For example, blockchain has implications for the Internet of Things- or Industrie 4.0 - infrastructures through its smart contract capacities. A coupling with machine learning might make these capacities particularly potent, as the system could learn or be teachable. As a thought experiment: Why could cars not only drive themselves autonomously but also act as separate legal units - 'own' themselves and sell their services as de centralised autonomous organisations? A car might then insure itself against any traffic accidents. Over time, it might even learn to negotiate better priced insurance contracts based on its stellar driving record!

3. Beyond business:

A blockchain-like technology offers a promise for a more inclusive, open, and democratic society. It is a promise that many feel the Internet failed us and that the blockchain is the new hope for the future. How can we use blockchain in a way that respects the legitimacy of our societies and institutions, while giving the technology a chance to serve its citizen-admirers with the unique features? Disruption is excellent, provided the transformation allows for a renewal of our societal constitution in both a respectable and inviting way.

These are examples of the questions we at the ReCon research project are thinking and experimenting on. We engage in pilot projects, hackathons, studies, workshops and keynotes. Our mission is to describe, analyse and experiment on the potential of blockchain-like technologies.

Outliers Wanted!

We are seeking outliers, people and organisations that are in the forefront of learning from things yet to happen, to connect and think with. More information regarding the ReCon research team and our partner organisations can be found at recon.site.



Prof. Liisa Välikangas Aalto University & ReCon Blockchain Research Project Tel: +358 50 496 7134 liisa.valikangas@aalto.fi www.recon.site

Cyber security concerns all of us

European Commissioner Dimitris Avramopoulos underlines the responsibility of companies, governments and citizens when it comes to cyber security

nsecurity, fear, instability. In governments, companies and banks. It is now proven beyond doubt, that cyberspace is one more battleground against organised crime and terrorism – whichever form this takes. We are lagging behind. This is a fact. We should have anticipated the urgency of cybersecurity. Now we must react. And it is better late than never.

Cybersecurity is critical both to our prosperity and our security. Cyber-threats threaten not only our citizens: they are threats to our democracies themselves. With so many experts in this room, you do not need ME to tell you about the global threat posed by cybercrime. As the European Commissioner in charge of Home Affairs, this issue is of course a top priority for me. In the Internet-dependent societies we live, it is an issue of truly global dimensions.

In the last year, we had more than 4,000 ransomware attacks per day, a 300% increase compared to 2015. The Wannacry attack in May affected more than 150 countries and over 230,000 systems. Even nuclear stations were affected. The nature of these threats has grown and changed in importance in three significant ways.

Firstly, by becoming strategic, because they endanger our critical infrastructure and threaten our democratic processes. Cybercrime has become instrumental in geopolitics and conflict – hybrid and otherwise. Secondly, by becoming endemic, as the threats spread like wildfire, from IT networks, into business-critical operations, and our critical infrastructure. Thirdly, by becoming universal: our omni-connectedness means that threats are more difficult to contain across networks, devices, or geographical regions.

Inaction is therefore no longer an option. This is an essential debate about the sustainability of our

economies and our democratic institutions. In the European Union, even with delay - we recognised the importance to act, and tomorrow in Brussels, we will present concrete actions to address our cyber-insecurity. The actions are European, but the perspective is of course global.

This new cyber-strategy is built on three key pillars: – resilience, – deterrence, and – international co-operation. The focus of all the actions in this strategy is first operational. That is why the centrepiece of the resilience pillar of the strategy is to strengthen our operational Agency for Network and Information Security (ENISA), which is based in Greece.

ENISA gets a stronger mandate, more resources, and an operational role to support our Member States deal with cyber-threats. A crucial aspect here is skills and expertise. Hackers will only be deterred by people that can match their skills. We need to ensure that programmes for education and training include cybersecurity as a core part of academic and vocational training curricula.

Our Responsibility

Cybersecurity is a responsibility for all of us. From companies and governments, to the last citizen using a connected device of any kind. Just think that 95% of successful attacks are said to be enabled by "some type of human error – intentional or not".

Cyber-hygiene for all therefore: awareness-raising, communication, training, skills-building, these are crucial and should be our priorities.

The second major pillar is deterrence. Successful deterrence requires effective detection, traceability, investigation and prosecution. We will only begin to



ICT

Dimitris Avramopoulos, European Commissioner for Migration, Home Affairs and Citizenship

turn the tide on cyber-attacks, when we increase the chances of criminals getting caught and sanctioned for committing them.

"Cybersecurity is critical both to our prosperity and our security. Cyber-threats threaten not only our citizens: they are threats to our democracies themselves '

Here, the Council of Europe Budapest Convention on Cybercrime, is the cornerstone of our international partnership to exchange information and electronic evidence. This is of course linked to the third pillar of our strategy: global cooperation, which is in my view the most critical – and the most relevant to our context this week at the United Nations.

Global cyber stability is a task that NO country, and NO region can promote alone. It must come from all of us. The European Union will continue to advocate strongly that international law applies in cyberspace. I said it before: our security systems will always be as STRONG as the weakest link in the cyber-chain. The UN and NATO will be a key area of focus on the international arena. Our cooperation with NATO will deepen, especially in relation to threats of the well-known, 'hybrid' type.

European Commission

Cyberspace - this amazing medium of interaction and innovation - unfortunately also offers unprecedented opportunities for criminals. Cybersecurity concerns all of us. All of us may become targets or victims. Our resilience, and our means to deter attacks, will be key to our future. Our perspective can only be global, for a threat which is borderless.

Remarks by Commissioner Avramopoulos at the event on 'strengthening the stability and international security of cyberspace', United Nations General Assembly (UNGA), New York New York, 18 September 2017.

Dimitris Avramopoulos European Commissioner for Migration, **Home Affairs and Citizenship**

European Commission Tel: +32 2 299 96 96 ec.europa.eu/commission/commissioners/2014-2019/avramopoulos_en www.twitter.com/Avramopoulos

How do we build safer digital environments?

Identify, Protect, Defend, Respond are the four key components to ensure safer digital environments. Here, Fujitsu provide insight

decade ago, primary security concerns were satisfied by deploying and maintaining an effective firewall, in addition to keeping the permissions for devices and physical locations up to date. While organisations used the internet to maintain a website and for communications, an online presence wasn't as ubiquitous as it has become today.

How things have changed! Today users expect to access information and departments on any device – and to do so from almost anywhere, at any time. Information really has become the new currency – and it's available 24x7. It is commonplace today that employees bring their own devices into the organisation's network, download and install software they have selected, and interact with corporate data on their own personal devices. What's more, these devices are taken outside the workplace – still carrying access to valuable and sensitive data.

Citizens want to be empowered to reach services as and when they desire which creates huge challenges for national and local bodies to provide platforms that are resilient and information that is protected. The issues of data management, storage, access, and rights need to be paramount within any business or organisation where there is a transaction of information.

This new level of being interconnected brings untold benefits but it also

creates new security challenges.

Against this backdrop, Fujitsu's Global Cyber Security business protects government departments around the world against cybercrime of all kinds, strengthening their resilience against cyber-attack, as part of a globally-integrated security offering.

Fujitsu provides Managed Security Services from Security Operation Centres (SOCs) in Japan, North America, UK, Germany, Finland, and Spain, and aims to bring to market a wider range of security solutions, upgrading its SOCs to Advanced Cyber Threat Centres.

Our philosophy: Identify, Protect, Defend, Respond

Fujitsu's portfolio of security solutions and services provides public sector organisations with peace of mind that their security is in good hands while they get on with running their business. Fujitsu aims to be the trusted digital security services provider, helping its customers predict and respond to cyber threats to protect their business reputation with an intelligence-led approach.

Our key services lie in 3 areas:

- Predictive intelligent threat detection;
- Trusted delivery expert-led professional and managed security services;
- Global 24x7 monitoring & response.

Managed Security

One key service that Fujitsu offers to address this lack of time and skills is a fully managed security service. A key feature of this is continuous system monitoring that constantly keeps a watchful eye on internet traffic, looking out for potential attacks before they can do harm.

Fujitsu takes an intelligence ledapproach to cyber security. Artificial intelligence systems monitor customers' internet traffic for potential risks. Once identified, the team of experts located in one of the global SOCs can help customers rapidly take action.

Advanced Biometrics

Security challenges are not limited to the cyber world and the implications of sensitive information falling into the wrong hands remain significant. The most basic level of prevention involves controlling physical access to hardware or facilities. Traditionally, access to doors, devices, computers, and border controls have been managed by PIN code entry systems or by door tags – both systems which can be easily lost, shared, or stolen.

Fujitsu's answer to the challenge lies in sophisticated biometric authentication – which can be applied to gain access to physical locations such as office buildings, server rooms or even to access personal mail boxes. Devices such as laptops can also deploy biometric authentication. The


authentication is deployed in the easy-to-use form of palm vein readers. Called PalmSecure, this technology that is uniquely offered by Fujitsu, takes advantage of the fact that everybody has a unique pattern of veins in their body which can be used for highly secure authentication. It is hygienic, as no contact is required – users just need to wave their hands in front of the sensor. And of course, vein patterns can't be lost or stolen and are only visible when blood is flowing through them.

Fujitsu Identity Access as a Service

Users of public systems today have dozens if not hundreds of usernames and passwords that allow them to logon to countless on-premise systems and cloud services. Fujitsu's identity as a Service is designed to reduce this complexity and to help businesses prevent hacks or fraud, by ensuring that only verified users can access selected systems, applications, data, and resources.

The browser-based service makes it easy to manage, create, adjust, and remove permissions from any connected device or location. It incorporates a variety of strong authentication methods, including user ID and password, Windows desktop login, single sign-on (SSO), CallSign authentication (based on a phone call and PIN code) and biometric authentication.

As well as the recent growth of ransomware, there are a number of trends that we expect to see in the near future which illustrates the increasing sophistication of cyberattacks:

- Many systems have 'a blind spot' this lies in the encrypted channels that are designed to give remote workers easier access to networks. If taken over by a cyber-criminal, these channels can essentially provide access to the heart of a critical computing system and mean that nefarious activities are largely undetectable.
- Our state-of-the-art Fujitsu SOCs also expect to see cybercriminals continue to target financial applications. In particular, our experts predict that the SWIFT global payment network will be targeted, in addition to further growth in banking Trojans that are targeting older, more vulnerable back office applications. Although SWIFT is moving to establish mandatory controls, we still think it is a window of opportunity for cybercriminals.

 Smart cities will also find themselves targeted – many of the protocols designed for smart connected devices have their own potential flaws and vulnerabilities. The implications of this are wide-ranging and could include allowing hackers to disable power supplies or other infrastructure services. This would plunge entire cities not only into darkness but into disarray – because it's also likely that phone systems would stop working – and could even impact on water supplies.

"Did you know?"

Fujitsu uncovered a massive 'hit list' of 385 million email addresses including many from government agencies and banks on a server hosted in Russia as part of its activity tracking a Dridex Trojan. The server was found in 2015, by following a trail of major customers who had fallen victim to hackers. For more information, see <u>this video</u>.

Further information:

The Fujitsu 2017 Security Predictions report.

Inside the Security Operations Centre:

Secure thinking: When it comes to cyber security there will always be vulnerabilities. How can you be confident that your information is protected?

Inside the Gates - The Banking Trojan Threat (Dridex Case study).



Rob Pinn Cyber Security Specialist, Public Sector, UK Tel: +44 7867 835237 rob.pinn@uk.fujitsu.com

www.twitter.com/fujitsu_uk www.fujitsu.com/uk/services/infrastructure/security/





Combining large corporations' market reach with start-up innovation power

Imec's programme manager Sven De Cleyn explains how imec.istart helps boost start-up innovation in large corporation markets

ccording to the Merriam-Webster dictionary, the first-known use of the word 'innovation' dates back to the 15th century. Yet, while the concept has been in place for more than six centuries and has become part of our daily vocabulary, it is becoming increasingly challenging for companies to continue to innovate / reinvent themselves in an environment of start-up innovation.

Larger corporations mainly struggle with the fact that the innovation land-

scape is very much scattered, making it difficult for them to keep a close eye on innovative, emerging technologies that might enrich their product portfolios and provide them with a competitive advantage. At the other end of the spectrum, lots of promising start-ups find it difficult to translate their market potential in a first big customer win or strategic partnership.

To bridge the gap between those two worlds, imec is introducing its 'Smart Brokerage' initiative. Set up under the umbrella of the imec.istart business acceleration programme, the initiative aims at helping larger corporations and start-ups interact more easily, and create a mutual win-win.

Bridging the gap between large corporations and innovative start-ups

A smart broker is an organisation that bridges the gap between larger companies' requirements and start-ups' innovation capacity; a gap characterised by following mutual concerns:

- Large companies do not want to contaminate their IPR or disclose confidential data in their search for partners.
- They do not have the time to continuously scan the market for relevant start-ups in their domain.
- Start-ups, on the other hand, are typically reluctant to share their ideas and advances with bigger companies.
- Moreover, they lack the corporate contacts to translate their market potential into concrete business opportunities.

In such a setting, a smart broker can put in place the necessary (intellectual property) protection mechanisms and create a trusted environment in which both parties can discuss potential collaboration opportunities.

In general, smart brokers work along the following main principles:

- They have a fully confidential relationship with the large corporation, governed by means of an NDA or another legally-binding contract.
- They have insight into its strategic roadmaps or innovation plans.
- This input is used to identify relevant start-ups that the company could partner with.
- The smart broker helps the start-ups prepare a business case.
- Finally, the smart broker presents the start-up proposals to the larger corporation; this can lead to a variety of collaboration types:
 - Paid proof-of-concept/commercial deal;

- Joint business offering;
- Distributor/reseller type of deal;
- Licensing deal; and
- Any other type of mutually beneficial relationship.

Imec's 'Smart Brokerage' approach: lightweight, lean & results-driven

Imec's 'Smart Brokerage' initiative features a four-step approach that is lightweight, lean and results-driven:

- 1 In the first phase, imec focuses on getting to know the corporate partner, its activities and its requirements.
- 2 Building on those insights, imec proposes a longlist of start-ups it could partner with; an exercise during which imec calls upon its broad entrepreneurship ecosystem – ranging from the start-ups supported by the imec.istart business acceleration programme to iMacs portfolio of spin-offs, its EIT contacts and potentially even other (international) partners/sources.
- 3 Together with representatives from the corporate partner's various business lines, this long list then gets translated into a shortlist – featuring those start-ups that show the highest collaboration potential.
- 4 Prior to the final (half-a-day) pitching event, imec specialists coach the shortlisted start-ups on the topic of successful deal pitching – after which the corporate partner decides with which start-up(s), to embark on a business journey (resulting in business discussions with the right corporate executives and the kickoff of proofs-of-concept).

Everybody wins

"We saw a clear need for this type of initiative – as to avoid that larger companies and start-ups continue to work on their respective islands; after all, by combining forces, they get so much stronger," says Sven De Cleyn, programme manager of the imec.istart business acceleration programme. "The first cases we have gone through clearly show that imec's role as smart broker makes everybody win.

"Our corporate partners, for instance, get in touch with a line-up of innovative start-ups they would not be able to easily find themselves. For the start-ups, this is a unique opportunity to talk to the business executives they have been longing to see; and they can learn from one another during the pitching sessions. Finally, from an imec perspective, we can help our start-ups with what they need the most – i.e. making deals and facing customers."

unec

Sven De Cleyn Programme manager, imec.istart imec Tel: +32 474 29 76 94 sven.decleyn@imec.be www.imec.be www.twitter.com/imec_int www.twitter.com/imecincubation www.twitter.com/sdcleyn ICT

Changing regulatory rules in financial institutions

Jean Noël Georges at Frost & Sullivan explains how RegTech providers can aid financial service organisations in meeting changing regulatory rules

or more than a decade, banks and financial institutions have had to comply with seemingly constantly changing regulatory rules. These changes can be relevant at either global or regional levels, and have been increasingly complex since the 2008 financial crisis.

As a result, the number of regulations has exploded: Foreign Account Tax Compliance Act (FATCA), European Market Infrastructure Regulation (EMIR), Financial Reporting (Finrep), Common Solvency Ratio Reporting (Corep), Automatic Exchange of Information (AEOI) or Analytical Credit (Anacredit) to mention just a few.

As a result, insurance companies, financial institutions and banks often struggled to comply with these new requirements and were, sometimes, forced to pay fines because of non-compliance. Regulation technology (RegTech) companies have emerged to help firms to simplify the compliance process.

In addition, financial services organisations must respect a set of procedures, laws or regulations to stop the practice of generating income through illegal methods: Anti Money Laundering (AML) or Counter Terrorist Financing (CTF) are part of this process. It is always coupled with a service: Know Your Customer (KYC) that creates risk profile and help institutions to better track improper usage of public funds, evasion of taxes, market manipulation or illegal trading.

By harnessing established technologies, RegTech providers can aid financial service organisations in meeting complex compliance requirements with relative ease. RegTech provides greater agility as such solutions can structure and organise data frequently to generate timely reports for compliance.

Automatic processes

Furthermore, big data analytics, machine learning (ML) and cloud computing can extract effective insights from various data points for a real-time decision process. RegTech can significantly reduce the need for human intervention, updates and manual checks by automating the process to deliver more efficient and cost-effective results.

As RegTech solutions are usually cloud-based, changes in the regulatory ecosystems can be mapped and recorded easily to ensure global compliance. More importantly, RegTech solutions allow companies to be proactive by automating regulatory risk and analysing business data from different services and to detect in advance potential risk in the regulation life cycle.

RegTech providers are now seen as third parties that can strongly support traditional financial business. This trend is strengthened by the rise of pure digital banks such as Atom, N26, Monzo or Fidor that have centralised their business strategies to digital banking and are keen on having RegTech solutions in place to handle the regulation processes.

However, the RegTech market is nascent, and in a changing regulatory ecosystem banks and financial institutions are reluctant to invest in a particular RegTech platform. As a result, flexibility should be at the heart of the RegTech offer. Furthermore, in a competitive market, there are a plethora of RegTech companies competing for attention, and it is extremely difficult for traditional financial players to select one unique provider.

Frost & Sullivan expects a degree of market consolidation to occur over the next 3-5 years, resulting in only a few



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RegTech winners remaining. In this context, agility is a key success factor. This approach should be followed for both the technology IT infrastructure than for the pricing structure. Indeed, banks and financial institutions will only be willing to invest in solutions that show tangible return on investment and concrete added value.

"RegTech providers are now seen as third parties that can strongly support traditional financial business."

RegTech is not a new buzz word, but an important market development that is based on established technologies that provide deep analysis to support a more accurate decision making process. Banks and financial institutions have to enter the RegTech age to benefit from innovative and agile services. Nevertheless, emerging technologies such as Blockchain are already entering the RegTech ecosystem. Blockchain-based RegTech solutions are in the early stages of development, and are currently targeting KYC and risk assessments. The first services based on Blockchain technology should be available by 2020. A Promising RegTech era is set to start sooner than we think.

Jean-Noël Georges

Global Programme Director, Research Manager

Digital transformation practices, Frost & Sullivan Tel: +33 4 93 00 61 87 Tel: +33 6 27 61 21 39 jean-noel.georges@frost.com www.frost.com www.twitter.com/Frost_Sullivan

Offering Certainty in an Uncertain World – The future of Agile in Government Services

It's hard to be Agile in government

ithin an elected government delivery is expected to mirror a published manifesto. Do something different, and the words 'U-turn' threaten within the corridors of power.

Government services have tended to be developed based on established processes that have been tried and tested over many years. Add in the expectation that they'll showcase the latest technologies and the route seems fairly fixed. But agility is becoming increasingly important in this world of Brexit, fast moving change and unpredictability.

We need to find ways for government to be more responsive, more adaptive and be able to follow the paths that bring the best results.

In 2011, the government mandated that all digital service delivery would be Agile, but transforming government itself into a truly Agile and responsive organisation is a tougher challenge.

This year's Agile Business Conference, organised by the not for profit Agile Business Consortium, was hosted by Daniel Thornton, Programme Director at the Institute for Government and featured a keynote address by Hugh Wallace, Transformation Lead in the Scottish Government.

Both proponents of the Agile approach, they shared their views

about the difficulty of embedding Agile practices within government.

"Within government Agile is reasonably well established for software development, but in terms of creating Agile organisations, there's a really long way to go," said Daniel.

"The processes and accountability requirements of the public sector, interaction with parliament, the fact you've got so much legacy legislation and processes along with legacy IT, all of that makes it very hard to be Agile in Government.

"But a lot of adaptation is necessary. Brexit is going to require a lot of big changes so Government needs to speed up."

Daniel warns that cultural change is a challenge in the public sector.

"Everybody has operated in this kind of myth of control, believing that you can predict the future, that you can say, 'Don't worry, we know what's going to happen in a year or two years, here's how much we're going to spend, here's how this project is going to run,' but nothing works like that, so that's a big change to work your way through.

"We've seen a real change in the last few years, digital teams coming into Whitehall and changing culture in a mixture of bottom up and top down ways. They've really been the leaders of the Agile cultural revolution in government in the UK and that thinking has spread to the idea of transformation and what transformation involves, but it still needs to go a lot further and a lot faster.

"Senior people in the civil service and ministers need to appreciate that successful transformation is not all about control, it's about creating the right environment. Set long-term objectives certainly, but don't specify how you are going to do something a long way in advance, because you need to interact with citizens and find out what they want, and then test and learn in rapid cycles."

It's an approach being applied successfully in the delivery of digital services by the Scottish Government as it grapples with complex projects such as the transfer of social security benefits from the UK government, as Hugh Wallace outlines:

"Agile is not the natural position of the civil service or the public sector where the tendency is to focus on solutions, to base thinking on what's been done before and, particularly in IT, to take a technology first approach.

"What we are trying to do is target areas of government we think are most ripe for transformation and taking a partnership approach to how we deliver Agile. It's about running projects and demonstrating new



An Agile approach is helping the Scottish Government change to meet the challenges presented by devolution

processes, sharing budgetary responsibility, sharing governance and trying to hothouse skills and move things forward by showing actual delivery.

"It's never going to all fall into place overnight, but if we are prepared to work through projects and processes openly and collaboratively, we see that as a route to success."

The views of both are echoed by Geof Ellingham, Chair of the Agile Business Consortium, who said: "Developing a concept of business Agility and helping the public sector work out how to implement that in a world of governance and public responsibility is imperative.

"If you're a commercial company it's really easy to go, 'This is our strategy, we've looked at the data, the data tells us this strategy is not working, we're going to do something completely different.

"If you're an elected official and you've stood on a platform that says this is

what we believe in, then making that pivot is not as easy, and there's a need to engage with the public sector in understanding how you justify that choice."

At delivery level, the Agile Business Consortium is working to support Agile in government through new guidance, including a new course and qualification, Agile Digital Services, which integrates Government Digital Service (GDS) guidance with established product, AgilePM.

"We delivered a prototype course at Newcastle City Council and the Ministry of Justice and are halfway through delivering a beta version to 12 public sector organisations," said Geof.

"We have user researchers getting feedback from trainers and delegates, which we'll review and either do another round of private tests, or launch the product."

So while delivery of digital services in government is Agile, there isn't enough

Agile leadership at a time when significant change is happening quickly and where the future is uncertain.

In the corporate world we see a real understanding of the need to be different in the way we lead, to flatten organisational structures, and empowering people to make decisions at the lowest possible level and expecting them to take personal responsibility for their actions.

That approach is something government needs to get to grips with – and quickly.



Geof Ellingham Chair of the Agile Business Consortium info@agilebusiness.org www.agilebusiness.org

Hugh Wallace Transformation Lead Digital Directorate Scottish Government

Daniel Thornton Programme Director of the Institute for Government www.twitter.com/DanOnGov

Why local government should embrace technology

Andrew Cowling at Fujitsu Scanners outlines how local government could benefit from document management for efficiency gains and a reduction in costs

ocal government bodies are under growing pressure as they are increasingly being faced with challenges that question the current status quo; demands for instant access to information online such as public records, freedom of information legislation, heightened security, compliance, and regulations are all areas that raise the need and desire for more efficient ways of working. Indeed, the upcoming GDPR that becomes law on the 25th of May next year poses several challenges, not least the ability to be compliant with stricter data protection rules but also to be able to prove it in a court of law.

Outdated, paper-based processes are draining departments of valuable time and money, thereby reducing the quality of public services and making having a controlled retention policy tough, threatening the privacy, security, and ultimately the ability to provide complete transparency or in the case of GDPR erasure and proof thereof.

Document management

Document management enables the demands for higher productivity and improved service delivery to be met at a significantly reduced cost, both in terms of money and time. Capturing, routeing, sharing and storing information effectively are simultaneously driving sustainable performance improvements and providing significant cost reductions. Technology is seen as a catalyst for change, not only will the service to the public be increased but embracing digital transformation will also help create and retain a more efficient and motivated workforce who are enabled for mobile working, for enhanced collaboration and ultimately seeing a shift in man hours from admin related tasks to those of higher perceived value to the overall cause.

With the benefits and rapid return on the investment, ECM deployments can provide core systems that will allow public sector organisations to tackle the challenges facing the industry in the coming years.

Find out more about how Fujitsu document scanners can help support local government bodies in adopting or developing their document management capabilities by contacting us at scannersales@uk.fujitsu.com.

Additionally speak to us today about a jointly developed Privacy Management solution that offers a methodical and structured approach to GDPR that has impressive deployment and proven track record success in addressing stringent German privacy laws over the last decade.

David Taylor, a Senior Information Governance Officer commented – "It's not just the removal of the manual file management processes or the ability to access the files wherever we are. It's



the all-round capability to manage the whole response process from request to disclosure and beyond from one system. Fujitsu's scanner hardware is integral to the whole solution enabling all documents to be digitised, reviewed, redacted, compiled and released electronically. We now respond to almost 95% of all requests electronically compared to approximately 55% just two years prior. Response times have fallen from an average of 12 days per request to under 8 and still falling."



Andrew Cowling Channel Marketing Manager Fujitsu Scanners Tel: +44 (0)208 5734444 andrew.cowling@uk.fujitsu.com www.emea.fujitsu.com/scanners www.twitter.com/ScanSnapUK



For more information please email us at scanners@fujitsu.com or visit http://emea.fujitsu.com/scanners



shaping tomorrow with you

Welcome to the era of open government

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Director, Policy & Community at BCS David Evans provides an expert insight into the world of open government digital services

pen government services have been going digital since the early days of computing, but for most of that time this has meant the same (analogue) structural approach to public services as has been in place since the middle of the 20th century – only with a website.

The last seven years have taken us to a more radical readjustment of thinking in the UK, and we are now seeing some of the direct and indirect benefits of what was started under the banner of the Government Digital Service (GDS). That said, digital disruption of the state has only barely begun.

The problem with digital technology is that it doesn't always sit well with traditional boundaries. Telephones used to be run end to end by one company, they now have an app store. Online shops or auction houses are places where anyone can sell you almost anything. Yet government still operates as departments with particular corporate functions; the online equivalent of a grand edifice behind which an army of bureaucrats sit and run their processes.

GDS represented a change to all this, and it was an incredible strain on departmental identity to start using information across departmental boundaries. This was maliciously flying in the face of Sir Humphrey (the archetypal civil servant), who was adamant that this couldn't be done. Sir Humphrey, smart chap, could see that this would be the thin end of the wedge.

There is – believe me – a quiet beauty and power to a well-designed technical architecture. The best of these go to places you never expect. When Amazon started to standardise its internal computer infrastructure in the early 2000's they were doing a 'proper' bit of technical and business architecture work. Now, a sizeable

chunk of the UK government digital infrastructure runs on a platform designed to support an online bookstore. Who could have predicted that?

It's a point of belief rather than of proof, but I certainly believe that well designed technical architecture can lead to serendipity, and that if you put an API in the right place fun things will happen...and that where to put an API to achieve serendipity is not beyond our collective capability.

"Government services have been going digital since the early days of computing, but for most of that time this has meant the same (analogue) structural approach to public services as has been in place since the middle of the 20th century – only with a website."

A vision for government digital services

Things like the famous <u>'gubbins' video</u> and the stupendous thinking of <u>Simon Wardley</u> give us a vision of how we can deliver government services in a different way, and not only predict but drive technological changes to create new services.

This, combined with a focus on how real people wanted to interact with government services, and designing to make that work (rather than departments) was a seismic shift in thinking that a) has only started to catch on, but b) is still building momentum despite various travails and traducements.

This is still the thin end of the wedge. The thicker bit is a major re-evaluation of what government does and how. We're a whisker away from seeing government as a technology platform in the way that Apple and Amazon suddenly saw their own infrastructure.

Government departments are not simply monolithic



Director, Policy & Community at BCS David Evans

service providers, but part of an ecosystem that could be drawn differently. It is as though we're in a world where all financial services are provided by government, and we can't imagine what a different (but crucial) role for government would look like.

This is not an argument for privatisation of government services, but an argument for a change in thinking about the shape of government in the digital age. What if state benefits and taxation ran over an API, not out of an office? What if government-provisioned health services were customers of our data rather than – bizarrely – thinking that the people who look after our health should also look after our data? Maybe charities like Citizens Advice or Macmillan Cancer Support could do their jobs so much better if they could run their infrastructure off a government API, rather than via bits of paper in the hands of their users. The focal point for real-world policy has to be the realworld person, but the delivery mechanism and the methodology must be an ecology and architecture rather than a service (or more accurately, a different type or shape of services). Just as Amazon did, if we architect things in the right way we might find that the result is a shape previously incomprehensible to us, but so much better; a world of great design and serendipity rather than ministerial edict 2.0!

In practical terms, the call-out is to use open data and APIs internally and externally, against a properly imaginative and design-led architecture. That would mean a total reconstruction of public service delivery, and is therefore radical, fundamental, and incredibly challenging to turn into a reality. But it's one part of what will be necessary to address the many, varied and complex issues which society currently faces, let alone those in the future that we've yet to imagine.

...and once that design challenge is overcome, the nascent concept of 'agile policymaking' will have to be taken seriously. In current form, agile policy tends to treat democratic representation as an externality, or assume that the very human process of politics can be solved through a government-provisioned digital discussion platform. This is no more the case than sticking a website over a government department turns it digital. The real journey for digital government has only barely begun.

David Evans Director, Policy & Community BCS, The Chartered Institute for IT Tel: +44 (0)1793 417 417 custsupport@bcs.uk www.bcs.org

www.twitter.com/bcs

Harnessing payments technology across government

Mastercard's Sam Mazloum explores why government should be doing more to benefit from recent developments in payments technology

ard payments now account for more than half of all retail transactions in the UK – presenting challenges and opportunities for government. Consumer and business demand for electronic payments technology over cash is growing. The greater convenience and security electronic payments offer is building trust and interaction with the digital economy.

We pay in person and online, we pay by card and mobile phone, and we pay with watches and countless other connected devices. Every month new payments innovations come to market, driven by the UK's flourishing FinTech sector.

The government can tap into payments innovation to transform services, drive inclusion and save costs. In the coming months, we will publish a series of articles on four core areas where the power of electronic payments can make a difference to government and the citizens they serve.

New approaches to procurement and accounts payable

From abiding by the prompt payment code, to increasing spend with small and medium enterprises, the government is asking a lot of its procurement and accounts payable functions and at the same time, to do it with smaller budgets and leaner teams. The good news is that there are plenty of digital solutions to help. Mastercard Purchase & Pay enables you to integrate procurement and finance systems with electronic marketplaces and our network and data services, meaning you need never process an invoice and reconcile manually ever again.

Supporting those in need

The government disburses over £100 billion in benefits every year. For the majority of recipients, those payments will go direct to bank accounts. But what about the 1.5 million people in the UK who do not have a bank account? Central government pays those benefits into the Post Office Card Account, where the only option is to withdraw the funds in cash. Local authorities pay out cash directly. Cash handling is expensive for everyone for both government and the recipient. The use of prepaid cards to distribute benefits by over 200 public sector organisations in the UK has been a great success, but there is much room for progress and tackling Universal Credit has only just begun.

Paying government

From bus fares to parking fines, school trips to museum donations, there are many reasons we need public sector bodies to collect money from us. With the average Briton carrying less than £5 on them, those organisations that rely on cash collections are facing a real challenge. Contactless payments are a natural evolution. Online pay-

ments are shifting from the desktop to mobile, which presents an opportunity to simplify the payment process.

Unlocking the power of payments data

This year alone, society will create more data than it has in the previous 5000 years of our history. More and more public sector organisations are tapping into this opportunity, using data for intelligent decision-making, to design and refine policy, and to enable the delivery of better outcomes for citizens.

As the economy moves towards greater use of electronic payments, the data it generates can be utilised to support sustainable urban planning across housing, transportation, policing and energy management, as well generating much needed revenue through business rates and tourism.



Sam Mazloum Director, Public Sector UK & Ireland Mastercard ukpublicsector@mastercard.com www.mastercard.co.uk www.twitter.com/MastercardUKBiz

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LED printer as of March, 2015. 3. Using HP SmartStream software compared with using equivalent software programs. For testing criteria, see www.hp.com/go/pagewidexlclaims.





Fastest based on internal HP testing and methodology compared to alternatives for large-format printing of technical documents, GIS maps, and point-of-sale (POS) posters under \$200,000 USD as of March, 2015, Production costs savings based on comparison to a setup consisting of one monochrome LED printer and one colour production printer, both under \$150,000 USD, as of April, 2015. Production costs consist of supplies and service costs, printer energy costs, and operator costs. For testing criteria, see www.hp.com/g/pagewide/claims.
With a maximum linear speed of 23 meters/minute (75 feet/minute), the HP PageWide XL 8000 Printer is 60% faster than the KP 9900 printer which, at 14 meters/minute (47 feet/minute), is the fastest rated

Meeting the Printing needs of the AEC Industry

How new technology enables the production of high-quality prints more efficiently and cost-effectively



Thomas Valjak, EMEA Head of Large Format Printing HP Inc in the Graphics Experience Center in Barcelona, Spain

Repro houses play a critical role in reproducing highquality technical drawings and other documents for AEC customers. This includes architectural and engineering blueprints and renderings, and folded and finished bid sets containing all the drawings and construction sets needed to complete a project.

Although traditionally a high number of AEC technical documents are produced in black and white, coloured prints are increasingly becoming a pre-requisite. The move into colour can be attributed to the belief that it improves communication, readiness and indirectly saves time and costs throughout the bid, design and construction process.

Eliminating complex workflows

Many repro houses use an LED printer for monochrome print runs and an inkjet printer for colour. Managing both monochrome and colour printing, along with bid sets that consist of a mixture of small format and large format pages, means having to rely on a wide range of printing hardware and software. This has often led to inefficient processes, where costs are greater and workflows can contain an increase in the number of stages needed. As AEC clients face tighter project completion times, repro houses are also under increasing pressure to deliver high-quality short-run print runs with quick turn-around capabilities.

Automation is one of the key factors of a smoother and faster print process. Technology including end-to-end workflow software, combined with peripherals such as on-line folders, makes print management more efficient. Additionally, automatic detection and correction of corrupted PDFs, automatic selection of small and large format pages and on-screen soft-proofing can all help reduce job preparation time by up to 50 per cent. This frees up time to take on more jobs. Easy-to-use workflow software like HP SmartStream can also make a repro house better able to weather workforce turn-over, as it minimises the need to train new workers in complex operations.

When speed matters

Streamlining workflows is one way to speed up turnaround times but increasing the speed of printers is also critical. In 2015 HP was bringing the record-breaking speed of HP's PageWide Technology to large-format printing. HP PageWide Technology uses tens of thousands of tiny nozzles on a stationary print bar rather than a scanning print-head. This results in print speeds of up to 30 A1 pages/ minute. Instead of using two separate devices, one printer can be installed for both monochrome and colour, and colour prints can be produced at the same cost as blackand-white. In addition, new graphic applications such as retail temporary posters and maps can be added to the offering.

Based on proven HP Thermal Inkjet technology, HP PageWide print heads are designed to have a long life. The reliable drop ejection process reduces print quality defects from 'nozzle outs'. Automated print head servicing and calibration, including nozzle compensation, ensure consistent operation and minimal service intervention.



HP 841 PageWide XL Printhead module

Costs under control

For print service providers looking to meet the demands of AEC clients, gone are the days of the LED and inkjet printer sitting side-by-side. Both colour and black & white printing will be able to be produced at much lower costs than ever before. This will make it easier to meet clients' increasingly high expectations whilst having a much needed positive effect on the bottom line.

Additional information under **hp.com/go/pagewidexl**

Why the EU Single Market has still not reached its full potential

Marco Hafner shares his insights into why the EU Single Market has still not yet reached its full potential and where it can go in the future

The European integration process has been motivated by political and economic concerns. The EU Single Market, which has led to the removal of barriers to trade in goods and services, as well as capital and people, across the European Union, aimed to promote intra-European trade, increase competition, create more jobs and make Europe more attractive to foreign direct investment.

However, despite allowing greater competition and boosting trade between EU member states, an argument exists that the Single Market has still not yet reached its full potential. There are still many regulatory barriers within the EU that means the Single Market remains 'incomplete' and fragmented.

"The economic benefits are clear, but closer integration requires political buy-in from individual member states and the EU. Ultimately, it is up to both sides to make the most of the many opportunities within the Single Market and emerging Digital Single Market."

Several studies have highlighted the huge economic gains from a 'complete' Single Market. The overview report from the European Parliament has shown that these range from between 650 billion and \leq 1.1 trillion per year, the equivalent of between 5 and 8.6% of the EU's GDP.

More recently, a RAND Europe study for the European Parliament investigated the economic impact of lower trade barriers on the Single Market. According to the study, the impact of improved trade flows, economic growth and job creation due to lower trade barriers would lead to economic benefits of between €183 and €269 billion per year. The result would be a more integrated and complete Single Market.



Marco Hafner, Senior economist

Looking beyond the free trade of goods and services, one area where significant financial gains could be achieved is through the EU's digital economy. A fully functional and integrated EU Digital Single Market would bring many benefits to European businesses and consumers. The European Commission states that it would promote innovation, contribute €415 billion to the EU economy each year and create hundreds of thousands of new jobs.

The size of the potential economic benefits leads to questions about why the EU is not doing more with the Single Market and more specifically, the Digital Single Market.

Challenges remaining

Ultimately, there are still many barriers which make the full integration of the Single Market challenging. These are mainly associated with regulation, private law issues, tax issues, logistics and other more nuanced differences across EU member states.

Another challenge is that the economic benefits linked



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with a more closely integrated Single Market may not be equally distributed across EU member states. It is likely that the newer member states will gain disproportionally. The potential benefits and effects will also vary across different sectors and different companies, depending on their size.

"Ultimately, there are still many barriers which make the full integration of the Single Market challenging. These are mainly associated with regulation, private law issues, tax issues, logistics and other more nuanced differences across EU member states."

There are many policy measures that could help to overcome these barriers and help retrieve some of the potential economic gains. For example, further harmonising product market regulation across EU member states would help the free movement of services and goods.

In unlocking the potential of the Digital Single Market, significant financial gains could be made by increasing the use of online services and improving digital infrastructure within the EU. An overview report from the European Commission recommends moving towards a fully functional e-procurement regime and e-invoicing. For example, estimates suggest that a full transition to e-procurement could generate €50 to €75 billion a year, if all public procurement was managed online. There is still enormous potential in the Single Market. Numerous studies have made a robust case for it to be more fully integrated. The growing digital economy in Europe provides yet more opportunities, with the potential economic gains being realised through a greater integration of digital services across EU member states.

The economic benefits are clear, but closer integration requires political buy-in from individual member states and the EU. Ultimately, it is up to both sides to make the most of the many opportunities within the Single Market and emerging Digital Single Market.

Marco Hafner is a senior economist at RAND Europe. He led the research project 'The Cost of Non-Europe in the Single Market: Free Movement of Goods.'

Marco Hafner Senior economist RAND Europe Tel: +44 (0)1223 353 329 marco_hafner@rand.org www.randeurope.org www.twitter.com/RANDEurope

Mont-Blanc project: preparing for next generation supercomputing through ARM chips

Low-power ARM chips dominate the mobile world of smartphones, tablets, and embedded IoT devices, here, Mont-blanc investigates how they could power supercomputers

Whith datacentres consuming ever more power, the idea of using highly energy-efficient ARM chips in servers is enticing, especially for energy-hungry High-Performance Computing (HPC) configurations. As early as 2011, several pioneering European companies and institutions recognised the tremendous potential offered by embedded processor technology, and decided to unite into the Mont-Blanc project to investigate the usage of low-power ARM processors for HPC.

However, making the leap from the mobile market to HPC was not trivial: HPC-optimised libraries, compilers and applications did not exist for ARM platforms. Mont-Blanc partners had to start from scratch building ARM HPC test systems based on 32-bit mobile phone technology, and porting and tuning software and tools to create an ARM software ecosystem. In 2015, Mont-Blanc deployed the world's first ARM-based HPC cluster, featuring over 2,000 mobile CPUs. This system helped demonstrate the viability of using ARM technology for HPC.

Six years on, the landscape has changed dramatically. ARM has introduced its first 64-bit architecture – ARMv8. The Mont-Blanc team put a lot of effort into extending and consolidating the ecosystem developed



Mont-Blanc team

under the first phase of the project: scientific libraries and runtime systems were ported to ARMv8, and a set of development tools was developed for debugging, performance analysis, performance prediction, and automated kernel optimisation.

Interest for ARM processors is rising rapidly in the HPC community, as demonstrated for example by the success of the GoingARM workshop at the ISC conference in June 2017, or by the announcement of the world's first large-scale production ARMv8 machine 'Isambard', made in January 2017 at a Mont-Blanc conference by the UK's GW4 Alliance.

European computing

Besides purely technological considerations, ARM processors are increasingly viewed as a major asset for Europe's self-determination in HPC, not only by the European Commission, but also by many leading HPC organisations in Europe.

In this favourable context that it contributed to create, the Mont-Blanc project, now in its third phase, is moving ahead. It leverages the findings of the previous project phases to imagine a new high-end HPC platform that will be able to deliver a high performance/energy ratio whilst executing real applications.

More precisely, the first technical objective of the project is to create a well-balanced architecture and deliver the design for an ARM based SoC or SoP (System on Package) capable of providing pre-exascale performance – and measured using real HPC applications. The second objective is to maximise the benefit of this new architecture for HPC applications with new high-performance ARM processors and throughput- oriented compute accelerators designed to work together.

"In 2015, Mont-Blanc deployed the world's first ARM-based HPC cluster, featuring over 2,000 mobile CPUs. This system helped demonstrate the viability of using ARM technology for HPC."

Finally, the third objective is to develop the necessary software ecosystem for the future SoC – a fundamental asset to maximise the project impact and ensure real life success for this ARM architecture.

For example, one of the issues we are investigating is the need to transform applications from being latency limited to being throughput limited. This was an essential finding of the previous phases of Mont-Blanc. In the same way kids throw a tantrum to obtain immediately something they desperately need; our programmes issue a request for a resource and stall until whatever they require is available.

Various costly techniques are implemented to achieve some overlap between computation and communication, but our belief is that much more aggressive levels of look-ahead in work/resource demand generation and less urgent synchronisation demands can be achieved, by resorting to an asynchronous task-based programming model such as OpenMP4.0 or OmpSs. This transformation from latency-limited (by the response time of individual resource requests) to throughput-limited (by the total amount of resources available) is a key enabler for the future, not only in HPC but also for general purpose computing.

One of the first outcomes of the Mont-Blanc 3 project is a new prototype based on 64-bit ThunderX2 processors from Cavium[®], relying on the ARM[®] v8 instruction set. The system is now live at the Atos R&D centre in Les Clayes near Paris, and leverages Atos' Bull Sequana infrastructure, such as cluster management, network, power supply, and cooling. It was christened Dibona, after the Dibona peak in the French Alps, and the full configuration will ultimately include 48 computes nodes, i.e. 96 Cavium[®] ThunderX2 CPUs, or 3000 cores.

Dibona is not the end-product of the Mont-Blanc project, but it is a key tool that will allow project partners to expand their research, validate Mont-Blanc performance models, and test the completeness and usability of Mont-Blanc's solution.

The really exciting news about this prototype is that it will not remain a

prototype: Atos has decided to productise it and commercialise it as a standard Bull product under the name Bull Sequana X1310. All project partners are very proud that their work led to an actual product within the timeframe of the project, and will continue to work hard to design software and hardware that directly benefits HPC end-users.

The Mont-Blanc 3 cooperative R&D project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 671697. The project partners are Bull (Atos group, coordinator), ARM, AVL, BSC, CNRS, ETH Zürich, HLRS, Universität Graz, Universidad de Cantabria, UVSQ.



Etienne Walter Mont-Blanc 3 coordinator Atos etienne.walter@atos.net montblanc-project.eu www.twitter.com/MontBlanc_Eu

SFCURITY

Searching for the silver bullet: towards a more effective Security Union

European Commissioner for Security Union, Julian King underlines the role of the EU and national governments in keeping citizens safe

s you approach Arsenal's Emirates stadium in North London, you are greeted with a giant, ornate, black cannon. Not, as you might think, to intimidate visiting Spurs fans; nor - or at least not only - to represent the club's logo. Their purpose is less evident but even more important: to protect 60,000strong crowds from ramming attacks, acts of terrorism carried out by moving vehicles. This is just one examples of using urban planning to make our public spaces safer, without making them less free or open. Security policy is most effective when you don't notice it.

Such foresight is welcome. In their propaganda and their actions, terrorists have in recent years shifted their focus towards open spaces like pedestrian precincts, tourist and transport hubs, shopping malls, and sports and music venues. The means used by terrorists are also evolving: from traditional weapons such as bombs and guns to lower-tech solutions, such as vans and knives; as we have seen in recent incidents like London Bridge, Westminster, Nice, Berlin and Barcelona.

National governments have the ultimate responsibility to ensure their citizens are safe, but there is an increasing recognition of the EU's role. The security of one of us affects the security of us all: tools and techniques are crossing borders, and we must continue to evolve to meet a changing threat.

In October, the EU set out an anti-terrorism package, which includes the highest levels ever provided from the EU budget for internal security and policing. We have just published an €18.5 million call for proposals for projects to protect public spaces against terror attacks; next year, a further €100 million will support cities investing in security, under the EU's regional development fund. This funding will be accompanied by guidance to ensure that innovative and discreet barriers can



Julian King, European Commissioner for Security Union

secure our cities, without changing their open character. Of course, the risk of higher-tech attacks has not gone away, even if it is not high - so we have proposed an action plan to ensure we are prepared against any chemical, biological, radiological or nuclear attack.

Anti-terrorism

The EU is also taking steps to cut the space in which terrorists can act. Member States are sharing information more, so that people of interest can be picked up even if picked up in other European countries: last year, 13,100 UK-issued alerts received hits on the EU's Schengen Information System.



We have already criminalised many acts connected with terrorism: terrorist-related training or travel to Iraq and Syria, and access to arms and explosives. In October, we set out how we want to further restrict access to the ingredients of home-made explosives used in recent attacks: applying the existing laws in full, while also reviewing whether those laws need to change.

We are also looking to cut off the financing that terrorist need for attacks. The European Commission is leading the way through initiatives to strengthen co-operation between financial intelligence units and other national authorities. The EU also runs a ≤ 20 million regional programme on the fight against organised crime in the Western Balkans and a ≤ 16 million action on anti-money laundering and counter-terrorist financing in South East Asia.

We support the use of strong encryption of digital information. But sometimes it poses a challenge to law enforcement during criminal investigations. The European Commission is supporting stronger capabilities at European level which can be used by all national authorities.

And meanwhile we need to tackle the root cause of terrorism – radicalisation towards poisonous ideologies. Through organisations like the Radicalisation Awareness Network (RAN), we work to identify the underlying drivers for extremism, and provide guidance for frontline practitioners, such as teachers, social services and prison officers. As much terrorist propaganda is found online, we are also working with the big internet companies who can ensure it is taken down instantly, and does not reappear. We will take legislative action in this area if necessary.

Terrorism's real, and insidious, purpose is to create fear and turn us against each other. Those who perpetrate it want us to abandon the fundamental values that we cherish as Europeans: of openness, freedom and tolerance. We will not let them.

Julian King

European Commissioner for Security Union European Commission cab-king-contact@ec.europa.eu https://ec.europa.eu/commission/commissioners/2014-2019/king_en www.twitter.com/JKingEU

Are you prepared for GDPR?

The General Data Protection Regulation (GDPR) will apply from 25 May 2018. Failure to demonstrate good data protection processes may result in enforcement action.

Lloyd's Register provides a range of training and assessment services that will help you understand GDPR, your role and responsibilities under the Regulation and demonstrate good data protection practices:

- **GDPR Training** From brief overviews on GDPR, to more in-depth support and guidance, Lloyd's Register can provide training to meet your requirements
- Data Protection Impact Assessments (DPIA) Seen as good practice under GDPR, Lloyd's Register can carry out a DPIA on your behalf
- ISO 27001 Training & Certification Services Demonstrating commitment to meeting GDPR requirements, Lloyd's Register can provide training, gap analysis or certification services to ISO 27001.

0800 783 2179 enquiries@lrga.co.uk

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Does GDPR apply to you?

If your organisation processes personal data about EU citizens, regardless of where the processing takes place, then your organisation will need to comply with GDPR.

GDPR is not just limited to the marketing or sales departments. With data being so widespread in how we all work, GDPR is likely to impact on all areas of your organisation.

It's important to remember that the personal data you process relates to an actual person and how you then deal with it, can have a damaging impact on them. Understanding the risks to processing an individual's data therefore becomes important when trying to mitigate these risks.

The six principles of GDPR have addressed these main risks. Article 5(2) sets out the accountability concept, which under the Regulation means your organisation is responsible for and must be able to demonstrate, how you comply with these principles.

How to prepare for GDPR

Organisations will be expected to comply with GDPR from 25 May 2018, so it's essential that you start planning your approach soon.

If you already comply with the UK Data Protection Act 1998 (DPA) this will remain valid under GDPR, so it's a great starting point. It's also important to understand any gaps you may have between the two regulations.

Identify what new processes or procedures you need to implement and start employing data protection by default in your processes.

GDPR's Six Principles

Lawful, fair and transparent data processing

Data must be processed as described at the point of collection and ensure individuals understand how their data will be used.

Collect data for specified, explicit and legitimate purposes

Personal data can only be used for a specific processing purpose if the individual has been made aware of its use.

Limit data collection to what is necessary

Personal data collected on individuals should be relevant, adequate and limited to what is necessary.

Ensure data is accurate and kept up-to-date

Data held on individuals should be accurate and updated when necessary. If inaccurate, it must be erased or rectified without delay.

Store data for no longer than is necessary

Personal data that is no longer required should be removed.

Appropriately secure your data

Individual's data should have appropriate security processes in place to protect against unlawful or unauthorised access or processing. Designate a representative to manage your data protection compliance and name your organisation's details and point of contact.

Start keeping records of the data you hold, where it came from, how you use it and who you share it with. Check your processes and procedures to insure they cover the individual's rights and review how you seek, record and manage consent.

How to demonstrate compliance to GDPR

Data protection policies, HR policies, staff training and internal audits of data processing can all be used to demonstrate compliance. GDPR also supports the use of approved codes of conduct and certification to international standards.

Lloyd's Register provides training and assessment services to help you understand GDPR and demonstrate you comply with the Regulation.

T 0800 783 2179 E enquiries@lrqa.co.uk

SECURITY

A vehicle for change: Today's combat vehicles market

We spoke to Alix Leboulanger and Samuel O'Toole at Frost & Sullivan to get their insights into the current state of the combat vehicles market

ntroducing the combat vehicles market today, research analyst Alix Leboulanger at Frost & Sullivan highlights that the market has suffered from a lack of investment for many years. In addition, budget priorities have been diverted to other combat weapon systems due to ongoing deployment, fighter jets programmes and maritime warfare. As such, the combat vehicles market will experience renewal, but they have not been the priority of navies or armies recently.

Leboulanger also reveals that vehicle fleets will be modernised in the future, but that it is now difficult to upgrade the existing vehicles because some of them are over 40 years old. In terms of operational efficiency, this is a situation that requires a drastic improvement, she underscores. Leboulanger goes on to expand this point in her own words.

"With an increasing number of potential conflicts all over the world, it's important to be combat ready. It's not just about renewal, but ensuring that you have the full operational capability for deployment in the future.

It is also important that people are trained and able to operate the platform properly. In this vein, we are looking at a very positive outlook for the combat vehicles market over the next 10 years."

Samuel O'Toole joins the conversation to offer his thoughts on the upgrading and renewal of the existing fleet, as opposed to buying new ones. The funding has basically been reactive rather than proactive, he explains, adding that the lift in Counter-IED equipment requirements can be attributed to the growth in the IED threat from countries such as Afghanistan and Iraq. "It was in Afghanistan and Iraq where you saw the investment reactively going towards armouring the vehicle, rather than upgrading the firearms part of the package.

More recently, civilian UAS, which can be purchased commercially, have become an aerial threat to vehicles, as demonstrated by current tactics in use by Islamic State.

"In summary, the movement from a counter insurgency capability to a near-peer conflict preparedness will drive the combat vehicles market in the future."

O'Toole adds that while much of the equipment is decades old, the issue now is how are militaries going to get out in front of what the requirement is going to be in future, instead of paying the price in blood, sweat and tears. He also tells us that the combat vehicles market today has not had the glitz and the glamour of other defence equipment programmes out there.

The mantra is that it has always been easier to get hold of £1 billion in defence than it is for £1 million and added to that, funding for an F-35 for example can always be found, but ground capability requirements tend to get left behind. He goes on to expand this interesting point to us in his own words.

"It is relatively small in terms of its footprint, but it is seen to be something that will have a greater prevalence in the event of a conflict, particularly due to the requirements to move at an increased speed around the battle space. The ability to manoeuvre quickly when you are facing a near-peer adversary, when looking at potential threats out there, will be of a much higher priority than it has been when combatting counter insurgency.

SECURITY

"When it comes to counter insurgency operations, the priority is to minimise collateral damage, avoid civilian casualties and really slow down the pace of operations, contrasting with those in a near peer conflict where you are dealing with heavy artillery and air strikes."

"With an increasing number of potential conflicts all over the world, it's important to be combat ready" Leboulanger adds, stressing that the vehicles need to be tailored so that more weapon systems can be added, and they need to be a bit more agile in terms of both energy and propulsion.

"With an increasing number of potential conflicts all over the world, it's important to be combat ready. It's not just about renewal, but ensuring that you have the full operational capability for deployment in the future."

There is a lot going on in terms of the hybrid engine for fuel efficiency and the vehicle design, but also at the systems level there is an ongoing trend over the last 10 years of open systems architecture, to ensure that different types of vehicle can communicate with each other. The fixed commonality of vehicle systems on the ground, as well as fighter jets and helicopters, is a point Leboulanger stresses so that those who are deployed have a full spectrum of information available to them.

A fleet of brand new and upcoming vehicles with a new communications system is what the future holds, she reveals. "There is also one exciting trend, which is more about unmanned systems and ground vehicles system robots, which have already been deployed, mainly for mine clearance. The trend now is to improve such small robots and use them for cargo supplies, without risking the lives of operators for example on a convoy. We are not at the stage now where we can have robots engaged on the battlefield, but that is the next thing which may come over the next 30 years. "There are many trials going on in this area now, mainly in the United States, potentially looking at manned platforms and robots to carry any additional equipment."

O'Toole concludes by explaining that modern vehicles will become increasingly modular in design, with easily removable components, so they become more agnostic in terms of what systems are on board. Previously, there were many different platforms for different tasks; the future concept is that you would have a range of very similar platforms. In some cases, the same platform will support multiple roles, such a communications hubs and armoured troop mobility.

"The intention now is to minimise the number of static headquarters on the ground, of the type seen in classic images of Afghanistan like tents and compounds. The principle in future conflicts will be to keep the headquarters on the move and to do that, you need to put all the communications capability into a vehicle.

"There is much endeavour going on now to create the mobile hotspot that operates much in the same way as the civilian world, in that you can have access to satellite, Wi-fi, broadband, HF and VHF on a truck. This would give improved situational awareness, information flow and improved decision making."

Alix Leboulanger Research analyst

Samuel O'Toole

enquiries@frost.com Frost & Sullivan Tel: +44 (0)20 8996 8500 ww2.frost.com www.twitter.com/Frost_Sullivan

Aesthetically pleasing crash barriers as 'street furniture' – why functional will no longer do

Abigail Kellett, Product Manager at Marshalls PLC explores the importance of crash barriers that can withstand vehicular attacks

sking whether architects value aesthetics is rather like asking if a mathematician appreciates numbers.

But if aesthetics in the built environment can be elevated only at the expense of security or safety standards, then architects must grudgingly concede to the demands of functionality.

The involvement of vehicles in recent atrocities in Europe in the last 12 months – such as in Nice during July, Berlin in December, London in March, and Stockholm in April – have tragically highlighted why the deployment of robust physical barriers is a growing priority in public spaces. Together, killing over 100 people and injuring more than 550, they were brutal reminders that vehicles can be every bit as destructive as bullets and bombs.

Crowded places such as shopping centres, plazas and sports stadia increasingly need barriers that can withstand vehicular attacks, and then there's also the ever-present threat of cars veering off the road because the driver is reckless, drunk or asleep. Protective design can deter, delay and prevent vehicle collision around accident blackspots.

But urban planners are mindful of the adverse psychological impact on citizens of imposing barriers. Another



consideration is permeability: pedestrians must not be impeded along with rogue drivers. Therefore, unsurprisingly, design-led forms of security barriers such as crash-tested seating, planters and cycle racks are gaining ground with architects and specifiers.

But how easily can urban planners find crash-tested street furniture that is not only visually appealing on its own merits, but also in keeping with the location's wider architectural style?

Marshalls, the UK's leading hard landscaping manufacturer and street furniture specialist, believes that, while security must always be paramount, traditional forms of protective street furniture can often be too imposing and have a detrimental effect on a landscape's visual appeal. Marshalls recruited IFSEC Global to test this assumption. IFSEC Global polled hundreds of architects, consultants, security professionals, facilities managers and specifiers.

With around four in five (79%) respondents involved in a growing number of projects specifying aestheticallypleasing, crash-tested perimeter protection over the last three years, there has apparently been a sea change in priorities when it comes to urban planning briefs.

There's a clear and growing appetite for aesthetically-pleasing, crashtested perimeter protection – but have manufacturers kept up with a trend observed even within a short, three-year timespan? Apparently not, the findings indicate.

The demand for a wider range of aesthetically-pleasing, crash-tested perimeter protection than is currently available is enormous – equally so regardless of who we asked in the design and procurement chain, or where they were based in the world. Asked if they thought there was demand in the market for more of these products, a resounding 94% agreed.

Security professionals were equally as emphatic in their desire for more visually-appealing security products, with 95% wanting more choice in the market.

Steve Reddington, street furniture commercial director at Marshalls, says the findings back up the company's own, anecdotal experience. "The research confirms the conversations we are having with our customers in the security industry," he says. "We work closely with many landscape architects, and from the conversations we are having, it is clear the market is changing" he adds.

Creating harmony

Mindful of this reservoir of untapped demand, Marshalls has pioneered a paradigm shift in how street furniture and crash-tested perimeter protection can coexist more harmoniously.

By combining the two, Marshalls hopes that architects never have to compromise on aesthetic when designing public spaces. Where once they might have to specify a seat and a bollard – or reluctantly jettison the seat – now they can just specify a protective seat such as Marshalls' Igneo75/40.

But not everyone has embraced the concept of protective street furniture. Many involved in the built environment fear that it fosters homogeneity and blandness in urban landscapes.



The challenge for manufacturers of street furniture is to prove such fears unfounded through an innovative, design-led approach. They must equip architects and specifiers with the means to complement, rather than jar with an urban landscape's prevailing style.

The aesthetic value of a product even trumps price when respondents were asked to rank their priorities when procuring crash-tested perimeter protection. Nevertheless, it is reasonable to surmise that only a lucky few in the architect profession can honestly claim that money is truly no object in their latest project.

Thankfully, street furniture can play a key role in preserving the architect's grand vision, even as 21st century spaces are fortified against vehicular or explosive attack. But is there enough crash-tested street furniture on the market to meet the eclectic demands of urban planners?

It is surely no surprise, then, that architects and specifiers should be overwhelmingly interested in at least 2-3 crash-tested versions of lighting, seating, bollards, planters, litter bins and post and rail products. Only 6% professed to not be interested in any.

Ranked third out of six options given, the demand for the tried-and-trusted bollard remains strong even as imaginative alternatives emerge. Nevertheless, comparable levels of demand for crash-tested lighting, seating, planters and litter bins suggests that bollards are no longer the default choice of protective barrier. Products such as Marshalls' Giove Planter, Geo Cycle Stand and Geo Litter Bins have increased in popularity over recent times.

But the dramatic elevation in the terror threat over recent years has thrown down a new challenge to architects, making public spaces as secure as possible without undermining the aforementioned gains.

The findings from our survey, along with the trends explored above, suggest that the future of protective street furniture will be defined by its discrete incorporation within design-led products like seating, lighting and planters.

You can read the full report here.



Creating Better Spaces

Abigail Kellett Product Manager Marshalls PLC Tel: 01422 312000 www.marshalls.co.uk/landscapefurniture

Crime, terrorist threat, and inappropriate public behaviour

Anton Pieterse, Managing Director of physical security equipment provider Safetell specialising in counter-terror solutions, comments on terrorist threat

hether you are concerned with the physical abuse of our public-sector employees or the protection of our nation's infrastructure from terrorism, the procurement of measures to mitigate criminal and terrorist threat is often seen as a grudge purchase.

Since 2010, the number of UK police officers has fallen by 21,500 and while crime did not immediately rise upon the first round of cuts, continued lack of funding and a wave of terrorism has triggered many to consider their options- albeit begrudgingly. A common response is to deploy a technology of choice, with CCTV often being the favourite. Which begs the question, if the number of CCTV systems deployed continues to grow, how effective is this mode of protection against an equally growing threat?

Inappropriate responses to crime and terrorism

One of the common misconceptions when first developing a security solution alongside a security audit is to focus on electronic security products, such as CCTV. However, as noted in a study by the UK College of Policing, which reviewed 41 studies on the effectiveness of CCTV, successful usage is only found through significant investment in constant, well-staffed live monitoring stations with effective deployment of security personnel to locate, identify and capture any aggressors. The study found that overall, CCTV can reduce crime in a certain area by displacement of crime to neighbouring areas. The most significant finding in the study was that there was no evidence of an effect on violent crime. CCTV was seen to be significantly more successful when combined with other deterrent and intervention methods in the form of physical security.

Now let me make it clear, I am not a critic of CCTV- in fact, it forms part of our product range here at Safetell. We simply believe that such a solution should be a consideration as part of a wider strategy that helps form a security plan that not only suits the threats posed and the budget available, but it actually improves the working environment and processes of a government organisation, whether they occupy an office in the Palace of Westminster or a council office in Lancashire. By adopting a security strategy, many of our customers soon find they can reduce the life cycle cost of their investment, whilst improving working practices and the general aesthetics of the environment they seek to protect.

Weighing up the threat

It is important to understand the nature of the threat first by analysing the benefits of a security solution and confirming if the cost is at least equal to the cost of the protected assets, while also considering the additional costs that might be incurred from an incident. It is easy to put a price on an



asset, but it is impossible to place one on the life of a staff member.

The potential risks and costs can range from loss of business during the investigation, replacement costs, loss of reputation, potential injury/stress, and overall downtime. We often find that once a client understands the cost associated with an incident, they have a better appreciation of the cost of protection.

Physical security is defined by the ability to deter and defend potential attacks and aggressors through a series of target hardening solutions before and during the event, for example- installing and implementing attack resistant screens on counters, doors, walls, and windows into a premises. They can deter the attackers and protect the staff in the



Case Study: Portsmouth City Council

Solution: A range of counterwork upgrades to improve workplace ergonomics and customer interaction. Safetell also secured the vault area with their ballistic resistant CityWall modular walling, and installed a ballistic resistant Staffline timber door to create an airlock system, accessed with staff swipe cards and a visitor video intercom.

"We chose Safetell because of their previous track record working with us, commented Andrew Malbon, chief project architect for Portsmouth City Council. "They already knew us and had a good understanding of our security needs and concerns. It was also really useful that they could draw up the master plan, and install both the counters and the security equipment. Their turn key service was a real plus point."

absence of Police or Security Guards to deal with the matter, while also still providing hardened resistance to the assets protected within.

A collaborative approach to suit exact needs

At Safetell, we have the capability to design and construct physical security products to exact requirements, allowing for protection against fire, manual attack, bullet and even blast explosion, providing protection to secure environments, such as cash office counters, infrastructure, and council offices. Terror is a crime and security solutions come in all forms, for all environments, and often require bespoke elements to be designed and installed for seamless integration. As a general rule, no standard is fit for all applications. Many physical security and electronic solutions can exist and work successfully, but a successful strategy for one environment doesn't necessarily translate exactly to another.

Reducing cost and effort at every stage

Allow Safetell's team of experts to examine the threats posed to your



organisation and we will generate a solution that will not only protect your organisation, it will reduce cost. Yes – we can mitigate the cost of an incident, and the cost of an overall solution – but by providing a solution that is backed up by an in-house team of experts, project managers and a national maintenance team Safetell can reduce the time, effort and life cycle cost for all; turning a grudge purchase into a solution that benefits all stakeholders.



Anton Pieterse Managing Director Safetell Tel: 01322 223233 sales@safetell.co.uk www.safetell.co.uk

GOVERNMENT

A renewed relationship with Indigenous peoples and Indigenous affairs

In this article, Minister Carolyn Bennett details her key priorities concerning the advancement of Indigenous Affairs in Canada

his year, Canada is celebrating the 150th anniversary of Confederation. Understandably, Indigenous people in Canada are feeling that there is little to celebrate, 150 years of colonial policies, 150 years of racism.

The late front man for a famous Canadian rock band "The Tragically Hip" helped us through this year with his observation: "We've got 150 years behind us to learn from and 150 years ahead of us. So, we'd better just get to work" (Gordon Downie).

As a government, we are determined to work with First Nations, Inuit and Métis people to ensure that the next 150 years is focused on reconciliation and righting the wrongs of the past.

Colonizing policies insisted that the 'settlers' ways were superior. From the *Indian Act* which divided nations into largely unsustainable villages to taking the children from their families, and placing them in heartless residential schools to ongoing patriarchy, Indigenous people in Canada have paid a terrible price.

The recent Truth and Reconciliation Commission issued 94 Calls to Action. Our government has committed to honour and implement all of them. We have also committed to implement the UN Declaration on the Rights and to breathing life into Section 35 of our Constitution, which enshrined the treaty and inherent rights of Indigenous people in Canada.

Our Prime Minister, the Right Honourable Justin Trudeau, has stated clearly that no relationship is more important to him and to Canada than the one with Indigenous peoples. He has affirmed that it is time for a renewed relationship with Indigenous peoples, based on recognition of rights, respect, cooperation and partnership.



In Canada, discriminatory policies and programmes have far too often led to tragic consequences for First Nations, Inuit and Métis individuals, families and communities.

Improving the relationship: changing structures A bold example of this transformative change occurred last August. Prime Minister Trudeau announced that our government would seek to dissolve the federal department of Indigenous and Northern Affairs, which is charged with implementing the *Indian Act* of 1876.

In its place, we are creating the Department of Crown-Indigenous Relations and Northern Affairs and the Department of Indigenous Services – a reform that was

GOVERNMENT



Minister Carolyn Bennett

suggested 20 years ago by the Royal Commission on Aboriginal Peoples.

The recognition of rights – the right of self-government and the right to self-determination – is fundamental to transforming the relationship between Canada and Indigenous peoples.

Through the creation of bilateral mechanisms with national Indigenous organisations and self-governing nations, for the first time in our history we are sitting as government Ministers with Indigenous peoples to identify priorities and co-develop solutions together.

Improving the relationship: other critical efforts The government is also changing the way it works towards resolving legal matters with Indigenous peoples, from land claims to class action lawsuits. With a focus on righting past wrongs, negotiation rather than litigation is the government's preferred route to advance reconciliation.

In this vein, the government signed an agreement-inprinciple with Indigenous people who were part of the "Sixties Scoop". Beginning in the 1960s, Indigenous children were taken from their homes by child welfare authorities and placed in foster care or adopted out to non-Indigenous families.

Another critical step in renewing the relationship has been the launch of the Inquiry into Murdered and Missing Indigenous Women and Girls. A national, independent Inquiry that will to do the work needed for Canada to put in place the concrete actions necessary to put an end to this national tragedy. Our government is also taking immediate action with investments in women's shelters, housing, education, and child welfare, and in improving safety on remote highways.

The Government of Canada has also made a historic investment in the last two Budgets – \$11.8 billion to begin to close the gap in quality of life and health, education and economic outcomes.

Whole-of-government approach

A Working Group of Ministers, led by my colleague the Honourable Jody Wilson-Raybould, Minister of Justice, is currently reviewing laws, policies and operational practices that affect Indigenous peoples and their rights and interests.

The Prime Minister said in his address to the UN General Assembly in September 2017: "There is no blueprint for this kind of change. There is no road map we can follow. But neither can we wait. The time has come to forge new paths together – to move beyond the limitations of old and outdated colonial structures, and to create in their place something new, something that respects the inherent right of Indigenous peoples to self-govern and to determine their own future."

The journey of reconciliation is about all Canadians – Indigenous and non-Indigenous people alike – working together to achieve a fundamental shift in the way we perceive and interact with each other for the benefit of all Canadians.

We know that more has to be done. We will continue to work in full partnership with Indigenous peoples to ensure we continue to make real and meaningful progress on reconciliation, based on recognition of rights, respect and partnership.

Carolyn Bennett Minister of Crown-Indigenous Relations

and Northern Affairs, Canada

Office of the Minister of Crown-Indigenous Relations and Northern Affairs http://pm.gc.ca/eng/minister/honourable-carolyn-bennett www.twitter.com/Carolyn_Bennett

Non-Indigenous individuals' responsibilities within higher education contexts

Dawn Zinga, from the Department of Child and Youth Studies at Brock University explore the responsibilities of non-Indigenous individuals within higher education settings and the inequalities that exist

s a non-Indigenous scholar working in the area of Indigenous education, I spend a lot of my time thinking about my own role in perpetuating inequality within higher education and answering questions posed by non-Indigenous faculty, staff, and students. These questions usually fall into two broad categories. The first category consists of questions about why I am raising an issue or why something is important, while the second category tends to focus on questions about what individuals can do now, so that they know about the inequities that exist. These two categories of questions point to some interesting aspects about the responsibilities of non-Indigenous individuals' within higher education settings. One of the first responsibilities is to become educated about the realities of Indigenous peoples and related the systems of inequality. The second responsibility that I will focus on is what to do with the knowledge that you gain when you become educated.

Starting with myself, I am a severalgenerations-removed immigrant to the ancestral lands on which I reside and I have experienced a position of some privilege in the mainstream structures of society, such as education, health services, and other governmental systems. While I grew up in a blue-collar home and experienced



the discrimination that can be associated with class and being a girl, I was afforded many privileges and rarely had cause to question that I belonged in the classrooms that I occupied. I frequently saw myself and my life experiences reflected in the classroom and my experiences within society. From a young age, I had a questioning mind and often challenged teachers about why some voices and some life experiences were not represented in the curriculum or were represented in very narrow and proscribed ways. Through my own search for knowledge and the generous teachings of my Indigenous colleagues, I became aware of the systems of racism and inequity experienced by individuals who are

minoritised by the mainstream systems of privilege and discrimination that continue to be reinforced throughout society and particularly within systems of education. In my role as a university professor, I am also responsible for exposing undergraduate and graduate students to these systems of inequity and to challenge their taken-for-granted assumptions.

Some of my students resist any challenges to their understanding of society and the status quo and remain facing the first responsibility of education. Other students engage in the teaching but sink into guilt and seem paralysed by the immensity and





complexity of the issues thy have just learned exist. The second responsibility of what to do with the knowledge once you have learned it is easier to address than the resistance to learning that the world does not necessarily operate in a way that you thought that it did, and that with or without your knowledge, you have occupied a position of power and privilege. The first thing for non-Indigenous individuals to realise is that guilt is an emotion that will not be helpful. It must be experienced but in the end we are not responsible for the actions of those who preceded us, but we are responsible for how we address the legacy

that was left behind. Essentially, non-Indigenous individuals must focus on how to act on the knowledge that has been gained.

Non-Indigenous individuals have a choice. They can choose to close their eyes to uncomfortable realities and continue on perpetuating them or they can chose to use their individual voices to make a difference. Using one's voice can be as simple as speaking up when an inequality is being perpetuated, or challenging a policy that negates other people's experiences or lived realities. It can be exposing others to knowledge they

may not be aware of or supporting someone when that person's viewpoint is being shut down as invalid or irrelevant. Sometimes it can be listening to another perspective and being open to being challenged and educated about how your own actions or lack of action may have reinforced inequalities or alienated Indigenous individuals.

Addressing these two responsibilities within educational contexts can lead to educational settings in which Indigenous students and other Indigenous individuals feel welcome and accepted. It can open up important spaces to talk about ways of moving forward together towards positive change that does not reproduce or perpetuate systems of inequality. While I have focused on higher education contexts, this can also be extended to other educational contexts. Making a choice to address these responsibilities daily is a choice to move beyond resistance and guilt to positive action and relationships that strong can help us all negotiate a new future of education for all students.



Dawn Zinga Associate Professor and Chair Department of Child and Youth Studies Brock University Tel: +1 905 688 5550 ext. 3152 dzinga@brocku.ca https://brocku.ca/social-sciences/departments-and-centres/child-and-youth-studies

GOVERNMENT

Rationalising the UK government estate through the Government Property Unit

The Government Property Unit aims to streamline the public-sector estate and generate better value for money from its assets, as OAG discovers

he Government Property Unit (GPU) was set up in 2010 as part of the Cabinet Office to get better value for money from the public sector's extensive property estate.

In 2014, the coalition government published a new estate strategy designed to "create an efficient, fit-forpurpose and sustainable estate whose performance matches the best of the private sector" by 2020.

The key aims of the strategy are to: remove boundaries between departments, local authorities and other public bodies; minimise the need for office space; use existing land and buildings more efficiently; and dispose of surplus assets in a way that maximises receipts while boosting growth and creating new homes.

"As part of the government's aim of delivering smarter working, the GPU runs the Government Hubs Programme. This aims to reduce the government estate from around 800 buildings to 200 by 2023 through the creation of shared, multi-departmental regional "hubs" and supporting offices. The programme is expected to save approximately £2.4 billion over 10 years."

The GPU implements the strategy through a number of core programmes. They include One Public Estate, which brings together the public bodies within a region to examine how they can use assets more effectively.

It has also set up the Government Property Agency, which formally launched in September 2017 to provide professional asset management services across the government's portfolio, including a more commercial approach to leases and property management. Properties worth around £3 billion transferred to the Government Property Agency. The GPU acts as the agency's sponsoring body, providing oversight and guidance to ensure it delivers its objectives.

As part of the government's aim of delivering smarter working, the GPU runs the Government Hubs Programme. This aims to reduce the government estate from around 800 buildings to 200 by 2023 through the creation of shared, multi-departmental regional "hubs" and supporting offices. The programme is expected to save approximately £2.4 billion over 10 years.

Flexible working will be encouraged and there will be collaboration zones where staff involved in crossdepartmental projects can work together. There will also be quiet zones and private zones for confidential or sensitive tasks.

Cloud-based technologies will allow staff to work away from their desks in the zones that best suit their needs. The hubs programme is being delivered in partnership with Common Technology Services, the body responsible for designing IT services to meet the government's digital transformation agenda.

Progress at the GPU

Since the GPU was established, the total size of the central estate has shrunk by around a quarter, or over 2m sq m. Between January 2012 and March 2016, 94% of the reduction in floorspace came from offices.

Annual estate running costs have been cut by £775 million in real terms since 2011-12 to around £2.55 billion in 2015-16 - a reduction of 23%. Over the same period, the sale of surplus land and properties raised £2.5 billion.

As of March 2016, there were around 4,600 holdings in the central estate. In April 2017, the public spending

GOVERNMENT



watchdog the National Audit Office (NAO) said that the GPU is making good progress in reducing the overall size of the government estate and is getting better value for money from its assets.

However, it cautioned that there is still much work to do to achieve the objective of creating a shared, flexible and integrated estate, adding that although the GPU has taken steps to improve its capabilities, increasing workloads mean that it faces shortages of property and project management experts.

The NAO said the Government Hubs Programme shows potential as a catalyst for transformation towards creating a shared, flexible and integrated estate.

Nevertheless, it added that the initiative is still in the early stages and, crucially, some departments have not shown strong commitment to relocating to hubs.

The GPU is also likely to face challenges in finding suitable buildings and negotiating leases in the right timescale, as well as local opposition to the closure of other offices, the NAO warned. "Departments have continued to reduce their estates and government is now getting better value for money," said Amyas Morse, head of the NAO.

"The Government Property Unit, however, still needs to make more headway to achieve a shared, flexible and integrated estate. It is not going to be plain sailing.

"The GPU should take stock and, if necessary, delay, redesign or consider phasing its programmes over a longer timescale."

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Is office rationalisation enough?

Alison White, Co-Founder of PLACEmaking reveals her thoughts on office rationalisation and smarter working

he Government Property Unit (GPU) is tasked with ensuring that all public bodies make better use of their real estate assets, releasing surplus buildings and land for development and/or regeneration. Initially focused on the extensive central London office estate, few public-sector bodies are isolated from the pressures being applied: do better, do more and at significantly less cost. Rationalisation of their extensive office estate in particular is under scrutiny.

Is office rationalisation enough?

With rationalisation therefore regarded as an attractive source of both capital and revenue savings, the challenge is deciding what to get rid of and what to hold on to. Making that decision is made more difficult as modern ways of working challenges traditional assumptions of what we want an office estate to look like. Without recognising that 'going to work' means something very different now to what it did just a few years ago when the 'office' was the Monday to Friday and 9 to 5 destination, is increasingly outdated.

Accelerated evolution and roll-out of mobile technology, remote access to digitally generated and stored information enables smarter ways of working and has increased expectations of choice about when and where we work. Going to work no longer means going to the office. So, if we don't need to go to the office, can we better optimise how we use the reduced office space.

So, what does optimising office space mean?

Optimising a reduced office estate demands a re-rethink of the purpose of the office and a change of expectations by building providers and users. Users need to reappraise what they expect to personally 'own', instead focusing on what sort of experiences they want when using the office, in the context of them having alternative workplace options. They need to consider space as a shared commodity used by them occasionally frequently but more often sporadically.

Building providers need to rethink their attitudes towards building users, from them being static occupiers to being temporary consumers of space, facilities and services. Building owners need to provide better quality space solutions that directly supports their customers productivity, which in turn increases the desirability and value of space. When most office buildings sit idle for 40% of the time they are officially open for use, facilities managers need to rethink how space is operated and if it can be used out of hours by others, focusing on design solutions that motivate and delight people not just what minimises operating costs and asserts operational control.

We may need to rationalise the total volume of office space, but what we hold on to needs to be used more efficiently and effectively. Otherwise people will simply find better places where they can work and the value of social interaction will be lost.

How do we rationalise and optimise space?

There have been several attempts to describe the changes in the way we work and the design of rationalised and optimised workplaces. New Ways of Working, Flexible Working, Agile Working and the GPU's own The Way We Work (TW3) to name but a few. Smart Working though has emerged as an accepted term as it refers to the adoption of modern working practices and the key constituents of the transformational programme of change that together enables optimisation and office rationalisation to be achieved and successfully sustained.

PLACEmaking support our clients deliver Smart Working solutions. Our expertise is in addressing the four key elements of change:


PEOPLE – transforming working practices and attitudes to how space, facilities and assets are used and provided;

PLATFORMS – maximising use of technology, access and use of digital information;

PLACE – providing efficient and economically viable workplaces that supports changing working practices and;

PROVIDERS – repurposing customer focused support services to better meet Smart Working requirements.

PLACEmaking expertise and skills enable us to deliver end-to-end professional services, developed to support our clients achieve their change objectives, including:

- Workplace change, communications & engagement;
- Interior architecture & design;
- Strategic asset management;
- Digital and technology advisory and;
- Programme management.

A recent case study, the 2017 TW3 award winning Bristol City Council project is regarded by the UK Cabinet Office as an exemplar for local government: reducing the office estate by 75%, increasing utilisation of retained estate by 250% and delivering £125 million savings over 5 years. The retained estate included a Grade 2* heritage building was refurbished and remodelled with English Heritage approval, reflecting changes of the council's way of working.

Now, only 30% of the workspace includes desks with the remaining

70% including multiple innovative, collaborative and interactive settings solutions. Increasing the proportion of the building to public access and increasing income generation opportunities has increased use of the building beyond normal corporate hours and provides a valuable asset for the cities Business, citizen and other agency use.



Interactive 3D video of Cash Hall

PLACEmaking's change approach is scalable to suit out clients' workforce headcount, a recent project included over 7,000 users. With a toolbox of over 135 change tools and methods deliverable via internet on-line, internal intranet communications networks or through structured face to face interactions. Our tried and tested approach is a 4-step transformational programme of change, profiled engagement and communications, sequentially supporting people through;

Pre-implementation

Raising awareness – relating the organisational programme objectives with personal self-navigated change journey;

Familiarisation – enabling people to explore and understand the proposed new space, facilities, assets and operational support service;

Preparation – pre-implementation induction, minimising operational disruption and maximising desired business benefits;

Post implementation

Aftercare – measuring results and ensuring desired objectives are achieved, reported and acknowledged.

Now is the time to update and upgrade expectations about the workplace, how it operates and how we function in it. If more than 30% of your office space has desks in it or meeting rooms are the only alternative spaces available to get away from the desk then it's time to review how your workplace is holding you back from achieving your future vision and business expectations.

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2017 National winner of the Cabinet Office's TW3 (The Way We Work) award





PLACEmaking

Alison White

Co-Founder PLACEmaking www.placemaking.co.uk www.twitter.com/PLACEmaking_uk Facebook.com/PLACEmaking.co.uk

Smart working – let us make your place work for you

Emmanuel CHAUTEMPS, Director of Bouygues E&S FM UK limited explains how smart working can transform workplaces to improve happiness, wellbeing, and productivity

The evolution of technology is impacting deeply the way people work, live, play and socialise. 'Going to the office' as we all did for decades has a completely different meaning in 2017. In Europe, people still spend 90% of their time inside buildings. The built environment has a key impact on our well-being and productivity. Happier and healthier people, places, neighborhoods and cities contribute to a more resilient, efficient and sustainable society.

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- Enable true collaboration;
- Contribute to people's well-being and happiness;
- Attract and retain talents;
- Improve your cost of operation;
- Foster innovation and productivity;



- Reduce your foot print, while increasing your capacity and resilience;
- Provide a return to investment of typically less than 3 years.

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Emmanuel Chautemps Director Bouygues E&S FM UK limited Tel: +44 (0)207 401 0020

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By investing our time, expertise and resources into all of our partnerships, we facilitate positive and lasting change.

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Shared innovation

Zero Waste Scotland on the government's drinks containers return scheme

Zero Waste Scotland reveals their thoughts on the Scottish Government's plans for a drinks containers deposit return scheme

ero Waste Scotland welcomed the news in this year's Programme for Government that the Scottish Government is pressing ahead with plans for a deposit return scheme for drinks containers. This is a step change in its ambition and Zero Waste Scotland are now charged with coordinating the design of the best possible system for Scotland, together with key partners.

Our work to date shows that a deposit return scheme could be feasible and would deliver several benefits: to recycling rates; to quality of recycled materials and potentially to litter prevention.

"The time is right both for a deposit return system and for wider work to create a circular economy."

There are a complex range of issues that need to be considered in the set-up of such a scheme. For example, the level of the deposit customers would pay; the types of drinks containers that would be included; the different options for how to return containers; and the way the scheme is run and managed.

These are important practical considerations and we'll be learning from other schemes around the world to model what we believe will be the best option for Scotland.

Changes made so far

In Scotland, we've already seen the difference that attaching a value to single use items can have in changing behaviour, through the success of the 5p carrier bag charge. As well as introducing a deposit system, the government has now signalled it wants to go further and set up an expert group to look at wider options for environmental charging, including on disposable cups. All this chimes with the government's ambition to transition to a more circular economy and furthering our recycling habits. Longer-term, we need to also change the mind-set of businesses who design and make products. Our vision for a circular economy, where we shift from being a throw-away society to one which eliminates waste entirely, will require system-wide change. At its heart that's about redesigning how we do things.

The aim would be to shape the economy in which products can be designed to last longer, be easy to repair, have guaranteed availability of spare parts, and ensure the manufacturer is responsible for the stewardship of the product to in a way that discourages wasteful disposal.

As well as the obvious environmental benefits, such an approach can also open up opportunities to create jobs and new economic value from things we'd otherwise have discarded. Such opportunities go entirely with the grain of Scotland being an innovative, purposeful and creative industrial nation that's fit for the future. The time is right both for a deposit return system and for wider work to create a circular economy.



lain Gulland CEO, Zero Waste Scotland Zero Waste Scotland Tel: +44 (0)1786 433 930 www.zerowastescotland.org.uk www.twitter.com/ZeroWasteScot



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Andy Jowett Editor ajowett@pbctoday.co.uk





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The future of the natural environment

The UK's Secretary of State for Environment, Food and Rural Affairs Michael Gove sets out his vision for the future of the natural environment

n 1970, the incoming Conservative Government of Edward Heath created this country's first Department of the Environment. The new department published a White Paper on our natural heritage in 1972 which was entitled 'How Do you Want to Live?'

In the 45 years since he wrote we have lost green space, cut down trees, sacrificed meadow and heath land, polluted our earth, air and water, we placed species in danger and we've run down the renewable resources – from fish to soil – on which our future depends. Farmland bird numbers have been cut in half, species have been devastated, bees and other pollinators threatened.

And at the same time, across the globe, we've seen climate change threaten both fragile natural habitats and developing human societies, we've allowed extractive and exploitative political systems to lay waste to natural resources and we've placed species of plants and animals in new and mortal danger while gambling with the future health of the whole world.

Unless we take the right environmental action, we risk seeing more species die out, with potentially undreamtof consequences in terms of the health and balance of nature. We risk flood damage to the homes in which we live and devastation to the islands that others know as their only home. We will see the forward march of deserts compelling populations to be on the move and the growing shortage of water creating new conflicts and exacerbating old rivalries.

Indeed, ultimately, the air we breathe, the water we drink, the food we eat and the energy which powers enterprise, are all threatened if we do not practice proper stewardship of the planet. If we consider the fate of past societies and civilisations, it has been, again and again, environmental factors that have brought about collapse or crisis. The Pulitzer Prize-winning academic Jared Diamond has, brilliantly, anatomised the forces which led to past civilisational destruction – deforestation and habitat destruction; soil problems such as erosion, salinization, and soil fertility losses; water management problems; overhunting; overfishing; and the effects of introduced species on native species.

He has also outlined the contemporary environmental threats that we now face with irresistible clarity – climate change, the build-up of toxins in our soil, air and oceans and the spiralling level of resource consumption, waste generation and demand for energy which all threaten human progress in the future.

Now, of course, there is a huge difference in the scale and duration of seventeenth century climate impacts and the current man-made crisis. And the technological breakthroughs that mankind has pioneered in recent years, the greater scientific knowledge that we now enjoy, the computational power of the machinery in our own hands, means that we live in a radically different world to our ancestors.

But we live on the same planet. The only one we know which can sustain human life. And the history of humanity on this planet tells us that, again and again, societies and civilisations have been gripped by hubris, by the belief that this time is different. That the cycles of the past have been broken. And we have seen, recently and all too graphically, how hubris in the financial markets, the belief among some that they had become not just a global elite but masters of the universe, led to economic disaster.

Science, technology, computational power are certainly critical to shaping our future, but if we imagine they can liberate us from the need to safeguard our environment, to protect the species we share this planet with, to protect and purify our air and our oceans, to keep our earth fertile and ensure that we can renew our natural resources, then we will have succumbed to the hubris which has wrought such devastation in the past, and which in the future may condemn us to much worse than economic hardship.

So, we should not aim simply to halt or slow the deterioration of our environment. We must raise our ambitions so we seek to restore nature and reverse decline. This government was elected on a pledge to be the first to leave the environment in a better state than we inherited it. While the need for action on the environment has rarely been greater there are also, at this moment, forces at work which make me optimistic about our capacity to rise to this challenge – and optimistic about the role our country can play.

The future can be better

The first reason for optimism is the idealism and commitment of so many in our society, of all ages but especially among young people. Environmental organisations – from WWF to the RSPB, the Wildlife Trusts to Greenpeace and Friends of the Earth – enjoy memberships in the tens and hundreds of thousands, and the support of millions more and a capacity to move hearts more powerful than any other set of institutions in our civil society.

And their campaigning energy and idealism, while occasionally uncomfortable for those of us in power, who have to live in a world of compromise and deal-making, is vital to ensuring we continue to make progress in protecting and enhancing our environment.

On everything from alerting us all to the danger posed by plastics in our oceans and nitrogen oxide in our air, to the threats posed to elephants by poaching and cod by over-fishing, it's been environmental organisations which have driven governments to make progress. They have demonstrated that we can, with sufficient will, halt and reverse those trends and forces degrading the natural world and we can, if we have that will, improve the environment we are handing on to the next generation.



The Rt Hon Michael Gove MP, Secretary of State for Environment, Food and Rural Affairs

Science is our guide to the future

Now I have been frank before when talking about animal welfare and my feelings for landscape, wildlife and natural beauty spring from sentiment. Growing up between the North Sea and the Cairngorms, spending weekends in the hills and weekdays with my head in Wordsworth and Hardy, Lewis Grassic Gibbon and Edward Thomas, I grew up with an emotional attachment to natural beauty which inevitably influences my feelings towards questions on everything from architecture to ivory.

But while natural beauty moves us deep in our souls, environmental policy also needs to be rooted, always and everywhere, in science. There will, of course, always be a need to make judgements about the best method of achieving environmental goals, in ways which improve rather than upend people's lives. But it is only by adherence to scientific method, through recognising the vital importance of testing and re-testing hypotheses in the face of new evidence and through scrupulous adherence to empirical reasoning, that we can be certain our policies are the best contemporary answer to the eternal questions of how we live well and honour the world we have inherited and must pass on enhanced to our children.

And it is science that guides my approach to another issue where my emotions have been powerfully engaged – fishing. My father, grandfather and great grandfather all made their living from the sea. My great grandfather was a fisherman, my grandfather and father fish merchants. My father's business closed in the 1980's when I was a schoolboy, one of many that closed after this country accepted EU control of our waters through the Common Fisheries Policy.

The CFP has had a profound impact on the UK's coastal communities. But its most profound impact has been on the sustainability of our fish stocks. Fisheries management should always be guided by science – by a hard-headed assessment of which species and stocks can be fished and which must be protected if their numbers are not to dip below sustainable levels. The tragic precedent of over-fishing off the Grand Banks, and indeed current overfishing practices off the coast of Africa, shows how easy it can be to destroy what should be a perpetually-renewable natural resource.

The CFP has been reformed in recent years, not least thanks to the efforts of my friend and colleague Richard Benyon. The benefits of improved environmental stewardship have been seen in the resurgence of North Sea cod. But it is still the case that 40% of fish stocks in the Atlantic, North Sea and Baltic Sea are being fished at unsustainable levels. By leaving the CFP, taking back control of our territorial waters, granting access to other countries and allocating quotas all on the basis of what is scientifically sustainable, we can ensure that we set and follow the very highest standards in marine conservation.

And that, in turn, should lead to the revival of our coastal communities. With UK control of waters in our exclusive economic zone we cannot just husband fish stocks more wisely – we can also ensure that we allow our fishing industry to grow sustainably in the future as well. Outside the EU, as an independent coastal state, we can be home to world class fishing fleets as well as proving ourselves environmental leaders.

And it is not just through reform of fishing policy that we can ensure the marine environment is restored to health. Eight million tonnes of plastic are discarded into the world's oceans each year, putting marine wildlife under serious threat.

In October 2015, the government introduced the 5p carrier bag charge. Figures released show that policy's enormous success – 9 billion fewer carrier bags distributed since the charge was introduced, a fall of 83%. More than £95 million has also been raised from the charge, has been donated to environmental, educational and other good causes.

But this work in order to protect our marine environment is not good enough. Last year the government launched a consultation on banning microbeads in personal care products, which have such a devastating effect on marine life. We are responding to that consultation and we will introduce legislation to implement that ban later this year.

But there is more we can do to protect our oceans, so we will explore new methods of reducing the amount of plastic – in particular plastic bottles – entering our seas. I want to improve incentives for reducing waste and litter, and review the penalties available to deal with polluters – all part of a renewed strategy on waste and resources that looks ahead to opportunities outside the EU.

As custodians of the fifth largest marine estate in the world, we have a responsibility in the UK to protect these unique and fragile environments. So, we will continue to fight to uphold the moratorium on commercial whaling. And by completing the Blue Belt of marine protected areas around the UK and working with our Overseas Territories we hope to create the world's largest marine sanctuaries, we hope to deliver over 4 million square kilometres of protected maritime areas by 2020.

Outside the European Union there is scope for Britain not just to set the very highest standards in marine conservation, but also to be a global leader in environmental policy across the board. Informed by rigorous scientific analysis, we can develop global gold standard policies on pesticides and chemicals, habitat management and biodiversity, animal welfare and biosecurity, soil protection and river management and indeed in many other areas.

We can take smarter and more targeted approaches to the improvements that we want to see – for instance, we can incentive recycling according to the environmental impact and value of the material, rather than a crude weight-based target that currently focuses recycling on things that happen to be heavy.

Shaping a greener future

Now in the past, the United Kingdom played a leading role in establishing the world's most successful envi-

ronmental treaty – the Montreal Protocol which has protected the ozone layer by phasing out the chemicals that UK scientists had shown was destroying it.

We are fortunate that in this country we do have innovative private sector players who can work with government and respond to smart, and ambitious, regulation and targets to help us meet new environmental demands while also generating growth. I hope to say more about some of the ambitions we want the private sector to help us achieve real gains around clean, green, growth.

"Unless we take the right environmental action, we risk seeing more species die out, with potentially undreamt-of consequences in terms of the health and balance of nature."

And it's important that government and the private sector work together because scientific advances and technological breakthroughs are rarely the sole preserve of the state or the market. The huge commercial success of America's Silicon Valley was built on Government investment. It was the state-run Defence Advanced Research Projects Agency and the federally-funded NASA which generated the initial breakthroughs on which subsequent commercial success was built.

Similarly, the success of Israel's amazingly creative tech sector has been built on that nation's investment as it happens in defence technology. And the private sector innovation which has been generated by state investment in R&D in America and Israel could be matched by private sector innovation here built on public sector leadership and investment in rigorous environmental science.

I hope we can say more in this area not just in the BEIS Clean Growth Plan but also in what will be its sister document – DEFRA's 25-year Environment Plan. Now I know there has been understandable impatience that the Plan has been longer in gestation than a baby elephant.

But I want to make sure our plan is as ambitious as possible. Critical to its success will be adopting as rigorous a methodology as possible to setting goals and reporting success or failure. Which is why I have written to Professor Dieter Helm, the Chair of the Natural Capital Committee, to ask his Committee to draw up advice on what our Plan should aim to achieve and how it should seek to do so.

And next year, I will also be publishing the second National Adaptation Programme, a comprehensive plan of action to improve our resilience to climate change – an area where Defra is the lead government department, a responsibility I take very seriously.

I have set out what I believe is a deliberately ambitious agenda because I believe the times demand it. Leaving the EU gives us a once in a lifetime opportunity to reform how we manage agriculture and fisheries, and therefore how we care for our land, our rivers and our seas. And we can recast our ambition for our country's environment, and the planet.

In short, it means a Green Brexit. When we speak as a Government of Global Britain it is not just as a leader in security or an advocate for freer trade that we should conceive of our global role but also a champion of sustainable development, an advocate for global social justice, a leader in environmental science, a setter of gold standards in protecting and growing natural capital, an innovator in clean, green, growth and an upholder of the moral imperative to hand over our planet to the next generation in a better condition than we inherited it. That is my department's driving ambition – and it should be central in the next five years to our national mission.

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You can read the full version at gov.uk/defra

The Rt Hon Michael Gove MP Secretary of State for Environment, Food and Rural Affairs Department for Environment, Food & Rural Affairs

Tel: +44 (0)20 7238 6951 www.gov.uk/government/organisations/department-for-environmentfood-rural-affairs www.twitter.com/DefraGovUK

How the Scottish Government is taking responsibility for global issues

In an exclusive interview a spokesperson from the Scottish Government speaks to Open Access Government about how Scotland is fighting climate change

spokesperson from the Scottish Government reveals the future where digital and low carbon technology and the investment ploughed into this sector. In addition, they explain the Scottish Government's future priorities for the environment, for example in terms of the plans to introduce Low Emission Zones into Scotland's four biggest cities between 2018 and 2020.

To support the circular economy and tackle climate change, we find out that the Scottish Government plans to develop a deposit return scheme, designed to increase recycling rates and reduce littering across Scotland. Looking at the wider picture, we also learn about the importance of developing a sustainable future for younger generations, in this special question and answer session with a Scottish Government spokesperson.

"We are confident that a deposit return scheme will increase recycling and reduce littering – this is clear from evidence in the many countries that already use deposit return."

Can you outline the New Innovation Fund, to accelerate innovation in new technologies, including low carbon and digital projects by 2020?

To send a clear signal that Scotland is the place for innovation in digital and low carbon technology, we have invested a further £60 million to deliver wider low carbon energy infrastructure solutions across Scotland, such as electricity battery storage and sustainable heating systems and electric vehicles charging, where the focus up to 2020 will be on innovation.

This will build on the momentum generated by the European-supported Low Carbon Infrastructure Tran-

sition Programme and will benefit consumers, communities and businesses up and down the country.

What are the Scottish Government's future priorities for the environment, for example in terms of the plans to introduce Low Emission Zones into Scotland's four biggest cities between 2018 and 2020

Protecting and enhancing the environment is a priority for the Scottish Government for the multiple benefits it provides; public health and quality of life, a natural asset available to current and future generations and inputs to key sectors of our economy.

The Low Emission Zones are one example of practical work with partners to deliver benefits that support health of individuals and the quality of the places that people live and work. It is important that this work is done in partnership with other partners such as local authorities and last week I announced a leadership group that will support this work.

What are the Scottish Government's views on how a potential 'deposit return scheme' will operate in Scotland?

To support the circular economy and tackle climate change we will develop a deposit return scheme designed to increase recycling rates and reduce littering and implement it across Scotland. This represents a step change in our level of ambition and over the next year we will build on detailed work already being carried out by Zero Waste Scotland, ahead of roll-out across Scotland.

We will ensure the scheme is tailored to meet Scotland's specific needs and we will work closely with the business community during its design and implementation. To this end, we are currently looking at existing schemes



and will shortly be launching a consultation on how a deposit return scheme could operate in Scotland.

Following on from this, what are the benefits of a deposit return scheme for recycling and reducing litter, and what potential impacts could this have on retailers and local authorities?

We are confident that a deposit return scheme will increase recycling and reduce littering – this is clear from evidence in the many countries that already use deposit return. We are also keen that a system should work for everyone in Scotland, including small retailers and local authorities, and will be working closely with experts and stakeholders to design a suitable system.

Why is it important to develop a sustainable future for younger generations?

As the Programme for Government set out in September made clear, we are determined to equip Scotland – not just for next year – but for the next decade and beyond. At its heart is the ambition to make Scotland the best place in the world to grow up and be educated and the best place to live, work and do business. It is a key responsibility of any government to leave the country in a better place than you found it; whether that be through protecting and providing vital public services that people expect; ensuring services are sustainable and affordable; and taking responsibility for mitigating global issues such as climate change or creating a fairer economic model.

I believe we have set out a programme of action that will enable us to develop a sustainable future for younger generations, and I am now getting on with delivering just that.

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Spokesperson Scottish Government Tel: +44 131 244 4000 ceu@gov.scot www.gov.scot www.twitter.com/scotgov

Shifting towards a circular economy

VP Head of Group Brand & Corporate Communications at TOMRA, Lorraine Dundon reveals her thought on how Technology will play an increasingly important role in achieving a sustainable future

Arine plastics pollution, climate change and our dependency on fossil fuels are complex public policy challenges, complicated further by the world's increasing population and associated resource requirements. For many it is clear that our "take-make-use-dispose" society is simply unsustainable.

In contrast, the vision of a circular economy, as set out by the Ellen MacArthur Foundation (EMF), we believe offers a constructive way forward and the opportunity to develop a transparent, goal-oriented plan for a sustainable future. TOMRA has committed itself to the EMF's New Plastics Economy initiative with the intention of shifting towards a circular economy that will benefit not only our business and our customers, but society at large.

Technology will play a key role

Technology will play an increasingly important role in achieving a sustainable future. Recycling is a key component of the New Plastics Economy initiative, and proven technical solutions that facilitate re-use and closed-loop recycling already exist today.

TOMRA, a global provider of sensor based solutions offers innovative technology to efficiently operate deposit-return systems for refillable and single-use beverage packaging, as well as the sorting of multi-material waste streams.



TOMRA provides recycling solutions in approximately 70 markets, each with common yet localised versions of recycling and waste policies. We have installed approximately 78,000 TOMRA reverse vending machines, and 4,800 material recovery optical sorters. Installing these systems throughout Europe, Asia and North America has given us much knowledge and insights into recycling needs.

One such conclusion is that **access to technology and recycling programs is not enough**. Low and often stagnant recovery and recycling rates tell us this much. That is why TOMRA fully supports the EU's ambitious Circular Economy Package (CEP). Europe-wide legislation promoting a circular economy will create a level playing field among member states, stimulate innovation in product design, and incentivise reverse distribution systems – all initiatives that are proven to increase the quantity and quality of recycling.

TOMRA also believes that deposit return systems, kerbside collection, and mixed waste recycling complement each other. Reverse vending systems provide an automated method for collecting, sorting and handling the return of used beverage containers for recycling or reuse. During the 45 years these systems have been utilised, they have proven to be an unmatched success for consumers, businesses and the environment. Reverse vending solutions are the centerpiece of modern deposit systems that for years have demonstrated return rates from 70 to almost 100% of sold beverage containers. Every year more than 35

Three strategies to transform the global plastic packaging market



billion used beverage containers are captured by our reverse vending machines; the avoided greenhouse gas emission equals the annual emissions from 2 million cars, each driving 10,000 kilometers.

In order to be able to sort valuable materials from the waste stream, you first need to collect them. Kerbside collection successfully engages many homeowners, encouraging the recycling of a variety of packaging and papers. The growing trend towards away-from-home consumption, especially noticeable with beverage packaging, often means that a significant proportion of this package never makes it into a kerbside system. The waste bin perhaps, but often the result is litter.

This combination of deposit return systems and municipal solid waste recycling helps capture litter, supports re-use and guarantees the highest recycling quantity and quality. Just look at the results in markets where both systems are present, and the fact that a number of governments are adopting new deposit policy in Europe and Australia. Considering these systems in a complementary way might shift us from debate towards a circular economy.

Fully automated systems for maximum resource efficiency

For example, in Skedsmokorset near Oslo, Norway, is the world's first fully automated plant for handling MSW using TOMRA's optical sorters. These machines enable the plant's Norwegian operators to efficiently manage a throughput of household waste from a surrounding urban population totalling 170,000. The sorting technology enables the company to recover a significantly higher amount of recyclable material from its MSW.

More support is needed

TOMRA hopes the European Union's Circular Economy Package will prove

an aspirational document. To realise its full potential in a world with finite resources, the EU needs to make a strong commitment to promote, fund and facilitate the new forms of collaboration this policy shift will demand.

Current projections suggest that the world's population will reach 8.2 billion people by 2030, before rapidly growing in the following two decades. Growth is expected to continue and surpass 11 billion by the turn of the 22nd century. Population growth, increased consumption and urban migration if left unaddressed can have serious repercussions for the planet.

TOMRA's ambition is to be among the leaders of the resource revolution, which aims to replace the present system based on consumption and waste instead of the recovery of resources. Providing smart solutions that optimise our available resources enables TOMRA to make a key contribution to shifting society's default perspective on the concept of sustainable resources.



Lorraine Dundon VP Head of Group Brand & Corporate Communications TOMRA Tel: +353 1413 6271 Lorraine.dundon@tomra.com www.tomra.com

The European union explores new approaches to marine health

Karmenu Vella explains how EU policies will innovate our approach to oceans and help to ensure the marine health of our planet

Ur oceans may be vast, but they are also fragile. Sea levels are rising. In the Pacific Ocean, entire countries risk being wiped off the map. Oceans are getting warmer and more acidic, putting coral reefs, fish populations, and overall marine health at risk.

Illegal fishing is rampant in many of the world's oceans. Up to 26 million tonnes of fish are caught illegally each year – at least 15% of world catches.

Marine litter is becoming a pernicious problem. By 2050, the world's oceans could contain more plastic than fish. So, we are at a critical juncture. At the same time, we need the oceans more than ever.

Oceans regulate our climate: they redistribute heat around the globe and absorb 25% of the carbon emissions we produce. So tackling climate change, starts and ends with the oceans.

The world population is expected to reach 9 billion by 2050. Demand for food could rise by 60% – and the oceans can help provide it.

And oceans cover more than 70% of our planet. Why should we squeeze our economic activities onto the other 30% of our planet's surface – especially when our land-based resources are already under strain?

Instead we need to see the full potential of the ocean economy: traditional activities like fishing and coastal tourism, but also marine biotechnology, aquaculture, and clean energy from the sea.

The output of this global ocean economy is already estimated at \leq 1.3 trillion. This could more than double by 2030.

The importance of our oceans

In short, there are plenty of reasons to turn our attention to the sea and to make sure our oceans stay healthy for generations to come.

That is why the European Union has been working for better managed oceans for many years now.

- We have reformed our Common Fisheries Policy, putting sustainable fishing at its very heart.
- Our Integrated Maritime Policy makes sure that we properly plan and coordinate our various activities at sea.
- We have asked EU Member States to set aside 10% of their waters as marine protected areas by 2020, in a bid to help the most fragile marine eco-systems recover.
- Our laws against illegal fishing are some of the toughest in the world.
- And our 'blue growth' strategy seeks to marry strong economic growth from the ocean, with sound environmental principles. For example, we are joining forces with financial institutions, WWF and the Prince of Wales' International Sustainability Unit, to ensure a sustainable approach to marine investment.

But focusing on European waters and coastlines is not enough. Fish swim freely across borders. So, increasingly, does plastic.

That is why we are also directing our attention beyond the EU.

One year ago, the European Union adopted an agenda



to improve the way the world's oceans are managed. Together with our international partners, we want to create a stronger system of ocean governance around the globe, reduce man-made pressures and advance international ocean research and science.

We realise that more international coordination and coherence are needed to achieve our goals. The more we work together, the bigger impact we will have.

And there is hope. In October this year, hundreds of ocean advocates met at the fourth international Our Ocean conference, hosted by the European Union in Malta to pledge tangible action for healthy oceans.

Action like making certain ocean areas off limits to fishing, giving marine life a chance to recover. Or tougher rules against illegal fishing and more patrols that make it harder for pirates and other villains to plunder our seas.

We also need to rethink our current economic model of consumption. Our grandparents grew up in a plasticfree world. Yet our grandchildren will still be finding the remains of our plastic, when they take their own grandchildren to the beach.

Many companies, big and small, are already considering ways to achieve a more circular economic model, focused on recycling and reusing resources.

This is the kind of innovation we need. And that is exactly what the Our Ocean conferences are about: bringing ocean advocates from all walks of life - policymakers and scientists, business owners and educators - together and asking them what they can do to keep our oceans healthy.

I am proud of the prominent part the EU is playing in creating a global alliance of ocean champions. So that future generations of fishermen around the world can continue to earn a sustainable living - and so that coastal communities around the world can thrive.

Karmenu Vella

Commissioner for Environment, Maritime Affairs and Fisheries European Commission Tel: +32 2 299 96 96 ec.europa.eu/commission/commissioners/2014-2019/vella_en www.twitter.com/KarmenuVella

The role of algae in sustaining our planet – past, present and future

Dr. Jaime L. Toney from the University of Glasgow highlights the vital role of algae in human existence, in both shaping and understanding the planet

Igae occupy a place at what we often refer to the as the bottom of the food chain; however, this language dismisses the exceedingly important role of algae in human existence, shaping and understanding the planet, and becoming an increasingly important resource for living sustainably.

Rather than being at the bottom of the food chain, algae should be recognised as a vital key to supporting all of life, with the unique ability to turn light energy from the Sun into carbon-based molecules that society harnesses and uses in countless ways. We rely on algae for their nutrients and proteins, but most importantly their lipids.

Lipids are molecules that are made up of carbon and hydrogen atoms and serve as the building blocks of countless other molecules. The most basic hydrocarbon lipids, such as, n-alkanes and fatty acids, provide the basic structure from which many other lipids are derived.

Lipids have a range of functions within algae and other organisms, such as structural features of the cell membrane (e.g., phospholipid fatty acids), energy storage (e.g., triglycerides), hormone precursor molecules (e.g., sterols), pigments (e.g., chlorophyll), and toxins – such as those involved in harmful algal blooms.



The significance of algal lipid research can be see through how often scientists reference algal lipid papers. While the field began in the mid-1950s when scientific papers received <10 citations, the citations have increased exponentially. In 2010, algal lipids papers received just under 6,000 citations, and only six-years later, they were cited >20,000 times (based on Web of Science, Clarivate Analytics).

Supporting Life and Shaping the Planet

Single-celled blue-green algae, or cyanobacteria, were the original, microscopic organisms that photosynthe-sized carbon dioxide (CO_2) from Earth's early atmosphere and converted it to oxygen (O_2) some 2.45 million years ago¹. This process made the world habitable by more complex organisms, like

modern humans who showed up some 200,000 years ago.

Studies show that the algal lipids classed as fatty acids, such as omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) are among the most important lipids. Many higher organisms cannot produce these on their own, so algal LC-PUFAs that get concentrated up the food chain to insect larvae and all the way to migratory birds, for instance, are essential to healthy ecosystems and biodiversity.

Research by the <u>Norfolk Ponds Project</u> in the UK, for example, is investigating how high quality, managed ponds support algal lipids and in turn insect larval lipids that are essential to farmland birds, farmland biodiversity, and migratory birds. Incentivising estate

owners to maintaining farmlands as healthy ecosystems will have longterm benefits to society.

Understanding the Planet through Environmental Change

Algal lipids also serve as molecular fossils, or biomarkers, that record environmental conditions in the oceans, lakes and waterways around the world. For decades, haptophyte algae, mainly *Emiliani huxleyi*, that are surrounded by calcium carbonate scales, called coccoliths, have been used to measure sea-surface temperature from sediment cores long before we have human instrumental records.

These records extend back 10s of millions of years, and identified that the Earth waxes and wanes between cold glacial periods, when Northern Hemisphere ice extends from the poles down to about 45°N latitude, and interglacial periods, like the last 15,000 years.

Applying the algal biomarkers from marine systems to lakes, now enables us to look at the rate of warming over the last 150-years and see that the rate warming in many locations is beyond anything that we have experienced during the Common Era (last 2,000 years).

The European Commission funded <u>NAOUKSIP project</u>, for example, uses a novel group of algal lipids called long-chain diols to quantitatively show that the rate of warming in high altitude sites of southern Europe has increased by two and half times over the last century.

These kinds of findings influence land management and require advanced, interdisciplinary research into calibrating these algal lipid biomarkers to



modern environmental conditions. The goal of the European Research Council funded project, ALKENONE (Figure 1 shows how alkenone molecules are related to temperature) is just that, and aims to make the application of algal lipid biomarkers more universal.

Resource for Living Sustainably

Finally, the same type of algae whose coccoliths accumulated over geologic timescales to make up the Dover cliffs, are also responsible for the production of fossil algal lipids that society extracts as hydrocarbons, or fossil fuels from depths of the ocean. Rather than continue to explore an increasingly depleted fossil source of fuel, modern algae – perhaps those that are related to the ancient algal fossil fuel producers – now hold promise to supply the needed hydrocarbon-based fuels.

The advantage of algal biofuel is that the algae remove CO_2 from the Earth's atmosphere which offsets their use, for example, in the transportation industry. They provide other harvestable resources, such as, triacylglycerols, proteins, and nutrients and can be cultivated on non-arable land. The opportunity to make algal biofuels a viable resource currently faces challenges associated with energy efficiency harvesting lipids and converting it to biofuel. Most of the research along these lines is still in pilot stages and despite great promise requires a boost in investment.

Algae are undervalued in society compared to the wide range of benefits that they provide globally. In the Biomarkers for Environmental and Climate Science (BECS) research group, we are exploring all these topics, including: the evolution of highly productive, lipid-producing algae; their role and efficiency in removing CO₂ from the atmosphere; changes in their food quality values forced by environmental conditions; algal lipids as recorders of past environmental conditions, and algal lipids as a promising source of energy for society's future.







Dr. Jaime L. Toney Senior lecturer University of Glasgow Tel: +44 141 330 6864 Jaime.Toney@glasgow.ac.uk http://environmentalbiomarkers.co.uk www.twitter.com/BECS_Biomarkers



The efficient use of resources from the environment

Norwegian Minister of Climate and Environment shares his thoughts on the struggle to reduce marine litter

The efficient use of resources is beneficial for both the economy and the environment. This is the driving concept behind two important initiatives from the Norwegian Government.

Marine litter is an increasing environmental problem and there is a growing recognition of the problem. The quantities of plastic waste that end up in the oceans are a serious concern.

Marine litter is an international problem, as waste is transported with sea currents. A lot of the marine litter we find in Norway comes from other countries. Marine litter is a serious threat to marine ecosystems, but also to food coming from the oceans across the entire world. Concerted international measures are therefore crucial. Norway has brought this issue to the agenda globally, among other things through putting forward resolutions at the two first United Nations Environment Assemblies in 2014 and 2016. Norway also provided support to UN Environment in implementing these decisions.

International efforts

Following a proposal by Norway, more than 170 countries agreed to the need to assess the effectiveness of governance strategies to combat marine litter and microplastics, both internationally, regional and national. It is necessary to identify gaps and measures to address the problems, such as the need to consider stronger international commitments to combat marine litter. The results from this study will be presented at the UNEA-3 meeting in Nairobi in December this year.



Vidar Helgesen, Norwegian Minister of Climate and Environment

Norway has prepared a draft resolution for the meeting in December. We hope this will push forward towards a coherent and comprehensive global response

On a global level, strengthening waste management and building knowledge and skills is very important. The Norwegian government has established a Development Programme for 2018 dedicated to fight marine litter and microplastics. In this programme, thorough considerations will be given to reducing waste, improving waste management systems and to other costeffective measures to combat marine litter. Norway will collaborate with other countries and international organisations to ensure that the funds are used in a way which provides concrete results.

Norway

Nationally Norway has a well-functioning waste management system. However, there is still a potential for reducing the impact from national sources. In June the government presented a white paper to the Parliament on waste policies in a circular economy. This included a strategy for the reduction of marine litter and microplastics.

An area worth mentioning is a newly signed agreement on the reduction of food waste between The Norwegian Government and the food industry. In June, five ministries on behalf of the Norwegian government and twelve food industry organisations, signed a binding agreement to halve food waste across the food value chain in Norway within 2030.

Food waste in Norway refer to the edible part of food waste. This reduction target is in line with the UN sustainability goal 12.3. It is in fact a bit more ambitious, because the goal applies to the entire food value chain from primary production to consumers.

One third of all food produced globally is spoiled or thrown away. In Norway alone, the average consumer throws away 42 kg edible food every year. Food waste in the entire food chain represents 68 kg per person per year.

"Marine litter is an international problem, as waste is transported with sea currents. A lot of the marine litter we find in Norway comes from other countries. Marine litter is a serious threat to marine ecosystems, but also to food coming from the oceans across the entire world. Concerted international measures are therefore crucial."

Both primary producers, manufacturers, wholesalers, retailers, restaurants, households and the authorities must take responsibility for reducing food waste. Both the food industry and the government believe that the chances of success are greater with collaboration between public and private interests across the value chain, including consumers.

Vidar Helgesen

Norwegian Minister of Climate and Environment Ministry of Climate and Environment Tel: +47 22 24 90 90 postmottak@kld.dep.no https://www.regjeringen.no/en/dep/kld/id668/ www.twitter.com/VidarHelgesen

CCS answers

How CCS can help to eliminate CO₂ emissions

or every gram of CO₂ emitted by human activity, we are consuming decisive time, crucial to minimise our undeniable impact on Earth's equilibria. The desirable scenario is to rely on renewable energy, hoping its fast implementation throughout the world. In a more realistic scenario, CCS implementation (CO₂ capture, transport, utilisation and long-term storage) is an indispensable parallel effort.

Only a combination of strong energy policies and research for implementing no-emissions technology, promoting energy efficiency and fully developing CCS will allow the transition towards a decarbonised economy.

Political commitment and funding frames supporting CCS account remarkable milestones already. Among these, the Paris Agreement, the European SET Plan and the 2020 and 2030 Climate-Energy packages, to lower EU's greenhouse gas emissions 20% by 2020 with respect to 1990, and 80 to 95 % by 2050. The Framework Programmes for research and technological development (FP and Horizon 2020) and other international initiatives have enabled RD&D on CCS.

Still, there are several challenges to overcome at the different stages of the CO_2 value chain. A major one is making CCS economically attractive over time. Business models and opportunities are currently unclear or underexploited. Besides the main



business areas for the core technologies, additional services for the practical implementation are not yet designed or developed.

Part of the reason is that CCS still needs substantial RD&D efforts to better assess economic parameters. A lack of sufficient political and legal frames and low social and industry awareness also contribute to the sense of uncertainty. Thus, larger joint efforts are needed from governments, industry and research actors to establish new market opportunities, promote social awareness and actively support CCS development.

On the technological side, there are remaining gaps that need to be solved to make CCS a reality. At present, there is no unique capture technology that is economic and suitable for all industrial sectors and for any location. Besides, the readiness levels vary considerably among the alternatives. Solvent-based technologies have been validated at large scale. Few of them can reach commercial scale in the short-term, though their investment and operation costs still need further reductions. Research on advanced solvents, membrane and adsorbent-based processes are showing encouraging progress.

Also in parallel, formerly less mature concepts are breaking in strongly with the latest advances. Among them, technologies based on solid looping cycles (e.g. calcium and chemical looping, Sorption-Enhanced Reforming for hydrogen production with CO₂ capture)

are turning into realistic alternatives. Hence, to a different extent, all these routes need additional RD&D for wide deployment at full scale.

"Only a combination of strong energy policies and research for implementing no-emissions technology, promoting energy efficiency and fully developing CCS will allow the transition towards a decarbonised economy."

Once captured, a small fraction of CO_2 will be diverted for utilisation, expected to contribute to reduce emissions to a quite limited extent. Meanwhile, the fate of most CO_2 will be safe storage for thousands of years. Thus, CO_2 needs to be transported to the storage sites through pipelines, ships or tankers. Large-scale transport of reasonable dry and pure CO_2 mainly from CO_2 -doomes in USA has been done for decades with satisfactory results, i.e. with no critical corrosion problems.

However, CO_2 captured from fossilfuelled sources might contain flue gas impurities that have not been transported before and could trigger corrosion. It is also regarded a challenge to design and to operate a CO_2 network connecting many point sources to offshore storage sites. To ensure safe transport of CO_2 , there is a manifest need of more experimental data and better flow assurance models.

Storing CO₂

Finally, geological storage of CO₂ in underground reservoirs has shown to be a viable technology. However, experience at the existing pilots revealed issues related to induced seismicity, visible surface uplift or pressure build up. It is still needed better understanding and quantification of various geological processes that may arise from the injection of high-pressure fluids into underground reservoirs.

Upscaling existing storage pilots will require adequate geo mechanical assessment to limit risk. Improved characterisation of candidate reservoirs is also an important prerequisite for establishing new storage sites. Besides, experience in long-term safety of CO₂ storage is limited at present and should gain deeper scientific knowledge. The risk of CO₂ leakage is another issue that needs to be considered and monitored during and after injection. The use of tracers is a wellestablished method for monitoring water and gas in oil reservoirs and has proven to be effective to obtain information about well-to-well communication, heterogeneity and fluid dynamics. However, the behaviour of CO₂ in a reservoir is more complex and still requires additional research efforts.

In summary, readiness of capture and transport technology, adequate geomechanical assessment and monitoring of short-to-long-term CO₂ storage have progressed considerably, but need further RD&D to launch largescale CCS projects in the coming years.

Norway has a strong potential to become the leading supplier of CCS technology in Europe. The competitive advantages are large storage reservoirs offshore, remarkable advances in CCS and world's leading expertise in shipping and offshore industries.

At the forefront research in Norway, the Institute for Energy Technology (IFE) is developing CCS and energy technologies at international level. Founded in 1948, with approximately 600 employees and €100 million in annual turnover, IFE is an independent foundation actively contributing for a more climate friendly energy system, based on renewable and CO_2 free energy sources, with a focus on technological innovation.

We apply a broad approach towards global sustainability, combining efforts on CCS, renewables, low value raw materials, and improved industrial processes. We maintain that CCS and low environmental impact energy and industry should be prioritised, by supporting their validation throughout their complete RD&D timeline to avoid the innovation gaps frequently found at up-scaling, industrialisation and commercialisation stages.

Co-authors:

Dr. Viktoriya Yarushina (Researcher and Group Leader at the Environmental Technology Dept.), Dr Arne Dugstad (CO₂ center coordinator and Research leader at the Materials and Corrosion Dept.), Dr Sissel Opsahl Viig (Senior Researcher and Group Leader at the Tracer Technology Dept.), Mr Julien Meyer (Senoir Researcher and Group Leader at the Environmental Dept.).



Asunción Aranda PhD, Head of Environmental Technology Department Institute for Energy Technology Tel: +47 93624893 suni.aranda@ife.no

Austria's climate change policy reflects its own research

Federal Minister of Agriculture, Forestry, Environment and Water Management Andrä Rupprechter reveals Austria's climate change policy

n Austria, records indicate an increase in the average annual temperature of about 2°C since 1880 (APCC 2014), which is significantly above the global temperature rise of 0.85°C (IPCC 2014). The effects of climate change can already be observed today, becoming visible through rapid melting of glaciers, thawing of permafrost and the increasing numbers of hot days, etc. This research informs Austria's climate change policy.

There is no doubt that global warming will continue and the effects of climate change will even increase over the coming years. Climate change today is affecting a broad number of sectors, systems, institutions, and individuals. An economic study conducted for Austria (Cost of Inaction – COIN), demonstrates that climate related damage costs will increase by 2050, compared to today and reach an average annual level of €3.8 to €8.8 billion (Steininger et al. 2015).

Therefore, in addition to efforts in reducing greenhouse gas emissions, the long-term planning and consequent implementation of adaptation measures is crucial. Adaptation, as the second pillar in climate policy, is requested in the Paris Agreement and represents an indispensable complement to mitigation efforts.

Action against climate change

Already in 2007, the Ministry of Agriculture, Forestry, Environment and Water Management (BMLFUW) has put adaptation to climate change on its agenda. A broad participatory process was conducted by the Environment Agency Austria (EAA) to involve more than 100 institutions, from national to regional level, in the process to develop the adaptation strategy.

The Austrian adaptation strategy was adopted first in October 2012, by the Council of Ministers and endorsed

by the Provincial Governors' Conference, in May 2013. In August 2017, a revised version of the strategy was adopted by the Austrian Council of Ministers.

The Austrian adaptation policy aims to build strong resilience to climate change. It intends to ensure coordination and harmonisation of the various climate change adaptation activities in all areas. The adaptation strategy consists of a basic framework (NAS, BMLFUW 2017a) and an Action Plan (NAP, BMLFUW 2017b). While the NAS focuses on the strategic components of adaptation (i.e. setting the scene, guiding principles, research activities, social aspects of adaptation, etc.), the NAP presents a comprehensive catalogue of adaptation options.

The recommendations, based on a qualitative vulnerability assessment, are presented for the following sectors: Agriculture, forestry, water resources and water management, tourism, energy, natural hazards, construction and housing, disaster risk management, health, ecosystems/biodiversity, transportation infrastructure, spatial planning, business/industry/trade and cities, with a focus on urban green.

Austria is one among a few European countries which has started to work on monitoring and evaluation of the NAS/NAP. In Austria, a two pronged approach has been taken. Firstly, a participatory approach consisting of a self-assessment by relevant stakeholders. Secondly, a data based approach focusing on a criteria catalogue (indicators) helping to put some light on selected aspects relevant for adaptation.

The joint consideration of these two components provide a broad picture of the state of implementation of adaptation, as well as key trends and progress in



Andrä Rupprechter, Federal Minister of Agriculture, Forestry, Environment and Water Management

Austria. A progress report was published by the BMLFUW in 2015, to present the state of implementation of the NAS and NAP.

As climate change impacts are mostly visible at the local and regional level, one important initiative of the BMLFUW is to support rural municipalities and regions in adapting to a changing climate. Thus, in 2016, the KLAR! – Climate Change Adaptation Model Regions Programme – was launched as a Europe-wide unique climate adaptation support programme for Austrian regions, and as an important component to implement the Austrian NAS/NAP.

To conclude, for Austria, the topic of how to deal with climate change impacts is high on the agenda. The summer of 2017, with its extreme weather events such as heat, floods and mudslides has shown that without any doubt, that adaptation efforts are necessary now and even more so in future. Thus, we consider it our responsibility to join forces for adaptation and work now for a climate-resilient Austria of the future.

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Andrä Rupprechter Federal Minister of Agriculture, Forestry, Environment and Water Management

Federal Ministry of Agriculture, Forestry, Environment and Water Management (BMLFUW) Tel: +43 1 711 00 - 0 service@bmlfuw.gv.at www.bmlfuw.gv.at @BMRupprechter

Less plastic waste in the future

Can plastics be removed from the environment and be biologically degraded? Chemical engineers at TU Wien (Vienna) are working on it – and on developing new, eco-friendly plastics

The use of plastics offers several advantages: they are cheap, versatile and easy to shape. However, they are responsible for today's severe ecological problems. Plastics are difficult to degrade, and despite the availability of several technologies for recycling, a massive amount of plastic waste is accumulated in the environment, bringing about the need for research into eco-friendly plastics.

"Today's fossil-fuel based economy should be replaced by a bio-based economy termed "Industry 5.0". The goal is towards a more efficient use of renewable raw materials, but also reducing energy consumption, strengthening food and energy security and replacing traditional chemicals by sustainable alternatives."

Scientists at the Institute for Chemical, Environmental and Biological Engineering (ICEBE) at TU Wien (Vienna) are trying to replace exploitation of the environment, by using ecologically balanced approaches. "There is no contradiction between technology and nature – quite the contrary", says Anton Friedl, the director of the institute. "Nature can teach us about new technological approaches, and new technologies will benefit the environment. It is a process we call 'imagineering nature", he adds.

Today's fossil-fuel based economy should be replaced by a bio-based economy termed "Industry 5.0". The goal is towards a more efficient



use of renewable raw materials, but also reducing energy consumption, strengthening food and energy security and replacing traditional chemicals with sustainable alternatives.

OCTOPUS – Ocean Tentacle Organic Particles Purification System

Gerd Mauschitz, Research Division Mechanical Process Engineering and Clean Air Technology

Tonnes of microscopic plastic particles are polluting the rivers, lakes and oceans-especially particles that are a few micrometres to millimetres in size. They are finely distributed at different depths, rendering them difficult to remove.

Nonetheless, scientists at TU Wien

have come up with a novel idea. Large numbers of flexible membrane bundles reaching deep into the water could remove plastic particles from sea water in an efficient and ecologically-friendly manner.

"Other methods have been proposed, such as large-area net structures. But unlike them, our flexible membranes are safe for sea animals", says project leader Thomas Laminger. Solar powered self-sufficient free-floating pontoons with these "membrane tentacles", could be a promising solution for the removal of microscopic plastic particles.

Bacteria producing biodegradable plastics from CO₂ Christoph Herwig, Research Division

Biochemical Engineering





Given the negative impacts of petroleum-based plastics on the environment, there is strong demand for bio-based plastics. "Indeed, there are several biodegradable alternatives to the plastics we use now", says the division head, Christoph Herwig.

"Polyhydroxyalkanoates, especially PHB (polyhydroxybutyrate) are the most promising polymers to replace conventional plastics."

PHB is naturally produced by bacteria for energy and carbon storage. There are established procedures to create PHB – using heterotrophic bacteria in a fermentation process. However, the production costs are high and therefore the use of PHB for biopolymer production is limited. "If these costs could be reduced, there would be widespread economic interest", says Stefan Pflügl who is working on the project. The solution could be provided by a different kind of bacteria: Cyanobacteria are emerging as the most promising alternative system, due to their autotrophic nature and minimal nutrient requirements. Several cyanobacterial species have been reported to accumulate considerable amounts of PHB – up to 10% of their dry cell weight.

"The most interesting enzymes for plastic degradation are those that hydrolyse ester bonds in cutin, a natural waxy polymer."

The project aims to develop the production of PHB by cyanobacteria using sustainable resources such as CO₂ and sunlight. "Using our processing methodology, Donya Kamravamanesh has developed a production pipeline resulting in a much higher PHB yields. It allows us establishing the cultivation in open ponds," says Christoph Herwig.

New enzymes for plastic degradation

Robert Mach, Research Division Biochemical Technology

Most conventional plastics are resistant to biodegradation; they stay around for a long time. Some microorganisms produce enzymes that may degrade synthetic polymers, usually through slow and inefficient processes.

"The most interesting enzymes for plastic degradation are those that hydrolyse ester bonds in cutin, a natural waxy polymer", says Irina Druzhinina, the leader of the Microbiology group. Cutin is present on plant surfaces where it protects tissues from dehydration or excess moisture. "We think, that microorganisms living in plants may possess novel enzymes for biological degradation of plastic waste", says Druzhinina. The most interesting habitat for such microorganisms has not yet been sufficiently studied: the high canopy of the tropical rain forests, where a humid, warm climate favours microbial growth and trees have long-living leaves with thick cutin layers.

"We have sampled and isolated an extensive collection of filamentous fungi, yeasts, and bacteria – many of which are completely new to science", says Irina Druzhinina. The genomes of these microorganisms contain genes encoding cutin degrading enzymes, which are being characterised and tested for application in the biological degradation of plastic waste. The next step will be engineering theses enzymes for increased plastic degradation efficiency.



Dr. Irina Druzhinina, Assoc. Prof. irina.druzhinina@tuwien.ac.at Dr. Thomas Laminger thomas.laminger@tuwien.ac.at Dr. Christoph Herwig, Univ. Prof. christoph.herwig@tuwien.ac.at

Institute of Chemical, Environmental and Biological Engineering (ICEBE) TU WIEN www.vt.tuwien.ac.at Tel: +43 1 58801 - 166 01

Science and policy in the Arctic States

Ambassador Aleksi Härkönen provides a compelling glimpse of the organisation's efforts on climate change and pollution in the Arctic States

The Arctic Council is the leading intergovernmental forum promoting cooperation, co-ordination, and interaction among the eight Arctic States – Canada, the Kingdom of Denmark, Finland, Iceland, Norway, the Russian Federation, Sweden, and the United States – in particular on issues of environmental protection and sustainable development in the Arctic. Indigenous peoples' organisations have been granted Permanent Participant status in the Arctic Council, and have full consultation rights regarding the Council's negotiations and decisions.

The Council celebrated its twenty-year anniversary on 19th September 2016. In that time, it has become a prime example of collaboration between the science and policy communities in global governance. With six Working Groups and two active Task Forces, and more than 90 distinct projects underway in areas as diverse as marine pollution, language preservation, Arctic economies, and climate change, the Council's portfolio is extremely broad.

Among the most serious issues the Council presently addresses are pollution in the Arctic environment and climate change. The latter, in particular, is pertinent even well outside the Arctic region, as the Arctic is a critical component of the global climate system.

The Arctic Council has six Working Groups, which have produced – and which continue to produce – many of the most seminal scientific and analytical reports on matters of particular relevance to the Arctic region. These reports present the best available data and provide recommendations for action that are pertinent for Arctic States, Arctic Council Working Groups, the indigenous Permanent Participant organisations, or others.

In 2017, the Arctic Council's Working Group AMAP pub-

lished a policy-makers' summary of their 2017 report "Snow, water, ice and permafrost in the Arctic", or SWIPA. It finds that the Arctic's climate is shifting to a new state, and that changes underway in the Arctic will continue through at least mid-century, due to warming already locked into the climate system. Warming trends will continue, as will declines in snow and permafrost. The melting of land-based ice will contribute significantly to sea-level rise, and the Arctic Ocean may be ice-free sooner than expected – possibly as early as the late 2030s. Indeed, while Arctic glaciers and ice caps represent only a quarter of the world's land-ice area, meltwater from these sources accounts for 35% of current global sea-level rise.

In addition, the 2017 SWIPA report finds that Arctic changes will affect both sources and sinks of important greenhouse gases, including atmospheric carbon dioxide and methane. The near-future Arctic will be a substantially different environment from that of today, and by the end of this century Arctic warming may exceed thresholds for the stability of sea ice, the Greenland ice sheet, and possibly boreal forests.

Adapting to climate change

Beyond the challenges of climate change, the Arctic Council also recognises that resilience and adaptation to climate change are important for Arctic communities and ecosystems. The Council's work on resilience can be seen in, for example, the 2017 Arctic Resilience Report and the project "Adaptation Actions for a Changing Arctic".

Increased activity in the Arctic (and elsewhere, as the Arctic is a sink for global pollutants) leads to an increased risk of pollution of many kinds in the Arctic environment. Some important pollutants – for example, persistent organic pollutants and mercury – have been addressed



in various ways by the Arctic Council's Working Groups for a long time. The Arctic Council's work in this area has contributed to the work taking place under the Convention on Long-range Transboundary Air Pollution (LRTAP) Protocol on Persistent Organic Pollutants, the Stockholm Convention on Persistent Organic Pollutants, and the Minamata Convention on Mercury.

But other pollutants are also gaining new relevance in the Arctic environment. These include oil pollution, marine litter (including microplastics), and chemicals of emerging concern in the region.

On oil pollution, perhaps the Council's most important contribution has been to serve as a venue for the negotiation of a binding agreement among the eight Arctic States on preparedness for, and response to, oil pollution in Arctic waters (2013).

In addition, the Arctic Council conducted a Task Force on Oil Pollution Prevention from 2013-2015, which produced broad-based recommendations for avoiding oil pollution in the Arctic marine environment.

As to marine litter, the Arctic Council's Working Group PAME is undertaking a desktop study on marine litter (including microplastics) in the Arctic. This may provide the first step towards developing a framework for a regional action plan on marine litter, although that is yet to be determined.

Chemicals

Finally, when it comes to chemicals of emerging concern in the Arctic, Working Group AMAP recently published a summary report that looks at a wide range of chemicals newly and recently detected in Arctic ecosystems. Changes to hydrology, declining sea ice, increased economic development, and changes in air and ocean currents – as well as changes in the way chemicals distribute between air, water, and soils – are all consequences of a warming climate that are expected to alter how chemicals are released, transported to, and moved around in the Arctic.

These are but a few of many examples of research and analysis being undertaken within the Arctic Council Working Groups that directly supports the governments of the Arctic States, and others, as they tackle pollution in the Arctic and the adverse effects of climate change. But the Arctic does not exist in a vacuum; the Arctic climate, ecosystem, and economy are inseparably tied to the rest of the world. As changes in the Arctic have consequences elsewhere in the world, so changes elsewhere in the world can have enormous impacts in the Arctic.

In an age, and in a region, that faces such challenges, cooperation among the Arctic States, Arctic indigenous peoples, and other Arctic inhabitants is an absolute necessity to protect the Arctic environment and to support sustainable development in the region. But intra-regional cooperation alone will not be adequate to address the region's challenges; cooperation on a global scale is essential.

Ambassador Aleksi Härkönen Chair of the Arctic Council's Senior Arctic Officials acs@arctic-council.org www.arctic-council.org www.twitter.com/ArcticCouncil

Assessing climate change in the Arctic

Norwegian Polar Institute's Director Jan-Gunnar Winther highlights the challenges associated with climate change in the Arctic and its global impact

t is a fact that no region of the planet is experiencing more dramatic climate change than the Arctic. In recent years, this has resulted in melting glaciers, rapid ecosystem changes, diminishing sea ice, and changes in the atmospheric circulation and ocean properties. Ocean temperatures are increasing due to global warming. The Arctic is undergoing changes unknown to have occurred during the last 1,450 years (Intergovernmental Panel on Climate Change (IPCC), 2013). Climate models project that the most pronounced warming in the future will happen in the Arctic. In a business-asusual scenario for greenhouse gas emissions, temperatures may increase by 8 to 10 degrees Celsius. Even in IPCC's most aggressive scenario for cutting greenhouse gas emissions, the Arctic will warm with several degrees and in turn fundamentally change this region as we know it today.

Global impact

The Earth's regions are connected by circulation in the atmospheric, ocean, climate and weather patterns. Arctic climate change therefore has profound global consequences and affects global conditions such as sea level rise, ocean acidification, permafrost thawing (which releases potent greenhouse gases) and changing weather patterns, such as the monsoon. Arctic climate change is therefore arguably relevant to the weather and climate in regions distantly located from the Arctic.



The lipid-rich zooplankton Calanus Glacialis is an important source of nutrition for seabirds and fish in the Arctic

Although the development is disturbing, climate change also provides some advantages. Increased biomass production in the northern waters – not at least in the highly productive Barents Sea – may become an important resource for the world's everincreasing need for food and proteins. Furthermore, the Arctic's special role in global change makes it a potential laboratory for developing new green technology and new solutions that may be utilised in a global context, under the idea that: What works in the Arctic will work elsewhere.

The opportunities in an Arctic with much less summertime sea ice are numerous. New shipping lanes, increased commercial fishing, new bioprospecting activities and harvesting marine ingredients for bio-production (including organisms at lower trophic levels in the food web and at greater depths,) are among the main gains from the situation. Oil, gas and minerals are other resources that may be possible to exploit increasingly further north in the near future.

A call for knowledge

However, today's rapidly changing climate and the major ecosystem changes that go with it, impose a fundamental challenge for management: the system is highly dynamic with large seasonal changes. We must avoid making decisions and investments for the future based on yesterday's situation. This calls for a



Female polar bear between ice floes in the Barents Sea

continuously updated knowledge base and sophisticated earth system models to project future changes.

Also, we experience a northward expansion of marine species from the south. The fishing fleet has recently taken advantage of this development and fishing grounds are relocated northwards into the shelves of the Arctic Ocean, especially in the North Atlantic region. This raises the question whether we may experience commercially viable fisheries in the Arctic Ocean in the future. The area of the Arctic Ocean beyond 200 nautical miles of Canada, Denmark/Greenland, Norway, Russia and the U.S is 2.8 million square kilometers. Up to now, scientists have documented an increase in zooplankton biomass over some areas of the continental shelf. However, scientists raise doubts about whether the same will happen over deep water in the central Arctic Ocean. An important limiting factor for increased production is available nutrients, which are much lower in abundance in deep water than over the shelves.

When the Arctic marine systems become warmer, expanding pelagic fish stocks will likely migrate into the Arctic Ocean to utilise the short peaks in production there, but will likely retreat to the more productive shelves when the peaks decline. Thus, most of the fisheries in the Arctic Ocean may be confined to the shelves. As a precautionary action to avoid illegal, unreported and unregulated fishing (IUU) in areas beyond national jurisdiction, the 5 Arctic coastal states signed an agreement in July 2015 where they agree to not fish in this area. Furthermore, a scientific research and monitoring programme was established in order to obtain more knowledge in support for future management. The longer-term goal is that other countries also commit to withstand from IUU-fishing in this area.



Norwegian Polar Institute Tel: +47 7775 0500 post@npolar.no www.npolar.no

Changes in the Arctic and Antarctic under global warming

T. Yamanouchi & H. Enomoto from the National Institute of Polar Research explore the abrupt and potentially worrying changes in the Arctic today

Since established in 1973, National Institute of Polar Research (NIPR) engaged in the Antarctic research with operating Japan Antarctic Research Expedition (JARE) for a long time. In 1990, NIPR established an Arctic Environment Research Centre and expanded its research area to the Arctic. Now NIPR is focusing on the research on global changes in the Arctic and Antarctic.

Arctic

What is happening now in the Arctic, under global warming? In warming, due to anthropogenic increases in carbon dioxide concentration, the surface temperature in the Arctic is increasing with a speed that is more than double the global average. We call this "Arctic warming amplification", and an understanding of its mechanism is urgently needed.

Sea Ice

Reduction of sea ice extent in the Arctic Ocean is continuing, and an abrupt decrease since the 2000s is especially noticeable. Owing to this change, potential for regular ship navigation through the Arctic Ocean has increased, and they have become broadly known as "Arctic sea routes." The reduction of the sea ice extent and the warming of the ocean are expected to lead to changes, not only in the physical and chemical ocean environment, but also to changes of marine ecosystems.

Looking at the land area, many glaciers distributed around the Arctic are retreating. The Greenland ice sheet, the largest ice mass in the northern hemisphere, is also melting markedly, and the flow-out or collapse from its terminal glacier is serious. This will be a concern in terms of the world sea level rise.

Cold Season

Moreover, the duration of the snow season is decreas-

ing. In such ways, snow and ice have been showing great changes, and thus great impacts on atmospheric circulation and terrestrial biology are foreseen. Changes in terrestrial biological activity will alter the amount of atmospheric carbon dioxide absorption by vegetation, and will affect global warming as feedback. Although it is far away from Japan, we cannot turn a blind eye to Arctic climate change, since we are affected by it, too.

To grasp these abrupt changes in the Arctic, to understand the mechanism, and to contribute to future climate change projection, NIPR conducted the Green Network of Excellence Program (GRENE) Arctic Climate Change Research Project "Rapid Change of the Arctic Climate System and its Global Influences" for five years, between 2011 and 2016. 39 institutions from all over Japan participated in the project, and more than 360 Japanese scientists tackled all aspects of the Arctic climate system. Comprehensive Arctic research incorporating multidisciplinary work and collaborations between observation and modeling had been realised.

The successor of the GRENE project, ArCS (Arctic Challenge for Sustainability), which lays delivering emphasis on robust scientific information to stakeholders for decision making and solving problems, was started in FY2015. This is also a national flagship project funded by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the NIPR, Japan Agency of Marine-Earth Science and Technology (JAMSTEC) and Hokkaido University are positioned as the key institutions.

Antarctica

Antarctica is an isolated continent surrounding by the Southern Ocean, and snow accumulation would hardly melt all year long, becomes compressed ice covering the continent. The Antarctic ice cap, a massive sheet of ice,



Melt water stream over a glacier surface darkened by glacier microorganisms in Greenland

has an average thickness of approximately 1860 metres, and together with ice shelves makes a size approximately 14 million km², 37 times the size of Japan.

Located far from civilisation, Antarctica functions as both an environmental monitoring centre that allows us to assess the impact of human activity on the planet (e.g. atmospheric CO₂ concentration), and a time capsule that gives us a glimpse into the global climate of the past. Japanese Antarctic Research Expedition (JARE) was started in 1956/57 as a part of the International Geophysical Year (IGY), and Syowa Station was established on Ongul Island in the Antarctic. Since then, various observations have been performed at the station and surrounding areas, and resulted in much of the outstanding scientific outcomes.

Ice Core

Paleoenvironmental study is conducted based on deep ice cores of ice sheet drilled at Dome Fuji Station, 3810 m a. s. l. and 1000 km inland from Syowa Station. Ice core analysis unveiled the temperature change during the past 720 thousand years, indicated periodic variations between glacial and inter glacial period in about 100-thousand-year frequency. The information

retrieved from the ice cores will greatly contribute to improving projections of the future global climate and environment. Under the current Japanese Antarctic Research Project Phase IX, entitled "Global changes and movements on Earth system through Antarctic observations", NIPR is planning to carry out a new deep ice coring project near Dome Fuji Station, aimed at retrieving the oldest ice core (more than 1 million years) in the world.



Dr. Takashi Yamanouchi **Project Professor and Professor Emeritus**

Dr. Hiroyuki Enomoto **Director of Arctic Environment Research Center, Professor** National Institute of Polar Research and SOKENDAI (The Graduate University for Advanced Studies) www.nipr.ac.jp

Permafrost ice as an important water resource for the future?

Martin Hoelzle, Martin Scherler and Christian Hauck from the University of Fribourg explore the possibility of melting ice-rich permafrost as a water resource

G laciers are currently melting at increased rates on a worldwide scale. At specific places, especially in dry regions such as Central Asia, their water constitutes an important fresh water resource for irrigation in agriculture or for drinking water. With the projected reduction of glacier volume during the 21st century, the glacial water contribution will considerably decline. This will change seasonal runoff patterns drastically and water availability during the dry summer months will be strongly reduced.

Many studies already confirmed this effect, especially for small local catchments, where glaciers have already completely melted and therefore, runoff is reduced to an extreme extent. Therefore, knowledge about future water availability in different catchments and on different scales will be of outmost importance for water engineers and water managers.

At present, still little is known about the ice melt contribution to total runoff from regions with extensive permafrost occurrence. As permafrost, unlike glaciers, is a phenomenon that is not directly accessible by remote sensing methods, it is difficult to estimate ground ice content over large areas. The knowledge about mountain permafrost has increased enormously during the last decades and it has been revealed that most of the ground ice within alpine permafrost is stored under thick accumulations of coarse blocky material.

The origin of the ice within these debris materials are manifold and can be classified as congelation ice and sedimentary ice based on snow deposition, the forming snow patches, glacierets or even glaciers. If the ground is supersaturated, meaning that the ice is filling all pore spaces and is connected over larger distances within the ground, it starts to creep and large morphologically well-distinguished features are starting to form the landscape. These features are called rock glaciers.

Available permafrost

Today, it is thought that a large part of the ice in mountain permafrost areas is stored within these creeping permafrost features. The ice volume content of rock glaciers is estimated at 10 to over 90 %. However, an exact determination of the ice content can only be achieved by detailed direct or half direct investigations through drilling or the application of geophysical sounding methods. Through repeated geophysical measurements even a first estimate of the temporal change in ice content is possible.

One of the main open questions is how the ice content in such frozen grounds can be related to local runoff



Permafrost

Permafrost is lithospheric material which shows continuously temperatures below the freezing point, for at least two consecutive years. In general, ground in permafrost environments can contain remarkably high ice content.

generation. Such studies in small catchments containing permafrost are very sparse and an assessment at larger scales has not yet been performed in detail. The available studies show that runoff generation in permafrost areas is a quite complicated subject because ground ice acts as an impermeable layer for water and is often distributed in an irregular way.

Therefore, the water percolation, the routing and the corresponding runoff



Rock glaciers

Rock glaciers are a form of mountain permafrost, showing distinct patterns of mass movement. They consist of rocks from talus slopes or from moraines containing large amounts of interstitial ice and/or solid ice cores. They are flowing downwards driven by the force of gravity and show typical surface topographies due to compressive flow. At and within the surficial active layer consisting of debris or large blocks, they exhibit various forms of heat exchange with the atmosphere. These heat exchange processes are important for the glaciers, as they modify the energy balance compared to bare rock faces or plain slopes.

coming from such areas, often show temporally and spatially inhomogeneous distributions. Some studies based on tracer experiments revealed a runoff behaviour which is normally driven by fast runoff based on strong precipitation and/or snow melt events.

The effective fraction of the runoff contribution based only on the melt of the ground ice is unknown. Only a few studies provide values of the annual mass balance of rock glaciers. These show the amount of ice melt being in the order of a few centimetres water equivalent per m² per year.

To get more reliable answers on these questions, the most promising option is the application of numerical models able to calculate energy and mass fluxes within the different surface and subsurface materials in a fully coupled way. Additionally, runoff measurements and geophysical soundings, would allow for the determination of an optimal set of parameters for the calibration of such models. One of the most extensive investigation campaigns world-wide has been performed on rock glacier Murtèl-Corvatsch in the Upper Engadin, Eastern Swiss Alps. On this rock glacier the longest borehole temperature series down to more than 60m depth exists (since 1987) and meteorological measurements are available since 1997.

In addition, several geophysical surveys have been undertaken since the end of the 1980s. These measurements reveal that the ice content of this rock glacier is as high as 90%, showing the particularly high amount of ice stored in this permafrost phenomenon. First calculations of runoff estimates, for such a rock glacier catchment in a dry mountainous region are maybe as high as 4% to 9% of the total runoff.

In addition to the total annual runoff amount, it should be noted that these water reservoirs will thaw at slower rates than glaciers and will thus provide meltwater during longer time periods in future. Keeping this in mind, it becomes evident that such sites must be investigated in more detail in the future – also to improve our understanding of the exact processes involved in the runoff generation from permafrost catchments.

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UNIVERSITÄT FREIBURG

Professor Martin Hoelzle

UNI

Department of Geosciences, University of Fribourg Tel: +41 2630 09022 martin.hoelzle@unifr.ch www.unifr.ch/geoscience/geographie/

Co-authors:

Professor Christian Hauck Doctor Martin Scherler Department of Geosciences, University of Friibourg



Open Access Government provides an insight into the work of The National Science Foundation's Office of Polar Programmes' research about the Polar Regions

he National Science Foundation (NSF) is an independent federal agency in the United States – that supports fundamental research and education – across science and engineering fields. This article will focus on the work of The Office of Polar Programs (OPP), within the NSF which exists to promote innovative and creative scientific research, engineering and education in and about the polar regions.

OPP exists to provide access to the polar regions and to support both research and education in the field, ranging from core discipline to systems levels. In addition, STEM (the academic disciplines of science, technology, engineering and mathematics) engagement and workforce development (education & people) are integrated into OPP's portfolio, as they endeavour to carry out their responsibilities in both a sustainable and collaborative fashion, working with a wide range of partners. These include native Arctic communities and Alaskan residents, as well as local, state, federal and international educational and research institutions and agencies.

In news from earlier this year, we learn that polar glaciers may be home to previously undiscovered carbon cycle. According to a new paper published by NSF supported researchers, it is argued that "the cycle could become a significant global source of carbon, as temperatures rise worldwide and microbial activity increases"¹.

An international team of researchers from the United States, Germany and Sweden revealed these fascinating results in the online journal, Nature Geoscience. This article revealed that microbes present in streams flowing on the surface of glaciers in both the Arctic and Antarctic – might represent a previously underestimated source of organic material and be part of a yet undiscovered "dynamic local carbon cycle."



Carbon release

Scientists previously thought that carbon released into polar streams by glaciers emanated from ancient organic material locked in the ice, or from other sources around the world. In the new study however, the researchers discovered that most of the carbon in the stream was produced by bacteria photosynthesizing, which means producing food from sunlight, rather than ancient carbon. In addition, the research could indicate that as global temperatures increase, so too might the microbial output of carbon.

The authors add that while individual glacial streams could harbor relatively small amounts of carbon, they are important globally due to both their sheer mass and surface area. Around 11% of the Earth's surface is covered in ice, and as such, the polar glacial streams "represent an important component of the global carbon cycle," the authors comment. Christine Foreman, a researcher at Montana State University and an author on the paper remarks that because the carbon is easily broken down by the organisms, "it is believed that the impact of this material on downstream ecosystems will be amplified."

The researchers call for additional studies, "to refine the picture of whether the balance of carbon produced by glaciers is weighted more to the release of ancient carbon or the production by microorganisms."

One final point to highlight, is that out of a national network of 28 LTER sites, NSF lends it support to two sites in Antarctica: McMurdo Dry Valleys and Palmer Antarctica. Through the work of OPP, NSF also manages the U.S. Antarctic Program, which basically co-ordinates all U.S. research on the southernmost continent.

Every year, the United States deploys about 700 people to Antarctica for performing scientific research, plus around 2,500 people to maintain and operate year-round research stations and provide logistics. Such people include research teams from academia, industry and government, as well as military personnel and contractor employees. Scientific opportunities in Antarctica focus on many fascinating areas such as glaciology, terrestrial and marine biology, medical research, meteorology, earth and ocean sciences, as well as astronomy and atmospheric physics².

- 1. https://www.nsf.gov/news/news_summ.jsp?cntn_id=191512&org= NSF&from=news
- 2. https://www.nsf.gov/geo/opp/opportun.jsp

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The role of antifreeze proteins in freezing avoidance of polar fishes

Arthur L. DeVries at the Department of Animal Biology, University of Illinois provides an expert insight into antifreeze proteins in polar fishes

he polar oceans are the coldest waters in the world and the Antarctic Ocean colder than the Artic, because of the presence of several massive ice shelves. Although the waters of the high Arctic and Antarctic are at their freezing point for much of the year, there is still abundant marine life associated with these waters indicating that they have adapted to the frigid conditions. The sea life includes birds, marine mammals and an abundant sub ice fauna of invertebrates and polar fishes. The birds and mammals are homeotherms, warm blooded, and they conserve their body heat by means of insulating blubber or feathers. The fishes and invertebrates on the other hand are poikilothermic, that is cold blooded, and thus assume the temperature of their environment.

For the aquatic organisms the lowest temperature of exposure is -1.9oC, the freezing point of seawater. The marine invertebrates are in no danger of freezing because their blood is as salty as seawater, although of a slightly different composition. Fishes on the other hand are hypoosmotic to seawater (their blood has only about one third the salt present in seawater). Therefore, in the presence of ice at -1.9oC, they will freeze and die. The abundance of fishes both in the Arctic and Antarctic swimming amongst ice crystals indicates that they can avoid freezing (Figure 1). Their avoidance of freezing is associated with the presence of blood antifreeze proteins



(AFPs). The AFPs are present in the blood at concentrations of 3 to 4% and lower its freezing point below that of seawater. The fish AFPs are either glycoproteins or small proteins.

In the Antarctic the major group of fishes are the notothenioids and they make up 90% of the fish biomass on the continental shelf and all possess same antifreeze glycoproteins (AFGPs), because they are closely related having evolved from a common ancestor many millions of years ago. They are present in a series of size isoforms that vary from 2.4 to 50 Kilo Daltons (KD) in mass. In the Arctic, the same AFGPs are found in the cod fishes (Family Gadidae) which are not related to the Antarctic notothenioids fishes.

In other Arctic fishes, the AFPs are small proteins with different struc-

tures and sizes. In the flat fishes (flounders), they are helical peptides while in the eel pouts (zoarcid fishes) they are globular molecules of about 15Kd. Despite the variation in composition, structure and size they all have the same antifreeze effect. The mechanism of antifreeze activity involves the recognition and binding to ice crystals that enter the blood of the fish either through lesions in the gill or skin. The AFs bind to particular ice crystal faces and divide the surface of the ice crystal into many small domains. As the temperature is lowered ice can only grow within these constrained patches and the growth assumes a growth front that is highly curved, the result which is the water molecules on the curved fronts have fewer neighbouring water molecules to bind to (figure 2). Therefore, their tendency is to escape into the liquid phase.


How AFPs prevent freezing

In order to remain in the highly curved front, energy must be removed from the system. This is accomplished by lowering the temperature and thus a local depression of the freezing point occurs. This is also known as the Kelvin effect. This mechanism of antifreeze function is known as adsorption inhibition. Because this mechanism is one of inhibiting growth the effect on the melting point of the ice is minimal, that is the melting point or equilibrium freezing point is normal. Thus, there is a separation of the melting point and the freezing point, also termed a hysteresis and is the hall mark of antifreeze proteins. This freezing melting separation for fishes living in the most frigid environments can be as much as 2°C, where as it is much less for fishes living in slightly milder icy waters.

X ray crystallographic and other studies involving the interaction of the AFPs at the water ice interface indicate that the AFPs structure water in an ice like manner and this may be the driving force for binding to ice. Other studies indicate that potential hydrogen bonding amino acid residues protrude from one side of the molecule and their spacing match some of the positions of oxygens in specific ice crystal faces. This lattice matching found in some of the AFPs is thought to be involved in their recognition of specific ice crystal planes and involved in their adsorption to ice while in others a lattice match is not obvious.

Despite progress in elucidation of the details of the mechanism of activity of the AFPs, there is still much that is not completely understood. In part this is due to the presence of a quasi-liquid layer that separates the liquid phase from the solid phase and the lack of physical techniques for directly probing the ice water interface.

In the high latitude polar regions, fishes maintain constant high levels of blood AFPs because they need them year-round to avoid freezing. Fishes of the warmer shallow north temperate regions synthesise AFPs during winter, but lose them during summer presumably to conserve energy.

The novel adaptation of AFPs in polar fishes has allowed them to exploit the niches that were vacated by temperate water fishes when the polar oceans cooled to their freezing points. Without the lifesaving AFPs the polar marine ecosystems would be a much different one because fishes are an important part of the food chain: seabirds feed primarily on them as well as seals and even some whales. Without fish, birds and mammals would be limited to feed on invertebrates whose distributions are often patchy. Thus, the AFPs in fishes play a vital role in structuring polar ecosystems.

Since the discovery of the AFPs in Antarctic fishes by the author, there have been several dozen patent granted for their potential use in the past 40 years. These include modification of crystal texture of frozen foods, improving cryopreservation of animal tissues and blood and preventing recrystallisation in frozen liquids. Although most of these appear to have limited use, one that has found commercial application is its use in preventing undesirable recrystallisation in ice cream which happens on long term storage. Unilever Corp markets an ice cream using eel pout AFP gene - expressed in yeast to limit recrystallisation in their product which they have appropriately named vaneela ice cream. This one of the few discoveries in polar science that has found a commercial application although rather specialised.



Arthur L DeVries Department of Animal Biology, University of Illinois Tel: +1 217 333 4245 adevries@life.illinois.edu **ENVIRONMENT**

Biodiversity loss – political will lacking in Europe

Member of the European Economic and Social Committee (EESC), Lutz Ribbe lifts the lid on biodiversity loss and nature protection issues

hile the erratic weather phenomena and biodiversity loss of recent years in particular have heightened public awareness of the need for us to live in a more sustainable, environmentallyfriendly fashion, this realisation – or rather its translation into action – is making very slow headway at the political level.

That said, there is still some good news: for instance, that farmers' spraying of poisonous substances in ecological focus areas will finally cease. The European Parliament voted in favour of this initiative of Agriculture Commissioner Phil Hogan. The result of the vote is very much attributable to the engagement of civil society organisations. Political pressure is needed, and the European Economic and Social Committee (EESC) endeavours to create such political pressure through its opinions.

There is much talk about nature and environmental protection at both EU and national level, but too little action is being taken still and what action there is has not been consistent enough.

Natura 2000 – 25 years behind

Several EESC recommendations for improving nature protection have so far elicited no response from the European Commission or the member states. European Commission president Jean-Claude Juncker even wanted to weaken the nature protection directives, a move that civil society managed to thwart.

The EESC has already repeatedly called for the European Commission to take immediate and resolute steps to implement the biodiversity strategy – especially the Birds and Habitats Directives, as well as the Water Framework Directive, which are instrumental in protecting biodiversity.

The Natura 2000 network of nature protection areas was supposed to have been fully completed back in the late 1990s, but not even all the sites have been designated yet, and only half of the designated sites have management plans.

The European Commission has now presented an EU Action Plan for Nature, People and the Economy, which



is intended to help stop biodiversity loss and speed up implementation of the Birds and Habitats Directives, on which the Natura 2000 network is based.

Nature protection is costly – but nature restoration is unaffordable

However, this new package of measures barely offers any new ideas. Above all it does not solve the problem, because the main issue for nature protection is lack of money. The Natura 2000 sites are currently funded almost exclusively from the European Fund for Regional Development (EFRD) and the European Agricultural Fund for Rural Development (EAFRD), which means that biodiversity protection is competing with many other – economy-related – projects, and those projects are generally given priority.

The EESC has been warning about this conflict of interests from the outset, and it once again calls on the European Commission as a matter of urgency to adopt a Natura 2000 budget that is based on an exact cost calculation. Some experts think that €10 billion would be needed yearly, in particular to compensate land owners.

Biodiversity and climate protection as overarching policy areas

Biodiversity cannot be protected solely by designating protected sites. Protection of nature and the environment must be mainstreamed in all policy areas, and especially in agriculture. As the European Commission and the Council themselves quite rightly point out, this sector is one of the biggest sources of pressure on terrestrial ecosystems. The EESC's members therefore hope that the mid-term review of the Ecological Focus Areas and the upcoming reform of the Common Agriculture Policy (CAP) will also focus on achievement of the biodiversity objectives.

Not only must agriculture become more sustainable, but biodiversity – just like climate protection – must be treated as an overarching policy objective and firmly established as such. Biodiversity is not just about preserving a few rare plants or animals but about preserving our ecosystem, which is ultimately the basis of our existence.

Much damage has already been done, and floods, landslides, melting glaciers, high winds etc. are now manifestations of human intervention in nature, a fact that sadly many people, including some politicians, still refuse to accept.

The European Union must be a pioneer in this area and must seek allies. We cannot stand by while our ecosystems slowly disintegrate. The European Commission has resources and tools, such as the European semester, to hold the member states to such objectives.

We therefore urge the European heads of state or government and the European Commission to finally do the job properly and make biodiversity as well as climate protection cross-policy priorities at EU and member state level and to act accordingly. If we do not tackle this issue now, the cost of repairing the system – if that is even feasible – will be incomparably greater.

Lutz Ribbe

Member of the European Economic and Social Committee (EESC) Tel: +32 (0)2 546 90 11 www.eesc.europa.eu www.twitter.com/EU_EESC

iDigBio: Serving biodiversity data and resources to the World

Pamela S Soltis, Director of the University of Florida's Biodiversity Institute shares a compelling insight into the digitisation of biodiversity data

he University of Florida (UF) Biodiversity Institute was introduced in the August issue of Open Access Government. Launched in 2016 to bring together scientists, social scientists, and policy experts to address critical societal issues of the 21st century related to biodiversity, the interdisciplinary UF Biodiversity Institute is accelerating synthetic research on biological diversity to serve stakeholders in Florida (a biodiversity hotspot) and globally through efforts to understand and manage biodiversity data, develop relevant conservation, educational, and outreach programmes, and shape policy to protect and enhance environmental capital.

The UF Biodiversity Institute is exploring the world's past and present biodiversity at all levels of organisation, from molecules to ecosystems, and the relationship of biodiversity to climate change and to healthy and sustainable natural and human environments. Institute scientists conduct synthetic research using data from all relevant sources to address fundamental problems in biodiversity science and solve pressing societal problems. Newly synthesised knowledge from the Institute is available to individuals and organisations seeking validated biodiversity information.

The UF Biodiversity Institute benefits from strong ties to iDigBio, the U.S. national coordinating centre for digitisation of biodiversity collections – that is, the integrated database that shares biodiversity data for the nation's natural history specimens. In this issue, we introduce iDigBio, describe the data that it serves, address how these data are being used in biodiversity science, and explain how this U.S.-sponsored resource engages with biodiversity resources worldwide.

Specimens in natural history museums – collected globally over the past four centuries and estimated at 3-4 billion specimens – document the world's biota, including how it has changed in response to human activities and population expansion. Until recently, the world's natural history specimens were accessible only to scientific specialists, but digitisation of these specimens is rapidly making them available to a worldwide audience.

Digitisation – that is, electronic capture of data, from label information to 2D and 3D images – began decades ago in some museums with databasing of basic information about a specimen (scientific name, collector, date of collection, locality, etc.). Through innovations in database design and usability, application of global standards for natural history collections, improved imaging methods, and the development of high-throughput workflows, the pace of digitisation has increased dramatically.

iDigBio (www.idigbio.org) was initiated in 2011 with a grant from the U.S. National Science Foundation as part of the Advancing Digitization of Biodiversity Collections (ADBC) Program, a 10-year, \$100-million commitment to 'unlock' the cabinets of the nation's natural history collections. Through ADBC, data and images for millions of biological specimens are being made available in electronic format for the research community, government agencies, students, educators, and the general public. Directed by Professor Larry Page of the University of Florida's Florida Museum of Natural History and his team (UF Professors Jose Fortes, Bruce MacFadden, and Pamela Soltis, who also directs the UF Biodiversity Institute, and Florida State University Professor Greg Riccardi), iDigBio coordinates the digitisation of U.S. natural history collections, the mobilisation of digitised data, and the aggregation of these data for a variety of uses.

iDigBio currently serves over 105 million specimen records, representing approximately 300 million of the estimated 1-2 billion specimens in U.S. collections. Media records, consisting primarily of images, but also including an acoustic collection of animal vocalisations, now number more than 22 million. Specimen records and images can be accessed through a querydriven portal and via an Application Programming Interface (API); both



oogle Custom Search

Making data and images of millions of biological specimens available on the web

Specimen Records 22,142,378 Media Records 1.634

105.070.571

Search the Portal



Why digitization matters Nore about what we do and why

Digitization Learn, share and develop best practices

Sharing Collections Documentation on data ingestion Working Groups Join in, contribute, be part of the community Proposals New tool and workshop ideas Citizen Scientists How can you help biological collections?

options offer download features for assembling large data sets of specimen information. This growing resource is driving innovations in management, analysis, and interpretation of biodiversity data, both in the U.S. and globally, with promise to address problems ranging from food security to invasive species to response of species to climate change.

Digitised data

In addition to serving specimen and media records, iDigBio has developed and promoted best practices in both digitisation and mobilisation of data. Through workshops, publications, videos, and webinars, iDigBio provides workforce training and development in digitisation, data management, data analysis, and data use for students and professionals alike.

Digitised specimen data can be applied to a broad range of research questions, from species identification and distributions, to shifts in flowering time associated with a changing climate, to expanding ranges of invasive species, to name a few. iDigBio scientists are developing new applications for the growing data resources, including the use of machine learning to extract information from the millions of images served by iDigBio. Research use of iDigBio data is growing rapidly, with over 100 scientific publications already in 2017, based on iDigBio data or other resources.

Likewise, iDigBio's educational resources – from K-12 lesson plans to university teaching materials to citizen science programmes and platforms – reach learners of all ages and stages. Finally, iDigBio data have tremendous potential for conservation and management of rare and endangered species and for application in a broad range of policy issues.

Although funded by the U.S. as a repository for digitised data and images from U.S. natural history collections, iDigBio has specimen records from around the world and serves data from many international partner institutions. Moreover, iDigBio interfaces with the Global Biodiversity Information Facility (GBIF) to share data and best practices. GBIF, funded by the world's governments, is a network of countries and organisations that share information, some of it based on natural history specimens, about where and when species have been recorded. Together, iDigBio and GBIF are working to enable global access to global biodiversity information to address a range of scientific and societal problems.

Upcoming articles in this series will focus on the role of the UF Biodiversity Institute in applying data science and informatics to biodiversity-centred problems, the need for innovative training programmes for students and practitioners to take advantage of ongoing developments in data availability and use, and case studies of how biodiversity scientists are addressing societal problems.



Pamela S Soltis Director University of Florida Biodiversity Institute University of Florida Gainesville, Florida 32611, USA Tel: +1 352 273 1964 psoltis@ufl.edu https://biodiversity.institute.ufl.edu/

The Smart City Charter and the missing link to climate resilience

Prof Dr Daniela Jacob, Climate Service Centre Germany, highlights the Smart City Charter and what it means for the future of cities

ites are confronted with many challenges in relation to urbanisation, natural hazards, climate change and their interactions. Cities are not only contributing to climate change, they will also be affected by expected climate change impacts such as urban floods after heavy rain events or heat stress. The concentration of people, assets, critical infrastructure and economic activities exacerbates the potential of natural hazards and extreme weather events. This is why cities need to adapt on time to enhance protection. The relevance of mitigation and adaptation efforts is also highlighted in the Global Risks Report 2017. Four environmental risks - extreme weather events, natural disasters, failure of climate change mitigation and adaptation, as well as man-made environmental disasters - were ranked both high-risk and high-likelihood, with extreme weather events emerging as the single most prominent global risk.

The Smart City Charter

At the same time, cities and regions all over the world are increasingly trying to become smarter, because smart cities are committed to sustainable and integrated urban developments to enable long-term economic growth. Recently the Smart City Charter has been presented and published by the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB) aiming to outline the standard model for a smart, future-oriented city. According



to that a smart city is – among others – climate-neutral, resource-efficient, responsive and sensitive. A missing point, however, is climate-resilience. The Smart City Charter is also intended as a basis for discussions on the future of cities in the digital age and aims to extend the public scope of these discussions. We herewith like to sensitise and highlight the need to broaden the view to risk perception and resilience as a whole by paying more attention to systemic risks regarding critical infrastructure.

Due to the fact that cities' stability and prosperity rely on vast networks of infrastructure which provide essential services, urban critical infrastructure needs to be smarter, too. This will be reached in a way that they are more intelligent and interconnected in order to integrate multiple information, as well as new information and communication technologies to manage city's assets. However, the interactions between interconnected critical infrastructure elements work smart in normal operation and everyday use. But, what happens to smartness during longer periods of dysfunctioning that are mostly not considered? Will smart city infrastructure elements still be smart and resilient when they are exposed to external shocks like natural disasters, climate change impacts, terrorist attacks or human failure? Or will smart cities finally be even more vulnerable due to their multiple dependencies?

Critical infrastructure element

In general, critical infrastructure describes assets that are essential to maintain vital societal functions. Therefore, failures or functional impairments can have immediate and high impacts on several sectors as

well as to the whole society. Furthermore, interactions between critical infrastructure elements – in particular in different sectors such as energy supply, communication, information technology, water supply, wastewater treatment, transportation, and emergency services - have become a growing phenomenon. Individual elements can be vulnerable against one or more impacts and can have the function of an interface that connects different infrastructure networks, enabling the transfer of disorders across multiple infrastructure sectors and elements.

Critical infrastructure is exposed to various kinds of threats. There are man-made or technical (terrorism, sabotage, software failures etc.) and natural threats. The latter differ from geological (mass movements, earthquakes etc.) to hydro-meteorological hazards (climate change impacts). Whereby in particular climate change induced extreme weather events have a high potential to act as a trigger for cascading effects. The effect generates a sequence of events in human subsystems that result in physical, social and/or economic disruption. Thus, an initial impact can trigger other incidents that lead to consequences with significant magnitude.

With respect to smart cities, the ongoing interlinking of infrastructure elements is leading both to opportunities for innovation, but also complex, specific and rather novel risks. Furthermore, the economic value of physical infrastructure networks in cities increases with its scope. For instance regarding information and communication technology, the more people a network connects, the more useful it becomes. For supply infrastructures like energy and water, the connection of more people is in theory often expected to lead to more flexibility for the operation, a higher intrinsic resilience of the network and leverage necessary economies of scale.

However, as different infrastructure networks become more interdependent, there is also a growing – and currently often still underrated – scope for systemic failures to cascade across different networks and affect society in multiple ways.

As an example the relations and interactions between the water supply and energy sector show, that a malfunction within the energy supply chain starting from the power production over distribution and transformation stations to power lines - can affect water supply in a broad sense. Pumps, control elements, water treatment and recently digital communication do not work without electricity. Finally this leads to a breakdown of the water works. The outage of the water supply even considered separately has a further impact on other public facilities such as health care. With respect to waste water treatment, the missing water supply starts a second cascading step, because the malfunction of sewerage system elements, like sewerage treatment plants, has a further impact on other public facilities too.

To reduce the vulnerability to climate impact, cities need to focus on the whole system including the complex interactions of non-climatic and climatic drivers, as well as all critical infrastructure elements. Local councils are key actors when it comes to the implementation of adaptation measures. Thereby, increasing a cities resilience to climate change impacts is highly context specific, due to its geographical location, structure, institutions, inhabitants, available information and operational capability. Therefore there is a need to understand risks and resilience jointly by paying more attention to systemic risks regarding critical infrastructure and cascading effects.

As a result of new threads for digital-based infrastructure elements, it must be guaranteed that all sub-systems remain functional in case of disruptions. Technical – most suitable analogue – redundancies must be provided for the core components of the critical infrastructure.

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An institution of Helmholtz-Zentrum Geesthacht

Prof Dr Daniela Jacob Climate Service Centre Germany (GERICS) daniela.jacob@hzg.de www.climate-service-center.de

THE BUILT ENVIRONMENT



The importance of cities as partners in successful governance

Anna Lisa Boni, secretary general of EUROCITIES, shares her reflections on the growing importance of cities as agenda setters

The growing importance of cities as agenda setters has been recognised globally in the Sustainable Development Goals and the New Urban Agenda of the UN. This reflects a movement more generally to reality check policy making, by giving more of a say to those that implement it on the ground. Cities are the right scale to build partnerships that bring policy closer to citizens.

In Europe, the Urban Agenda for the EU, launched in May 2016, is a good starting point. It recognises the added value of bringing cities, member states and the Commission together on matters that concern us and our citizens. It is a new way of working together and a learning process for all partners. We need to keep the process flexible and adapt as we move along, to be able to make the most of this opportunity to join up all levels of government to work together for better solutions.

One year in, the 12 thematic partnerships envisaged in the Pact of Amsterdam, as the key instrument to deliver the agenda, have all been set up. They are at different stages of implementation but all are working on better regulation, better funding and better knowledge sharing on their specific topics. We are invested in these partnerships and we want to continue to work with partners to match urban challenges and solutions to EU objectives and ensure clear outcomes for cities.

THE BUILT ENVIRONMENT

Using the tools of the urban agenda to involve cities in finding solutions to common challenges will help create a stronger EU, especially if these outcomes are used to feed into longer-term EU policy development. The Urban Impact Assessments also offer cities a channel to flag up potential concerns with policy developments directly to EU decision makers. As such, they recognise the role of cities as implementers of a broad range of EU legislation, and the importance of including cities in governance processes.

Better collaboration on policy in this way should mean better ownership across the different levels of government in how policy is implemented. This is particularly important when considering the financial framework post-2020. Cities need a more effective approach to funding that addresses urban challenges, allowing cities to draw on and combine different EU funding streams to deliver integrated solutions locally.

Strategic challenges encountered on the local level are also European ones. City authorities tackle issues around worklessness, migration and the environment (and many others) on a daily basis. City authorities play a pivotal role in meeting these challenges by connecting EU investments with local needs. But cities' say in long-term investment decisions, notably through EU cohesion policy, is minimal.

Beyond the specific tools of the urban agenda, we need to continue to 'urbanise' existing work process at EU level, such as the European Innovation Partnership (EIP) on Smart Cities and Communities, where EUROCITIES coordinates the action cluster on business models, financing and procurement. We want to boost integrated approaches to EU financed projects that involve cities as partners and in policy developments that impact cities.

Another way to share ownership of decision making and outcomes, can be through knowledge exchange. Sharing rather than competing is also a core function of city-led networks, like EUROCITIES. We directly engage over 140 of Europe's largest cities at both political and expert level across a broad range of policy issues. Our well-established working practices act as a multiplier for the debates and outcomes of the urban agenda, allowing our broader membership to contribute and benefit.



We want to make partnerships and multi-level governance a priority. Cities are the perfect scale to test out innovative solutions that benefit their citizens. These solutions often make sense in different contexts and can be shared between cities or upscaled by feeding into national and European decision making.

In the coming months, our campaign 'cities4Europe, Europe for citizens' will be doing exactly this, by sharing innovative city practices that engage our citizens directly. A stronger EU starts with the citizens, and cities can help make that happen.

EUROCITIES is the network of major European cities, with over 140 members, representing more than 130 million people. Visit: <u>www.eurocities.eu</u> to learn more.

Anna Lisa Boni Secretary general EUROCITIES Tel: +32 2 552 08 88 info@eurocities.eu www.eurocities.eu www.twitter.com/EUROCITIEStweet



TOWARDS a 2025 Standard

he Active House standard concerning energy, comfort and sustainability can be used to firmly communicate the important task of integrating renewable energy into the buildings of the future.

Currently in Denmark there is no energy vision for 2025. The Nordic Built Charter stated that "Buildings should be CO_2 neutral over their lifetime", and agreed to use the Active House standard and prosumer levels 1-4 to document this in practice.

Cenergia – now a part of Kuben Management – aims to document 'low cost BIPV solutions' as part of an Active House standard. Several example projects have been developed, including the small Active House test house, "Living in Light Box".

Building integrated PV

Based on the huge reduction in costs of PV panels, there are now many examples of electricity producing building skins, which have very marginal extra costs compared to normal building skins.

Energy visions for 2025

The passive house standard has documented that you can actually realise buildings with a very limited heating demand. A vision for the Active House standard is to include a standard for different levels of zero energy building with the help of renewable energy (by different prosumer levels).



In Denmark we have the low energy class 2020 as an option for an improved low energy standard, which currently can be used instead of the existing building standard from 2015.

This has introduced new factors for district heating, where you can multiply the demands by a factor of 0.6, and for electricity by a factor of 1.8 (normal building regulation factors are 0.8 and 2.5). This makes it possible to reach an energy use of only 20kWh/m² per year, perhaps with a small contribution from PV panels as well.







Active House Denmark, Building Green, Copenhagen 2015

The AAU-IDA 2050 plan suggests around 200MWp per year to be implemented until 2050, reaching 5,000MWp (covering around 5% of electricity use).

Active House building in combination with Low Energy Class 2020, with prosumer level 1, 2, 3 and 4 for new buildings, larger renovations and new city areas, could help secure a stable BIPV market, which would pass regulation and could help secure good architecture, a stable BIPV market and Active House quality.

It has been argued that it could be beneficial to avoid the renewable energy contribution in building standards towards 2025. In that case you would need to find another way to highlight how you would try to reach an almost zero energy building standard.

As mentioned before, a solution here could be to introduce different "prosumer" levels, e.g. 1-4, the same way as the Active House Radar works. Prosumer level 1 being at a 100% zero energy or CO₂ neutral level.

TOWARDS a 2025 Standard

Illustration of how a low energy class 2020 building can look like with respect to windows to avoid overheating (new housing example from Aarhus)



Only limited window area towards south to avoid overheating



Large window areas towards north will not give problems with overheating and secures good daylight



www.activehouse.info

www.kubenman.dk

The UK's untold stories

EPP-coordinator for REGI, MEP Lambert van Nistelrooij sheds light on the importance of engaging citizens and improving communication with the EU

n the Brexit-debates there was hardly any evidence of the EU's contribution to urban and rural development. Many stories were kept untold. I am convinced that there are many beneficiaries ready to tell about the outcome of their work. Europe-wide there is a need for a more profound citizen communication with the EU. How to modernise?

Jean-Claude Juncker discussed in the State of the Union the importance of the Citizen's Dialogues. Europe by doing, putting experiences in the centre of it. Although the dialogues originally started in 2012, they became a focal point to the debate on Europe's future, initiated in March 2017. Since that period over 130 Citizen's Dialogues were held, spanning 27-member states and more than 80 towns. All European capitals hosted dialogues, but also many smaller cities got the chance to organise events.

The 160,000 citizens that attended these events got the chance to exchange views with members of the European Commission and express their concerns. In the light of this initiative I have launched the action "Let the Stars Shine", together with eight fellow EPP Members. It is our goal to engage citizens and find ways to improve communication about and by the EU. We want to encourage citizens to share their experiences with the EU programmes. There are countless of examples: companies who could develop innovating new technologies thanks to EU support. Thousands of students who can study in other European countries due to the Erasmus-project.

These personal narratives are our "stars". With our initiative "Let the Stars Shine", we want to highlight projects and proposals from our member states that tell a story to the community. My action started in the Netherlands in the small rural town of Diessen on 30th

August together with Commissioner Cretu. During the coming months, my colleagues from 8 different Member States will take this action further. We invited beneficiaries of EU funds to step forward and submit their results. By the end of this year we look at their innovative ways of communication used to involve citizens, cities and regions in the project.

"The EU flag has 12 stars, a symbol of unity. I believe the EU has many more stars out there, waiting to shine. It remains unclear what such stars might have delivered in the Brexit debate. But there is room for improvement."

We invited several communication experts to share their fresh perspectives on how to tackle this communication issue. Their conclusion was clear: not just communicate more, but communicate in a different way. Martijn Groenleer, professor of law and governance at Tilburg University: "I believe it is not about better communication on the EU, but about more and better internal communication within the EU. It is expected that this will lead to a more coherent and visible EU policy with a more uniform impact throughout the Union".

New strategies

Ryan Heath, senior EU correspondent at Politico, shares this opinion: "The EU flag and signs attached to EU projects are a good visual clue to the EU's wide impact. Another way for the EU to have more of its impact felt is to focus on what only it can do well. Instead of having a finger in every pie, the EU could afford to focus more on projects that simply couldn't happen without it".

Luckily this view has been gaining momentum lately. The "Let the Stars Shine"-initiative does not stand on its own. The European Commission has recently launched

THE BUILT ENVIRONMENT



MEP Lambert van Nistelrooij, EPP-coordinator for REGI

a call for proposal on new communication strategies on EU Cohesion policy.

"We invited several communication experts to share their fresh perspectives on how to tackle this communication issue. Their conclusion was clear: not just communicate more, but communicate in a different way."

Moreover, the parliament's recent proposals on communication in the Omnibus-trilogue are positively received by European Commission and Council. The aim is to enable beneficiaries to communicate on the effects of the EU programmes and measures, also in the years after the project is finished. This is clearly what was missing during and after the Brexit referendum.

The EU flag has 12 stars, a symbol of unity. I believe the EU has many more stars out there, waiting to shine. It

remains unclear what such stars might have delivered in the Brexit debate. But there is room for improvement. If we do not tackle these issues seriously, we spoil the support the EU has built. Let the Stars Shine.

MEP Lambert van Nistelrooij EPP-coordinator for REGI

Tel: +31 70 342 48 20 lambert.vannistelrooij@europarl.europa.eu www.lambertvannistelrooij.nl www.twitter.com/LvNistelrooij



The Municipality of Varberg is ideally located in the most expansive regional belt in southern Sweden. Right in the middle between the Greater Gothenburg region to the north, and the Greater Copenhagen region to the south, lies the region of Halland. Here, Varberg is the friendly and rapidly growing coastal community and creative hotspot that has inspired people seeking an active, healthy and creative lifestyle, and are continuing to do so.

For example, the beaches are close to the city centre and attract surfers from across northern Europe – all year long. You can quite literally catch a train from the busy streets of Gothenburg and bring your surfboard, and after less than 40 minutes leave the train in Varberg and enjoy the waves! And lots of surfers have found that this is the place to live, to network and contribute to the thriving business life of the community. It is quite fitting that the yearly event 'Hallifornia' was voted the best Swedish Placebrander event of 2017, which makes us very proud.

For Varberg, investments in infrastructure are crucial for contributing to regional growth and a more sustainable future. Fortunately, increasing the commuting capacity on the west coast railway has high national priority, and will benefit connectivity and growth in all communities and cities along the southwest coast of Sweden.

Getting the most out of Varberg

To maximise the benefit from these investments, the city is in the midst of planning for a new city waterfront where old railway and harbour instalments are now located. The railway will be built to higher capacity in a tunnel under the city, which will, after moving some of the harbour instalments, eventually free up space for city development.

The new city waterfront has been named Västerport ('The gate to the west') through a dialogue with the residents. The new west coast railway, with an entirely new station in Varberg, will be taken into operation by 2025. A much higher commuting capacity means more people in Varberg will enjoy better work and education opportunities in a larger and more connected region. But it is also an opportunity for the city of Varberg to attract more businesses to locate their facilities near a great commuting node, our attractive city centre, the coastline, and Västerport. We believe this can make Varberg an interesting place to invest in education, culture and business. This is how we act on our vision to build on creativity, to make Varberg the most vibrant and attractive hotspot in southwest Sweden.

Come to Varberg. Be inspired.



REINVENTING THE COMMUNITY

building on creativity

reativity, innovation and a strong focus on social and cultural aspects of sustainability are at the very heart of developing the Municipality of Varberg to become the Swedish West Coast's Creative Hot Spot by 2025.

In our vision for the future, the municipality has unique opportunities. The city of Varberg is one of the most attractive cities in Sweden, ideally located with the city centre right next to the coastline. Our location is exceptional – right in between two of Sweden's fastest growing regions, The Greater Gothenburg region, and the Greater Copenhagen region.

Our aim is clear, and we are acting on it. We are building a community converging around means of

public transportation and a sustainable lifestyle. And it shows in the many awards we get.

Best place to live

The Municipality of Varberg has been appointed Sweden's Best Place To Live in the category of smaller communities for four years in a row now. Our thriving city centre was winner in Sweden's City Centre of the Year award. And living in the wonderful coastal province of Halland, it is certainly very fitting that the yearly Varberg event Hallifornia was awarded 2017 Placebrander of the year. We are proud of these awards and regard them as appreciative of our chosen path towards the future.

Come to Varberg. Be inspired.



varberg.se

Diversity in the neighbourhood drives support for a generous asylum policy

Dr Gideon Bolt at Utrecht University, shares his expert perspective on attitudes towards asylum seekers in Europe

n 2015, Europe received 1.26 million new asylum claims. Although the numbers are slightly lower in 2016 (1.20 million) it is not to be expected that European's largest refugee crisis since the Second World War will soon be over (Bansak et al., 2016). European countries struggle with finding policy solutions in a context where extreme right-wing parties seem to profit from concerns about asylum issues and where a vote for Brexit can largely be attributed to rising anti-immigrant sentiments. Therefore, it is crucial for both researchers and politicians to understand why some citizens are welcoming asylum seekers and why others oppose them.

To analyse the support of a generous asylum policy, I used data from round 7 of the European Social Survey (ESS). On average, 47.5% of the people in the countries that are included in the ESS survey agree that governments should be generous when judging applications for refugee status, while 26.0 disagrees (table 1). The difference in these two percentages is used to order the countries by generosity.

Israel turns out to be the least generous country. There are much more respondents who disagree with the statement than those who agree, while the reverse is true for Portugal. There are only six countries where the people who advocate a generous asylum policy are outnumbered by those who object to a generous policy.

	Agree	No Opinion	Disagree	Difference Agree-Disagree
Israel	18.9	38.2	42.9	-24.0
Czech Republic	21.0	34.3	44.6	-23.6
Estonia	25.6	27.6	46.7	-21.1
Hungary	23.1	38.2	38.7	-15.6
Netherlands	32.0	20.9	47.2	-15.2
Belgium	30.3	25.1	44.6	-14.3
Switzerland	34.9	30.7	34.4	0.5
Austria	40.5	23.9	35.6	4.9
Lithuania	28.3	48.9	22.8	5.5
Germany	39.5	26.8	33.7	5.8
Denmark	45.0	25.1	29.9	15.1
Slovenia	39.4	36.8	23.8	15.6
United Kingdom	46.6	26.4	27.1	19.5
Finland	50.0	27.4	22.5	27.5
Ireland	56.5	22.9	20.6	35.9
Norway	57.4	24.4	18.3	39.1
France	58.8	23.0	18.2	40.6
Spain	60.0	24.3	15.7	44.3
Sweden	59.5	30.1	10.4	49.1
Poland	63.5	27.7	8.8	54.7
Portugal	68.5	23.7	7.8	60.7
Total	47.5	26.5	26.0	21.5

"The government should be generous in judging people's applications for refugee status"

Table 1: Support for a generous asylum-policy by ESS-country measured in % (Countries ranked from least support to most support)

* Source: ESS Round 7: European Social Survey Round 7 Data (2014). Data file edition 2.1. NSD – Norwegian Centre for Research Data, Norway – Data Archive and distributor of ESS data for ESS ERIC.



Out of the Western European countries, The Netherlands is the least generous country. Meulemans et al. (2016) show that there is a weak positive relationship between a country's affluence and agreement with the statement (r=+0.25). People in wealthy countries are more willing to admit asylum-seekers. Belgium, The Netherlands and Switzerland are countries for which the generosity is much lower than could be expected based on their affluence, while the reverse applies to Portugal and Poland.

Determinants of generous attitudes

On the basis of a multivariate analysis of the Dutch part of the dataset (tables available on request), it can be concluded that the effect of the (perceived) presence of out-groups' members on the attitudes towards asylum seekers appears to vary between different scale levels. The respondents have been asked to estimate how many people are born outside the country out of every 100 people. The mean estimated percentage is 23.7, which is more than twice as much as the actual number of 11%. The more people overestimate the presence of immigrants, the lower their support for a generous asylum policy.

Research in Germany has shown that (at the regional level) the perceived size of the out-group population invokes anti-minority attitudes, while actual minority size does not have an impact (Semyonov et al., 2004). More research is needed to explain why there is such a mismatch between perceived size – a psychological construct – and actual size and which people are most inclined to overestimate the presence of the out-group.

At the neighbourhood level, more interethnic exposure leads to more support for a generous policy. Contacts with (or at least exposure to) out-group members works as a counterforce to the negative sentiments towards immigrants (see also Oliver and Wong, 2003). This is encouraging finding is corroborated by our research for the DIVERCITIES-project in 13 European cities and Toronto. As reported earlier in this journal (Bolt et al., 2017), residents living in places with more diversity were less likely to have a negative attitude towards newcomers than residents in more homogeneous neighbourhoods.

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Dr Gideon Bolt Faculty of Geosciences – Utrecht University Tel: +31 30 253 1399 G.S.Bolt@uu.nl www.uu.nl/staff/GSBolt/0

The 21st Century belongs to Canadian agriculture

Canadian agriculture has deep roots and the government is working to build a future for the next generation of farmers, says Minister Lawrence MacAulay

The Canadian agriculture and food industry is one of the key drivers of Canada's economy. The sector "from gate to plate" generates over \$100 billion of our GDP and over \$60 billion of our exports. With our relatively small population and high productive capacity, Canada is the world's leading agricultural trader on a per-capita basis, and a top-five importer and exporter. At the foundation of this economic engine are over 200,000 farmers and thousands of food processors.

"The future is bright for Canada's agriculture and food industry, with a growing global middle class looking for products our farmers and food processors can deliver. A report by the Finance Minister's Advisory Council on Economic Growth argues that Canadian agriculture can be a key part of Canada's path to prosperity in the coming decades."

Agriculture is a core priority for the Government of Canada. As Minister of Agriculture and Agri-Food, my mandate is to support the agricultural sector in a way that enables it to be a leader in job creation and innovation.

This past July, agriculture ministers from across Canada reached a historic agreement on the Canadian Agricultural Partnership. Agriculture is a shared jurisdiction in Canada. Under the Partnership, the federal government, provinces and territories will invest \$3 billion over 5 years in programmes to help Canada's agriculture and food sector innovate, grow and prosper.

Trade is a key priority of the Partnership. On average, about half of the value of Canadian agricultural product is exported. We are the world's top exporter of canola, flax, pulse crops and wild blueberries, and a top-three exporter of wheat and pork. Canadian agri-food exports have been climbing at about 10% annually, and the recent Canadian budget set sights on \$75 billion a year by 2025. We continue to strengthen our global trading partnerships, pursuing agreements such as the Comprehensive Economic Trade Agreement with the European Union, as well as discussions with China and other key Asian markets, while strengthening our ties with our largest trading partner, the United States. To ensure our products get to our global customers reliably and efficiently, we have introduced legislation to strengthen Canada's rail transportation system.

Research and development is at the heart of Canada's global agricultural success, dating back to the development of Marquis Wheat, which opened up Canada's Prairies to agriculture a century ago. Our ongoing private and public sector investment in research, including investments in the federal budget, will be critical to Canada's ability to help feed the world.

Action on the environment is also key to helping the sector meet the growing global demand for food sustainably. The government is investing in programming to help farmers practice climate-smart agriculture. As well, new crop varieties with built-in disease and drought resistance, and precision farming technologies, are all helping farmers reduce pesticide and fertiliser use, while conserving water.

Looking forward

The future is bright for Canada's agriculture and food industry, with a growing global middle class looking for products our farmers and food processors can deliver. A report by the Finance Minister's Advisory Council on Economic Growth argues that Canadian agriculture can be a key part of Canada's path to prosperity in the coming decades.



As Canadians celebrate 150 years of our country this year, exciting opportunities lie ahead for the next generation of food producers. Youth is a key priority for the Government of Canada, and we are working hard to inspire young people to become the agricultural leaders of tomorrow.

"Agriculture is a core priority for the Government of Canada. As Minister of Agriculture and Agri-Food, my mandate is to support the agricultural sector in a way that enables it to be a leader in job creation and innovation."

Young Canadians have the talent and drive to lead the future growth of Canada's economy – and to do that, they need practical work experience. Under the federal Youth Employment Strategy, the government has invested over CAD\$7 million in the Agricultural Youth Green Jobs Initiative, which brings young people and farmers together to gain job experience and improve the environment. The government also offers an agricultural internship program, and we are proud supporters of 4-H Canada, including their recent global summit in Ottawa. The government also offers loan guarantees and Young Farmer Loans to help new and beginning farmers get established in this capital-intensive industry. As well, youth will be key focus of the Canadian Agricultural Partnership.

Over a century ago, Canada's Prime Minister Wilfrid Laurier said that the 20th century belongs to Canada. Well, I firmly believe that the 21st century will belong to agriculture.

Lawrence MacAulay Minister of Agriculture and Agri-Food Agriculture and Agri-Food Canada http://www.agr.gc.ca/ www.twitter.com/AAFC_Canada

Water and Agriculture in Europe

Commissioner Phil Hogan recently shared his thoughts on the role of agriculture in water sustainability, during a speech at European Policy Centre Dialogue

The role of water and agriculture sustainability is a complex policy issue and must be approached in a holistic way. We know that a clean and reliable water supply is absolutely fundamental to human, animal and plant health.

We know that agriculture is a water-intensive industry. We know that as the global population continues to increase, there will be more mouths to feed from a farming point of view. And we know that farming and food production need to do meet this challenge while also doing more to fight climate change, preserve biodiversity and maintain the environment.

So how do we make progress? The first step is to create a broad awareness among policymakers and stakeholders about the magnitude of the challenge.

Thankfully, there are positive signs that water and agriculture are growing in importance on the international agenda. The Agriculture Ministers' Declaration at the 2017 G20 meeting underlines that agriculture and forestry can provide valuable solutions for water sustainability.

Water and agriculture are also at the core of the 2030 Agenda for Sustainable Development. The Sustainable Development Goals on sustainable water management (SDG6) and sustainable agriculture (SDG2) outline some of the challenges involved, and present some useful targets.

Sustainable water management is the explicit target of Sustainable Development Goal (SDG) 6, which calls for a global agriculture able to enhance farming productivity while reducing the impact on the availability and quality of water. At European level, we take these international commitments seriously and we are in the process of formulating a roadmap for action. And it is clear that we have to act now. We cannot wait, the challenges are pressing and we all have an interest in tackling them immediately.

For this reason, EU Environment Commissioner Vella and I established a Task Force on Water to develop a long-term alliance between different Commission services. The task force looks at various ways of improving water status in the EU in a cross-sectoral manner and with immediate effect.

Joint work has been initiated to improve the implementation of existing legislation, to boost necessary investment and spread best practice with a view to improving water sustainability in EU agriculture.

The Water Task Force spearheaded the Commission Staff Working Document on "Agriculture and Sustainable Water Management in the EU", published on 28th April 2017.

This document shows in a clear and specific way the Commission's commitment to achieve these goals. It finds that current EU agricultural and water legislation provides a wide range of adequate policy tools for improving water status, boosting investment and increasing knowledge and innovation roll-out.

Dedicated rural development measures can do important work by supporting environment and climate action, Water Framework Directive-targeted measures, knowledge transfer, and especially investment support.

But using existing legislation is not enough. Sharing best



practice and boosting innovation and related investment is the key to success. Numerous EU research and innovation funds are already supporting projects to improve both the quantity and quality of our water supply. We have compiled a detailed report outlining farm level adaptation strategies which already exist or can be developed to deal with water scarcity.

"It is absolutely crucial that we ensure the sustainable use of fertiliser and pesticides, including proper management of manure and slurry. Many of the challenges we face related to water stem from an inappropriate use of inputs."

We have invested in new technologies such as robots measuring water consumption in wine production, 3D sensors to measure plant growth, and Unmanned Aerial Vehicles (UAVs) for precision agriculture applications such as water stress monitoring, detection of nutrient deficiencies and crop diseases.

And this year we are backing new projects to tackle the pollution of water sources from pesticides and fertilisers used in farming systems. In addition, my services in DG AGRI have demonstrated a clear commitment to the Commission's Circular Economy Action Plan. Water reuse is an area that can have both quality and quantity implications. The minimum quality requirements currently under preparation aim to support the reuse of treated wastewater in safe and cost-effective conditions.

All these measures have a role to play, but the mobilisation of additional funding for necessary investment is crucial.

On top of the Structural Funds, the potential provided by new financial instruments should be seriously explored. In this respect, the new agriculture window under EFSI 2.0 is an opportunity to be seized. Work is currently ongoing to identify a portfolio of investments and projects.

But whatever we do, there is one obvious fact that we must not forget: We need to work with farmers and incentivise their ability to achieve environmental and climate targets. This means giving them better tools both from a policy and practical point of view.

Improving poultry production through precision fertility management

University of Oxford's Tommaso Pizzari argues that fertility management of commercial flocks requires a precision approach

The poultry food system is one of the largest and fastest growing food industries worldwide. It is estimated that more than 50 billion chickens are reared globally every year, for both eggs and meat (broilers). The poultry sector currently outcompetes other meat markets, and more than half of all the meat produced by 2025 worldwide is expected to be from chickens. Meeting the demands of such an expanding market presents a formidable challenge of fertility management for the poultry industry.

A fundamental component to this challenge rests on ensuring consistently high rates of fertility. Yet, the growth of the poultry industry has corresponded with drops in fertility of commercial stocks. Last June, the Wall Street Journal reported that over the first five months of 2017, the percentage of eggs that hatch in US broiler chickens was the lowest in over a decade, with drastic financial repercussions for the poultry industry. A 1% drop translates to an estimated \$121 million loss.

Whilst the poultry industry has historically regarded fertility as a physiological problem of some males, on-going research is revealing that this view is misleadingly simplistic. The reality is that variation in fertility is a complex issue, because fertility is determined by the interaction of male and female factors at multiple levels.



Male effects

Artificial insemination experiments combined with recent technological advances in computer-assisted sperm analysis (CASA), have illuminated the mechanisms underpinning the fertilising efficiency of an ejaculate. Both, the number of sperm inseminated and their motility, often measured as swimming velocity, determine the probability that an ejaculate will fertilise the eggs ovulated over successive days following insemination. These factors are especially important in predicting paternity when the ejaculates of different males compete to fertilise the same set of eggs, as often happens in chickens.

A significant development is the discovery that sperm performance is strongly

influenced by seminal fluid, the physiological non-sperm liquid component of an ejaculate. Recent proteomic studies indicate that chicken seminal fluid is very complex, comprising of 1,400-1,500 proteins implicated in a diverse array of functions. Experimental evidence suggests that seminal fluid can influence sperm swimming velocity, and whole-genome proteomics of the seminal fluid of ejaculates with divergent sperm motilities have begun to shed light on the proteins implicated in sperm swimming velocity. This is a promising approach that can capitalise on the publication of the chicken genome to pinpoint those proteins responsible for male fertility.

Ejaculates characteristics vary hugely within individual males. Much of this

variation is explained by sexual behaviour. The number of sperm, sperm motility and the abundance of individual seminal fluid proteins change drastically because of depletion over successive mating and because of male preferential investment in certain mating opportunities.

For example, males often invest preferentially in mating with sexually novel females or females that mate with other males. As an extreme form of differential sperm allocation, males often mate without delivering any semen. We have shown that this puzzling behaviour makes evolutionary sense, because it reduces the receptivity of a female to mating with other males while simultaneously enabling a male to save resources for more valuable mating opportunities soon. These behavioural responses have crucial but little appreciated - repercussions on patterns of fertilisation.

Female effects

It is becoming clear that females play a fundamental role through their mating behaviour and their response to inseminations following mating. For example, our work has shown that females can control mating frequency and can change when in the day they mate plastically in response to the social environment. This is important because the probability that an insemination results in fertilisation changes drastically over the day. Female responses after mating also have a crucial impact on the fertilisation success of an insemination.

Our work has shown that females can eject up to 90% of an insemination immediately after mating, and that the probability of semen ejection changes predictably across males and with mating order, drastically reducing the chances that some males will achieve fertilisation despite mating. Other post mating responses are more subtle, but no less influential. Sperm are stored in specialised female sperm storage organs for up to three weeks.

While the mechanisms underpinning female sperm storage remain unresolved, our work suggests that ejaculates are not treated equally by the female reproductive tract. Differential female sperm utilisation is influenced by the genetic similarity between a male and a female and female immunological responses to his sperm. These female effects are important in determining the fertilisation success of different partners, and can also reduce the number of eggs fertilised, particularly in conjunction with male effects.

Flock-level effects

While the notion that fertility is strongly influenced by male or female effects may come to no surprise, less appreciated is the fundamental role played by social interactions among individual birds within the flock. In fact, this is an aspect of fertility that has been largely ignored by the poultry industry. Chicken flocks are tightly structured in sex-specific social hierarchies. The position of individual birds within the hierarchy determines access to mating opportunities and the exclusivity of these mating interactions.

Factors such flock size, sex ratio and the structure of the environment further modulate these effects – by determining who gets to mate with whom, how often and when in the day. These effects can result in physiologically fertile individuals underperforming with consequences for the fertility of the entire flock, with drastic consequences for the reproductive success of individual birds and the fertility of the whole flock. Importantly, social dynamics that lead to poor fertility often also lead to poor animal welfare with intense male sexual harassment of females.

"Our work has shown that females can eject up to 90% of an insemination immediately after mating, and that the probability of semen ejection changes predictably across males and with mating order, drastically reducing the chances that some males will achieve fertilisation despite mating."

New approaches

The complex nature of fertility means that traditional tools based on single assays of male fertility traits are often inadequate. Instead, a precision approach is required, developing management strategies tailored to individual flocks. These strategies must integrate information at different levels, combining multiple male fertility traits with data on female sperm utilisation and - crucially - patterns of socio-sexual behaviour. This integrated approach promises to deliver a more efficient management of fertility in commercial flocks, with possible benefits for animal welfare.



Tommaso Pizzari Professor University of Oxford tommaso.pizzari@zoo.ox.ac.uk



← Continued from page 345

This is why the Commission has taken concrete action to support data-driven farming and precision agriculture as one important step in dealing with the problem.

Water efficiency and water can only be fully addressed by making proper use of new technologies, such as big data, remote sensors, and artificial intelligence. These will help farmers to maximise both the economic output and environmental performance of their farms.

"Water and agriculture are also at the core of the 2030 Agenda for Sustainable Development. The Sustainable Development Goals on sustainable water management (SDG6) and sustainable agriculture (SDG2) outline some of the challenges involved, and present some useful targets."

It is absolutely crucial that we ensure the sustainable use of fertiliser and pesticides, including proper management of manure and slurry. Many of the challenges we face related to water stem from an inappropriate use of inputs.

Therefore, I deem it absolutely essential to enhance

our policy tools in relation to inputs. Proper nutrient management on farms is vital and will receive more attention in the future CAP than is currently the case.

New solutions

In this respect, I am happy to announce that various Commission services are collaborating to set up a platform for on-farm nutrient management.

This tool will be directly accessible for farmers and integrates information from various sources including satellite data. On this basis farmers can make informed decision about nutrient requirements for each land parcel.

This will enable not only a more efficient nutrient use overall but can also have the positive knock-on effects of boosting water use efficiency and emissions reduction.

If we can apply this tool on a majority of farms across Europe, it will be a major achievement and a game changer in farm management practices. And I am happy to announce another major achievement: we are setting up a Knowledge Hub on Water and Agriculture.



Whatever we do, information is the key to success. Knowing where the real problems are crucial if we want to develop appropriate solutions. Therefore, one of the first steps of our water task force was to make sure that all relevant and existing data is compiled and accessible to the wider public. This is why we set-up a Knowledge Hub on Water and Agriculture in partnership with the European Joint Research Centre.

This Knowledge Hub will link and integrate existing sources of information and generate new knowledge as well. The information will be widely accessible via an internet portal. It can therefore be used by the Commission, by Member State administrations, as well as by stakeholders to identify the best solutions for developing targeted and tailor-made policy tools in the field of water and agriculture.

As you can see, my colleagues and I have worked hard over the past two years to place water sustainability at the core of our work. The Commission is pleased to be leading from the front in this shared challenge, but we need our national, regional and local authorities to also take up the fight. I therefore call on all participants to highlight these possibilities at national level and encourage your Member State authorities to actively engage with the Commission services in these endeavours.

"We have invested in new technologies such as robots measuring water consumption in wine production, 3D sensors to measure plant growth, and Unmanned Aerial Vehicles (UAVs) for precision agriculture applications such as water stress monitoring, detection of nutrient deficiencies and crop diseases."

This is an issue that concerns all of us, and it is only when all of us are working together that we will begin to make real headway. It is a field which will remain relevant – today and in the future.

Water sustainability will remain a central challenge for the future CAP. But as I hope I have outlined, we can already make real progress with the tools we currently have and this is what we should focus on.

This article is based on a speech given by Commissioner Phil Hogan at European Policy Centre Dialogue on "Water & Agriculture in Europe", Thursday 28th September 2017, Brussels. You can read more at: https://ec.europa.eu/commission/commissioners/2014-2019/hogan/announcements/speech-european-policy-centre-dialogue-water-agriculture-europe_en

Phil Hogan

Commissioner for Agriculture & Rural Development European Commission Tel: +32 2 299 96 96 https://ec.europa.eu/commission/commissioners/2014-2019/hogan_en www.twitter.com/PhilHoganEU

How can minor cereals enhance diversity and contribute to human nutrition

Dagmar Janovská and Martina Eiseltová from HealthyMinorCereals project explain the scope of their research concerning five minor cereals

The multidisciplinary HealthyMinorCereals project respond to consumers' increasing demands for nutritious and innovative food produced sustainably

he intensification of agriculture that took place since the Second World War has resulted in impoverished agricultural landscapes with many negative impacts on the environment. Increased mechanisation and farm size, simplified crop rotation and an increase of less-diverse cropping systems along with the loss of landscape features, such as field noncrop margins, tree alleys and other important landscape elements, e.g. wetlands, have led to substantial reduction in landscape diversity and opening of water and matter cycles.

Whilst nature tends to recycle water and nutrients in short, localised cycles, modern conventional agriculture is dependent on high external inputs (fuel, fertilisers, pesticides and irrigation) and typically results in increased soil erosion, nutrient leaching, and water loss through artificial drainage systems as well as fast surface runoff.

Further problems have been brought about by intensive crop breeding, focused primarily on achieving high yields. Crop production has doubled, but at a high cost. As the breeding programmes have focused only on few crop species, the variation of crops



Emmer wheat – black glume colour

grown commercially for human consumption has been greatly diminished.

As a result, cereal production in Europe is today dominated by two cereal species – common wheat and barley – that have been intensively bred for high yields, whilst many traditional cereal species and varieties have vanished from fields or their cultivation areas have substantially decreased.

New interest in traditional cereal species

Demands for a more sustainable agriculture, less dependent on external inputs and better suited to local conditions, have revived interest in diverse traditional cereal species. No longer widely grown in Europe, they are now classified as 'minor cereals'. Yet these minor cereal species are well suited to organic and sustainable agriculture. They can also have higher concentrations of micronutrients and bioactive compounds essential for a healthy nutrition. As the demand for healthy, nutritious food is growing amongst consumers, the interest of food producers in traditional cereal varieties has grown.

The EU-funded HealthyMinorCereals project has focused its research on five minor cereals – einkorn, emmer, spelt, rye and oats, in particular, investigating genotypes that have fallen out of use but have been stored in gene banks. It is being found that some of the less-developed cereal species and varieties may have higher concentrations of nutrients and bioactive compounds, and hence higher nutritional value than the high-yielding varieties. Also, they are more robust to with-



The HealthyMinorCereals project team

stand adverse climatic conditions, resist crop diseases, grow better on marginal soils and are suitable for low-input, more sustainable, agriculture. the successful development of minor cereals products and marketing strategies and;

- Aims of the HealthyMinorCereals project:
- Employ state-of-the-art methods for genetic characterisation of minor cereals and their wild relatives, to identify genetic markers related to disease resistance and nutritional quality that can be used in minor cereal breeding programmes;
- Test minor cereal genotypes with promising traits for yield, resistance to fungal diseases, and nutritional quality in field trials performed in European regions with differing soils and climates, to optimise cultivation methods under organic and conventional agricultural systems;
- Analyse grain nutritional composition of minor cereal varieties and evaluate nutritional impacts on human cells using human cell cultures;
- Optimise grain processing methods (such as milling) and final product manufacturing (baking, etc.) to preserve high nutritional quality of final products;
- Study producer and consumer behaviour and expectations to aid

 Provide effective knowledge and technology transfer especially to European small and medium sized companies (SMEs) involved in minor cereal production, for rapid and comprehensive utilisation of project results.

In an upcoming series of articles, we will focus on new findings concerning the genetic variability of minor cereal species and varieties and reveal genotypes with promising traits for yield, resistance to fungal diseases and nutritional quality, present results on the nutritional composition of the studied minor cereal varieties and their nutritional impacts on human cells, address suitable grain processing methods that preserve a high nutritional quality of the final food products, and present case studies on producer/consumer behaviour that may help to develop suitable marketing strategies to promote minor cereals in the human diet.

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Project partners

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Dagmar Janovská Project Coordinator Tel: +420 233022406 janovska@vurv.cz

Martina Eiseltová Dissemination Manager Tel: +420 233022295 eiseltova@vurv.cz http://healthyminorcereals.eu

The approval process of pesticides and the science behind it

Graeme Taylor, director of public affairs at European Crop Protection Association reveals the impact of technology on the pesticide approval process

Today we live in an era where misinformation can spread at an alarming speed and where the intuition of what should be right is more important that what is fact. An era of Facebook science, of twitter science, where science is judged not by its voracity but based on the number of likes it received or the number of times it was retweeted.

Industry studies are not biased

For our industry, the pesticide industry, the impact of this is felt particularly acutely, when NGOs opposing glyphosate launch attacks on Europe's regulatory authorities as not being independent and their conclusions having been improperly influenced by industry, simply because they don't like their conclusions.

There is 90,000 pages of evidence, and 3,300 peerreviewed studies, and regulatory authorities around the world that support the re-approval of glyphosate. Only the International Agency for Research on Cancer (IARC) has said that it is probably carcinogenic and that is the one study – an outlier – that those opposed to its approval, hang on to; dismissing all other studies for a host of non-scientific reasons.

One of the main accusations is that the science that the industry produces is biased, as it is of course selfserving. What is forgotten is that all studies that we carry out have to be in accordance with demanding international standards such as the OECD's Good Laboratory Practice (GLP), and must be performed by certified third-party laboratories. These standards ensure that all data submitted is of high quality and is reliable testing data. This is why ECHA and EFSA have considered our studies in their reviews.

Industry studies are not hiding anything This also means that all our studies can be reproduced - so any researcher considering the same parameters will arrive at the same conclusions. We are also very often accused of not submitting data that would be unfavourable to us – that is simply not true. All tests – whether we like the result or not – must be submitted; there is no cherry picking.

Anyone is free to submit studies in to the approval process if they can meet these standards. The conclusions of studies that do not meet standards, like GLP, are not reliable and cannot be reproduced.

Unfortunately, this doesn't stop them being published or influencing the public debate, because NGOs of course don't want to point out the inherent weaknesses in their conclusions.

Regulators are not "in the pocket" of industry Another accusation that is also very often thrown our way is that studies are not available for public scrutiny. While indeed some elements of the studies that are withheld from full public release are done so to protect proprietary or personal data, it is false and misleading to claim that studies are not available to the public.

In almost all cases, summaries of the aggregate data are released to the public by regulators, industry, or both. For Glyphosate, on the basis of full transparency, an Open Reading Room in September and October 2016, whereby any person could come and review all of the documents in a searchable, electronic format.

Perhaps there are better ways of making this information available – however it is wrong to say that the data is being hidden.

The requirements for such studies are so robust that they leave no chance for the company's own interpre-



tation or for omission of data. They are not essays – we submit hard data to the regulator. The company submits more than 100 tests covering chemistry, biology, toxicology and environmental chemistry. In 2008 it took 8 years to develop and register a product, now it takes 11. This is mainly due to the increased level of tests that the companies need to conduct and submit. The European process is the most stringent in the world. This is why Europe enjoys the safest food in the world.

Very often we hear that these evaluations should be based solely on studies from "independent" scientists and laboratories. Because Europe's regulatory authorities have such strict and requirements for safety evaluations, to meet OECD's standards, the cost to fund such evaluations is incredibly high. The total amount to develop and register one substance is around € 250 million – this is increasing all the time. As such, in the EU's current regulatory system, the only viable option is for regulators to require that companies fund these studies themselves through third-party, GLP-certified laboratories.

The alternative is the use of tax money or other public funds for this purpose. This would of course significantly reduce the cost for the manufacturer, who is ultimately the main party that would benefit from the commercialisation of the approved substance, but doesn't seem particularly fair on public funds.

On the other hand, anti-pesticide activists often promote non-industry funded studies and claim such studies as "independent," while in reality such studies are typically developed and funded by special interest groups.

The propensity for NGO papers to be hailed as an "important new study" while a rigorously researched, industry-funded study is dismissed as an "industry cooked report" needs to end. ■

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Graeme Taylor Director of public affairs

European Crop Protection Association Tel: +32 2 663 15 50 ecpa@ecpa.eu www.ecpa.eu www.twitter.com/cropprotection



Food production: The role of the animal health industry in Europe

Secretary General of AnimalhealthEurope Roxane Feller, outlines the important role that the animal health industry plays in food production in Europe today

urope benefits from a sophisticated and highly integrated food safety system, supported by comprehensive scientific advice all along the food chain. As the world's largest exporter of agri-food, valued at over €135 billion, with animal-sourced products representing 43% of EU agricultural output, livestock farming in Europe today consists mainly of pigs, cattle, and poultry, and a small percentage of sheep and goats, for meat products. Other animal products include milk, eggs and honey.

Innovation through science and technology has allowed European agriculture to play a major role in securing a safe and sustainable food supply, and animal medicines offer innovative solutions for livestock farmers to help optimise health management and prevent and cure disease outbreaks.

Animal disease

The OIE estimates that 20% of global food production is lost due to diseases in farmed animals. While this figure may be slightly lower in Europe, trade restrictions or bans placed on animal produce after disease outbreaks, coupled with control measures imposed (e.g. culling of animals) and the associated costs of managing disease, can have a major impact on the agri-food economy.

Recent disease outbreaks such as the H5N8 avian influenza strain in 2016, serve as a stark reminder. Going back further, the eradication of foot and mouth

disease (FMD) in Europe in the 1990s, led to lessened disease prevention measures and a non-vaccination policy. This had disastrous consequences for several Western European countries in 2001 when FMD resurfaced, with over 4 million animals being slaughtered in the UK as part of disease control efforts.

Innovation

For agriculture in Europe to remain viable there is an urgent need for innovation-driven policies. Advances in science and technology provide the potential to develop new or improved vaccines (such as DIVA vaccines for FMD), pharmaceuticals and diagnostic tests for the prevention and control of animal disease. Further research and the use of biotechnology can also lead to improved stability of products or deliver more effective and simpler routes of administration, making the veterinarian's job easier.

New developments in formulation technology for example, can bring significant improvements in animal health solutions, but applying these improvements to existing products requires a major investment, as regulatory studies need to be repeated, and there is currently no data protection period for such advances.

EU legislation

In the forthcoming legislation on veterinary medicines, a proposal has been made in the draft text for a 4-year protection period before a second company can crossrefer to the originator's new data – limited to antibiotic products only. The animal health industry recommends that this proposal be opened up to all products as the role of other important product classes such as parasiticides, needs to be recognised.

Fostering innovation through a harmonised system where resources can confidently be invested in R&D, means that new medicines can be developed to fill gaps in treatment options, ultimately contributing to a safer and more sustainable food production.

About the author: Roxane Feller is Secretary General of AnimalhealthEurope (formerly IFAH- Europe), the representative body of manufacturers of animal medicines, vaccines and other animal health products in Europe. With membership covering 90% of the European Market, AnimalhealthEurope represents innovators and generics alike, as well as large, medium-sized and small companies.



Secretary General of AnimalhealthEurope Roxane Feller

More information on www.animalhealtheurope.eu, on Twitter as @animalhealthEU, and on Facebook: www.facebook.com/WeCare.petsEurope .

You can also visit the Discontools project at: www.dis-<u>contools.eu/</u>. This online database identifies research gaps on vaccines, pharmaceuticals and diagnostics for the control of more than 50 priority infectious animal diseases.



THE VOICE OF THE ANIMAL **MEDICINES INDUSTRY**

Roxane Feller Secretary General AnimalhealthEurope Tel: +32 2 543 7560 info@animalhealtheurope.eu www.animalhealtheurope.eu www.twitter.com/animalhealthEU

USDA's high-tech tools to identify dangerous pests

Greg Rosenthal of the U.S. Department of Agriculture's (USDA) lifts the lid on their work with digital identification tools to identify dangerous pests

very day, the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service and its partners intercept beetles, flies, moths, snails, slugs, and other creatures at U.S. ports of entry. Most are harmless, but others could devastate our crops and ecosystems.

The agency's Plant Protection and Quarantine (PPQ) programme must quickly and accurately figure out which is which to keep international cargo – and economic activity – moving as efficiently and safely as possible. PPQ's Identification Technology Programme (ITP) has developed an array of high-tech pest identification tools to do just that.



PPQ Biological Scientist Terrence Walters leads a workshop on pest identification software for a Rutgers University Course called "Plant Biosecurity Issues and Technologies."

"Our digital identification tools are some of the go-to resources for PPQ pest identifiers at plant inspection stations and for U.S. Customs and Border Protection agriculture specialists at our ports," said ITP biological scientist, Terrence Walters. "With these tools, they can quickly identify certain types of pests and determine the appropriate safeguarding action to take."

Over the last 10 years, Walters' team of three, with the help of scores of experts, created three forms of digital pest identification products, that are freely available to the public:



ID Tools

<u>ID Tools</u> includes more than 40 websites covering insects, mites, mollusks, plants, seeds, and dried

botanicals. Nearly 18,000 users visit these websites each month. The sites use identification key software called "Lucid", that lets users select a specimen's distinguishing characteristics – colour, shape, size – with the aid of illustrations and photographs. Each characteristic they choose can eliminate up to hundreds of possibilities and narrow the search to the exact species.

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This Lucid Mobile app includes a key, fact sheets, and an anatomy guide for	🛱 SEP 29, 2015	This Lucid Mobile app includes a key and	This Lucid Mobile app includes a symptom-based key and fact sheets for
	This Lucid Mobile app includes keys and	fact sheets to assist in the screening of	

Mobile apps

Mobile apps make the identification keys and fact sheets from 13 of the ID Tools available to you, anywhere and anytime on your iOS or Android device. Once installed, they can be used offline. They are available for download from iTunes and Google Play (search for "ID Tools").



Screening aids

Screening aids present valuable, visually rich identification information and directions in a PDF document. They are specifically designed for pest surveyors to use when they screen insect traps, looking for pests targeted by PPQ's Cooperative Agricultural Pest Survey programme. ITP created 36 screening aids, ready for downloading.

The international plant protection community has shown keen interest in this technology. Walters presented his team's work to more than 120 country delegations at the 11th annual meeting of the International Plant Protection Convention's (IPPC) Commission on phytosanitary measures in Rome, Italy. The IPPC Secretariat, impressed by the quality, quantity, and accessibility of PPQ's digital screening tools, has asked ITP to help other countries develop similar tools.

Closer to home, PPQ grasshopper surveyors in Western States use the web-based version of the <u>grasshopper</u> <u>app</u>. They bring field specimens back to their offices in the spring and summer, to identify the species and developmental stage. This information helps PPQ determine the right pesticides, to use or recommend protecting rangeland forage from large, damaging grasshopper and Mormon cricket outbreaks.

Nationwide, ITP's work taps the expertise and resources of the greater plant protection community. For example, in 2015 the programme partnered with the University of Georgia's Center for Invasive Species and Ecosystem Health – also known as "<u>Bugwood</u>" – to significantly update four of <u>Bugwood's image sites</u>, making them more user-friendly.

Even more recently, ITP has been collaborating with several university museums to solve one of its biggest challenges: obtaining images of pests not available in any existing image collection. The museums provide specimens that the team photographs in ITP's high-tech imaging studio. These new images will supplement the images in <u>Bugwood's ITP Node</u> and the more than 100,000 images in imageID, ITP's online imageID database for port identifiers.

"Each year we build new products, and we continually update and revise our tools," said Walters. "Safeguarding work is non-stop and worldwide. ITP's many tools make that work even more effective."

Greg Rosenthal Communications specialist at USDA

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service Tel: +1 844 820 2234 www.aphis.usda.gov/aphis/home Twitter: <u>@USDA_APHIS</u>

Artificial chromosome technology in the modification of plants

James A. Birchler from University of Missouri, Columbia gives an absorbing insight into research around the modification of plants for food crops

f egos, politics, greed and "us versus them" attitudes don't get in the way, are we humans capable of elevating our standard of living, or at least maintaining it, going forward? At 7+ billion people on Earth at present, there can be no debate that we have altered the state of Nature. As the human population expands, as is apparently inevitable, what are the consequences? Never before in world history do we know more about the workings of the universe through scientific investigations than now and never before has the general populace confounded the use of that knowledge for their own benefit. What kind of world do we want our descendants to inherit?

The whole of civilization as we now know it depends on the modification of plants for food crops. Since the advent of agriculture, human civilizations have continued to modify plants for their medicinal and nutritional benefit. This human tradition must continue to satisfy the coming needs for the food supply. Considering the impending global population pressures and limited resources of the planet, crop improvements must continue to forestall internecine misery in our irreversibly interconnected world.

Genetic technologies for crop improvement will undoubtedly be needed going forward to improve production processes and nutritional content. Molecular breeding, genome editing and a better understanding of the basis of quantitative traits will be important contributors to the future success of agriculture. And within that realm transgenic technologies will be needed to advance the work.

"The whole of civilization as we now know it depends on the modification of plants for food crops. Since the advent of agriculture, human civilizations have continued to modify plants for their medicinal and nutritional benefit. This human tradition must continue to satisfy the coming needs for the food supply."

However, current transgenic technologies are confounded by several factors. Firstly, the introduction of genes into a target genome is currently quite cumbersome and time consuming for basically all crops. Further, the transgenes are randomly integrated into the chromosomes and thus can be mutagenic if they land within an endogenous gene. This random insertion results in unpredictable expression levels from one site to another. And the insertion will be linked to resident genes that will be difficult, if not impossible, to separate from the transgene if the latter is to be exchanged to the genetic background of other varieties of a crop through multiple generations of genetic crosses.

It is the hope of artificial chromosome technology that these issues can be overcome for transgenic studies and the benefits that they provide. Small artificially constructed chromosomes carrying multiple transgenes and a means to amend them will be independent of the endogenous chromosomes and thus will facilitate transfer across different varieties. Such minichromosomes would also use so called "stacking systems" to continue to add sequentially new genes for various plant properties to the chromosomal entity. These targeting integration methods, as opposed to random integrations, would help insure faithful and robust gene expression. They could also be combined with haploid breeding procedures that are commonly used for many crops to produce new lines with improved characteristics.

Haploid breeding procedures are used to produce varieties with new genetic configurations. The procedure works by generating individuals with only a single set of the chromosomes instead of the normal two. These individuals are then treated in various ways to double the chromosome number creating a unique constellations of gene variants with the usual two sets of chromosomes that are identical to each other. Very often in these haploid-inducing procedures there is an additional chromosome that is retained in the otherwise haploid. If it is a normal chromosome, those individuals are highly defective.

However, one might imagine that if an artificial chromosome could be thusly

transferred, the ability to introduce the transgenic cargo to multiple target varieties would be greatly facilitated. This would be especially useful if there is a varietal specific limitation on plant transformation, in which case the transgenes would be introduced readily into the recalcitrant variety without the need for several generations of recurrent crosses.

A related application would be if genomic editing machinery were introduced onto an artificial chromosome that could then be transferred to a haploid for editing at multiple sites for a massive scale edit during the haploid phase. This would provide the machinery a whole generation to perform its edits and would not be complicated by different changes on the two chromosomes in a diploid that are known to occur. Each edit in a haploid would be unique and captured at the chromosome doubling stage. With the editing machinery on an independent chromosome, it could be easily removed in the next generation.

Also, at present, there appears to be a size limit on genome additions using editing; artificial chromosomes can provide a means for much larger additions. Current developments in progress are centred toward adding 100 kilobase increments to artificial chromosomes. As this becomes possible, artificial chromosomes can be grown in leaps and bounds to sizes that were not conceivable previously. One can imagine an artificial chromosome carrying innumerable genes for various properties.

Creating chromosomes

The process to generate artificial chromosomes has now been demonstrated in several plant species by various laboratories. These include maize, rice, wheat, Brassica, barley and Arabidopsis. Thus, it would seem that the technique to set the foundation for artificial chromosomes in most crop species is at hand. The vast majority of calories used by humans are derived from maize, wheat and rice; it is now possible to develop artificial chromosomes in all of these species for future crop improvement.

"An area that has received little attention is the potential application of artificial chromosomes in breeding programs for otherwise vegetatively produced crops such as cassava, banana/plantain, potato, sweet potato, sugar cane, cacao and rubber."

Artificial chromosomes have the potential to carry whole biochemical pathways for new properties to be conferred onto plants or to use plants as biochemical factories for useful metabolites or proteins. Biochemical pathways that confer tolerance to various stresses such as drought or to various biological agents such as fungal, bacterial, viral or insect pests could be combined on the chromosome. There are likely many such compounds and proteins in the biosphere that could confer these properties and that have yet to be discovered. When discovered, modified if need be and combined appropriately, they portend potential benefit to crop plants.

An area that has received little attention is the potential application of artificial chromosomes in breeding programs for otherwise vegetatively produced crops such as cassava, banana/plantain, potato, sweet potato, sugar cane, cacao and rubber. The use of transgenes on an independent chromosome would facilitate their transfer to new genetic backgrounds. Many of these species are difficult to transform and breed to develop the best combinations of genes for improvements. Artificial chromosomes could be used to transfer the desired characteristics to new genetic backgrounds with selection for the best performers that could be propagated as clones to the field.

In the future, one could anticipate crop improvements to which artificial chromosome technology might contribute include enhanced nutrition, reduction in fertiliser and herbicide usage to reduce pollution, increased biomass, yield and harvest efficiency, tolerance to drought and other abiotic stresses and resistances to viral, bacterial, fungal and insect pests among other possibilities.

Of course, genetic manipulation does not stand alone. There is a need for maintenance of diverse crops together with their existing natural variation and conservation measures on cropland to insure their continued fertility. Homo sapiens translated from the Latin is "Wise man". Can we live up to our name by a collective effort to insure food security?

University of Missouri

James A. Birchler Curators' Distinguished Professor of Biological Sciences University of Missouri, Columbia Tel: +1 573 882 4905 BirchlerJ@Missouri.edu http://maizeminichromosomes.missouri.edu

DNA markers for wheat genetic improvement

Director of USDA Central Small Grain Genotyping Lab, Guihua Bai turns the spotlight on to the wonderful world of wheat and DNA markers

heat is the second most produced crop, with about 700 million tonnes of grain produced every year worldwide and provides more than one fifth of the calories and protein consumed by the human beings (FAOSTAT 2014). A rapid growing human population demands faster increases in wheat yield globally in near future. In addition, climate change adds more abiotic and biotic stresses to wheat production, which brings great challenge for breeders to meet the increased demand, which is where DNA markers can help.

Wheat traits including yield, quality, as well as resistance to different biotic and abiotic stresses are all critical for yield improvement and stability. These traits are controlled by many genes and affected by their growing environments. Breeders' tasks are to make crosses between wheat lines that carry different beneficial genes and select plants that carry the best combination of these genes to develop new cultivars for production. Classical breeding can only select a few traits such as plant height, spike size, or heading time etc that can be visually scored. As increase in demand on high yield and quality for modern wheat cultivars, many traits are not visually selectable using classical breeding and need to be selected at a gene level.

DNA marker is an emerging technology that can speed up breeding process and improve selection accuracy by breeding selection to stack multiple genes/traits simultaneously by selecting DNA markers that selecting either tightly linked markers to the target genes or part of gene sequences. The selection is non-destructive, and can be done in the seedling stage to determine the genes that control traits, expressed in different stages of plants. DNA isolated from a small piece of leaf tissue is enough for evaluation of hundreds of genes/markers. The recent quick development of new sequencing technologies has revolutionised marker technologies by increasing throughput and reducing cost of marker assays, which make it possible for the DNA marker to be used in routine breeding process.

To successfully use DNA markers in routine breeding, however, a breeding programme needs to have specialised equipment and well-trained personnel for DNA marker analysis, which is often unaffordable for many small breeding programmes. To solve this problem, US Department of Agriculture set up the Central Small Grain Genotyping Laboratory (CSGGL) in Manhattan KS during 2002, to serve hard winter wheat (HWW) breeding programmes in the US Great Plains.

Later, three other USDA Genotyping Laboratories were set up in Forgo, ND, Raleigh NC, and Pullman WA to cover other classes of wheat in the rest of the States. These Genotyping Labs provide free marker service to the breeders in each region, therefore, all the wheat breeding programmes have access to newly developed marker technologies and use them in their routine breeding. In the last decade, almost all released wheat cultivars from the US public breeding programmes involved marker work contributed by these Genotyping Labs.

Identifying Genes

The mission of our Genotyping Lab in Manhattan are to: (1) Identify genes controlling important HWW traits including yield, quality, and disease resistance, and tightly linked markers to these genes for their application in marker-assisted breeding; (2) Develop innovative DNA marker technologies for breeding application; (3) Apply high-throughput DNA marker-assisted selection to maximise the efficiency of wheat breeding programmes and facilitate the early release of superior germplasm and cultivars and ; (4) Develop diagnostic markers for marker-assisted selection by fine mapping and map-based cloning of important wheat genes.

Using new genomics and marker technologies, our Genotyping Lab identified new genes or quantitative trait loci (QTLs) controlling many important wheat traits including wheat resistance to aluminium toxicity, stem rust, leaf rust, soil borne mosaic virus, Fusarium head blight, tan spot and preharvest sprouting and yield and quality related traits.
"A rapid growing human population demands faster increases in wheat yield globally in near future. In addition, climate change adds more abiotic and biotic stresses to wheat production, which brings great challenge for breeders to meet the increased demand, which is where DNA markers can help."

Breeder-friendly markers were developed for most of these genes/QTLs i and have been used in routine breeding practice, to help breeders to select for the target genes in their breeding of materials. Our lab cloned two important wheat genes for resistance to (pre-harvest sprouting and Fusarium head blight, and developed diagnostic markers for these genes. We also involved in cloning shattering and tannin genes from sorghum and leaf number and seed size genes from Medicago.

To improve throughput of marker analysis and use next generation sequencing technologies in breeding, our lab developed a new technology called genotyping by multiplexing amplicon sequencing (GBMAS) for high-throughput assays of wheat target genes. GBMAS can analyse hundreds of markers in one assay using next generation sequencing technology, which significantly increases marker analysis efficiency and reduces cost of marker assay for marker-assisted breeding. Besides, the lab adopts genotyping-bysequencing (GBS) technology in research and breeding work. This NGSbased technology has been routinely used to identify genes or markers for important traits and selection of plants by genomic selection.

One of the most important traits we focus on is Fusarium head blight (FHB). FHB is a detrimental wheat disease worldwide. It can cause 100% yield losses in heavily infected fields. FHB infection also reduces grain quality by producing a mycotoxin called deoxynivalenol (DON) during infection. DON is harmful to the health of human beings and livestock. We found that growing FHB resistant cultivars is the most effective and economic approach to minimise the disease damage.

Our research showed that many Chinese germplasm have a high level of FHB resistance and can be good sources of FHB resistance genes for breeding. Using DNA markers, we identified many QTLs/genes conditioning FHB resistance in these sources. Most of these QTLs contribute minor effects to resistance. Only one of these QTLs, Fhb1, showed a consistent large effect on FHB resistance. However, it could not be transferred into US HWW after more than 10 years effort through classic breeding. More recently, we used markerassisted backcrossing successfully transferred Fhb1 into 16 US HWW backgrounds and these selected Fhb1 HWW lines are being used as parents for further breeding. Meanwhile, we cloned the gene underlying Fhb1 resistance to FHB and developed diagnostic marker for Fhb1. This marker will be powerful tool for introgression of Fhb1 into new wheat cultivar to improve wheat resistance to FHB.



Guihua Bai Director USDA Central Small Grain Genotyping Lab Tel: +1 785 532 1124 Guihua.bai@ars.usda.gov http://hwwgenotyping.ksu.edu https://www.ars.usda.gov/plains-area/mhk/ cgahr/hard-winter-wheat-genetics-research/

Nanoparticles – a new weapon to fight plant disease and increase yield

Wade Elmer of The Connecticut Agricultural Experiment Station explores the utility of nanoparticles to enhance health, fight plant disease, and increase yield to meet the challenges of a growing global population in a warming climate

Recent projections have stated that global demand for food production will need to increase by 70% by 2050. Coupled with this alarming statistic is the estimation that climate changes will cause a disruption of food production cycles by extending drought events and raising average daily temperatures in many agriculturally sensitive regions. These predictions become a daunting challenge for agricultural scientists.

However, one new weapon in our arsenal is the discovery and utilisation of nanoparticles for agricultural management.

Nanoparticles of metallic oxides (<100 nm) have great potential as fertilisers and as tools to increase plant health. We have found that nanoparticles of metallic oxides of the plant micronutrients Cu, Mn, and Zn tend to have positive effects on plant health and perform better than their larger bulked or chelated equivalents. Surprisingly, we observed that when nanoparticles of these metallic oxides were sprayed onto the leaves of plants that were infected with root pathogens, they did better than their untreated controls.

In the case of nanoparticles of CuO, we frequently found that it was more consistently associated with disease suppression. We also noted higher concentrations of Cu in the root tissues when compared to untreated



plants or in plants that were treated with the bulked equivalent or the sulfate salt. The more surprising finding was that a single application to young seedlings was providing season-long benefits in enhancing yields of eggplants, tomatoes, and watermelons. The effects were more strongly observed when these plants were grown in pathogen-infested soils.

Many soil-borne diseases are caused by species of fungi and fungal-like organisms that are very hard to manage. Genetic resistance has been the best strategy, but many plants have only marginal resistance. So, the search for management tools continues. In our laboratory, we have long sought for ways to increase the availability and function of micronutrients in plant roots. These elements, although required by plants in very low concentrations for normal plant growth, play pivotal roles in maintaining plant health by fuelling important enzyme systems such as those of phenol metabolism.

We have found that the plant concentration of a micronutrient needed to overcome a deficiency symptom is often much lower than the level necessary to maintain a robust physiological defense against pathogen attack. Since these metals have relatively poor intraplant mobility and tend to be less available in neutral soils, disease is often more severe in plants where these micronutrients have become limiting.

Can nanoparticles really make a difference? In the case of eggplants that were grown in soil infested with *Verticillium dahliae*, a root-infecting fungus, we noted a 17 to 31% increase in yield



in 2013 and 2014 when seedlings were sprayed with a 500-ppm suspension of CuO nanoparticles (roughly 1-2 mg of CuO per seedling). If we take the average yield increase (24%) and apply that to a hectare of eggplant which, on the average, generates about 25,000 kg, we predict about 6,000 kg increase per hectare. At the wholesale price of roughly \$0.90 (US) per kg of fruit, this boost profits by \$5,400 per hectare. More importantly, this yield increase was achieved without the additional cost of cultivating new land with added chemical inputs. All of this was obtained following a single application of nanoparticles of CuO to young transplants that may cost as little at \$20 US.

What about toxicity to humans and danger the environment? When we analysed these eggplant fruits for elemental content, we found no more Cu in the fruits that were treated with the nanoparticles than in fruits from untreated plants, suggesting the nanoparticles or the active ions of the metals did not translocate to the edible portions. The same effect was observed with tomatoes and watermelons. Likewise, inasmuch as very small seedlings are being exposed to the nanoparticles, we minimised environmental exposure.

So, what is happening? Why would such as small amount of nanoparticles have such lasting effects? We are currently testing the hypothesis on different plants that Cu, although sufficient in most soils to prevent foliar deficiency symptoms, is limiting when it comes to early-season root infections by pathogens. Copper serves as a cofactor for the synthesis of important defence products in plants that help protect roots from pathogens. These defence products are quickly manufactured in response to pathogenic infection.

"Many soil-borne diseases are caused by species of fungi and fungal-like organisms that are very hard to manage. Genetic resistance has been the best strategy, but many plants have only marginal resistance."

One particular enzyme of interest is polyphenol oxidase. This enzyme produces antifungal phenolic barriers in root cells. The activity of polyphenol oxidase enzymes is increased many fold in the presence of Cu ions when the plant is being attacked by a pathogen. These defence reactions are broad spectrum and may protect plants against a wide array of pathogens. On watermelon, transcriptomic analysis of root RNA revealed the polyphenol oxidase enzyme was upregulated between 9 to 29 times more when treated with nanoparticles of CuO and then exposed to the pathogen.

Our laboratory and that of Dr. Jason White of the Department of Analytical Chemistry at The Connecticut Agricultural Experiment Station are currently partnering with other chemistry laboratories, to determine how these particles move in plants when applied foliarly. A basic question remains as to whether or not the nanoparticle itself enters into the plant and distributes or if the nanoparticles stays in the cuticle and in adjacent tissues, and then continually releases ions into the plants.

It is exciting to see how a manipulation of mineral nutrition using nanoparticles can have such a marked effect on growth and yield. The future of using nanoparticles in fertilisation appears extremely promising. Chemists have and will continue to play a major role in developing new nanoparticle composites that could deliver multiple nutrients. Formulation chemistry will also need to be advanced to overcome the propensity of these nanomaterials aggregating into much larger and less active particles. While these issues are being addressed, we will continue to work to better understand the interaction between the different forms of micronutrient nanoparticles, the plant, and the wide array of plant pathogens that attack them.



Dr. Wade H. Elmer Chief Scientist of the Department of Plant Pathology and Ecology The Connecticut Agricultural Experiment Station Tel: +1 203 974 8503 Wade.Elmer@ct.gov http://www.ct.gov/caes/site/default.asp www.twitter.com/CT_CAES

Integrated pest management (IPM)

Professor of Entomology at Louisiana State University Agricultural Center, Timothy D. Schowalter outlines the fundamentals of IPM

ntegrated pest management (IPM) is based on the perspective that 1) insects are not always "pests", 2) management strategies should be consistent with ecological processes to avoid detrimental effects on nontarget species and ecosystem services. Examples of this include the production of harvestable resources, recreational activities, and supporting services such as primary production and decomposition, 3) control efforts are only warranted when insect abundance exceeds an action threshold that is based on resource management goals, and 4) multiple tactics should be employed to minimise insect adaptation to any single tactic.

Insects play critical ecological roles in their native ecosystems. Most terrestrial and fresh water ecosystems would collapse in the absence of insect pollination of 35% of our food supply, virtually all decomposition of dead organic matter, and regulation of ecosystem processes that are fundamental to delivery of ecosystem services that are critical to human survival.

Obviously, some species can interfere with essential ecosystem services or threaten human health or structures. However, it is important to distinguish a species' role as a "pest" when it interferes with human interests from its role(s) in natural ecosystems. For example, termites often pose serious threats to cellulose-based building materials, but eliminating termites beyond human-dominated habitats



would threaten the integrity of decomposition processes that sustain ecosystem productivity.

Insects most often become pests because of management practices that favour insect population growth, such as when host (crop) species become widely planted at high density or when altered disturbance frequency allows host species to become more abundant. Furthermore, plants become more susceptible to insects when adverse environmental conditions lead to stress and reduced production of defensive chemicals. Crop species often are bred to reduce bitter (defensive) flavours.

Humans have transported many species across natural barriers. Some of these species have become serious invasive pests in new habitats, their intrusion threatening native species and altering ecosystem structure and function in ways that threaten ecosystem services. Recent increase in the incidence of arthropod-vectored human diseases reflects anthropogenic changes in landscape structure, that favours vector species. In fact, deforestation is a primary factor contributing to increased abundance of mosquito species that vector human diseases.

Controlling pests

Efforts to control pests are expensive and not always effective. Control often resembles the nursery rhyme about the woman who swallowed fly, then a spider to eat the fly, a mouse to eat the spider, etc. That story does not end well. We do not know enough about food web interactions or ecosystem processes to engineer solutions that do not adversely affect ecosystem services. A better approach is to work with nature to avoid pest induction or use natural regulatory mechanisms.

Advances in understanding the complex effects of insects on other

organisms and ecosystem services have influenced evaluation of the need for pest management. Management goals for native forests and grasslands have become more complex as societal needs have shifted from a focus on protection of harvestable resources to protection of biodiversity and carbon sequestration and mitigation of climate change.

In many cases, the net effects of native insect species on ecosystem services are neutral or positive, or the cost of control is not warranted by marginal benefits. The IPM framework provides a strategy for deciding when insects pose a sufficient threat to ecosystem services to warrant suppression. Two examples demonstrate the value of the IPM approach.

Concluding thoughts

The cotton boll weevil entered the USA from Mexico in 1892 and quickly threatened cotton production in the southern USA. Destruction of cotton residue following harvest was one of the few early practices that reduced weevil damage and became a recommended control tactic.

However, calcium arsenate dust was introduced for weevil control in 1918 and became the primary control method until the 1950s, when DDT became the preferred control option. Weevil populations were resistant to DDT by the late 1950s, and persistence in the environment and serious nontarget effects were soon recognised.

DDT was replaced by organophospates, then by pyrethroids and carbamates. Growers became dependent on inexpensive insecticides and relied less on non-chemical options. Increasing concern about environmental costs and insecticide resistance finally led to consideration of non-chemical options during the 1970s. Newly identified weevil pheromones were used to trap weevils and indicate where weevils were most abundant.

Mandated crop residue destruction deprived weevils of late-season resources and overwintering sites. Isolated weevil refuges, resulting from crop diversification, were targeted for application of malathion, the most effective insecticide. As a result of this integrated approach, insecticide use declined from 10-14 applications per season to 1-4. The boll weevil was largely eliminated as a cotton pest by 2010.

A Douglas-fir tussock moth outbreak in the Pacific Northwest brought demands for application of DDT to protect forest resources. The EPA had cancelled use of DDT the previous year in response to increased awareness of its detrimental effects on non-target species. However, DDT also had become largely ineffective against most target species because of adapted resistance. The EPA finally issued an emergency authorisation to apply DDT, based on the apparent lack of practical alternatives for control of tussock moth.

However, as part of this authorisation, the FPA mandated that research on alternative methods of control be intensified and that replicated experimental plots be established to demonstrate the efficacy of, and need for, DDT. Following application in 1974, tussock moth populations declined in all experimental plots, regardless of DDT treatment, leading to recognition that epizootics of viral disease naturally end tussock moth outbreaks in 3-4 years, a natural biological control previously undermined by chemical applications. Aerial application of virus, rather than chemical insecticides, became the

preferred means of control for outbreaks of this insect.

These examples illustrate three major points. Firstly, the spread of both insects was facilitated by widespread planting of their hosts. Secondly, crop diversification in the South reduced and isolated the remnant populations and facilitated final elimination. Thirdly, the successful management of both insects was finally achieved through an IPM approach that targeted critical aspects of their life histories, with insecticides no longer primary control options.

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Timothy D. Schowalter Professor of Entomology

Louisiana State University Agricultural Center Baton Rouge, LA 70803, USA Tel: +1 225 578 1634 tschowalter@agcenter.lsu.edu http://entomology.lsu.edu/schowalter.html

AGRICULTURE

Leading America towards a better future through in-house research

The Agricultural Research Service (ARS) is the U.S. Department of Agriculture's scientific in-house research agency, as Open Access Government discovers

he Agricultural Research Service (ARS) is the U.S. Department of Agriculture's scientific in-house research agency. Their job is finding solutions to agricultural problems that affect Americans daily, from the field to table.

To give a flavour of ARS's work, they are responsible for 690 research projects within 17 national programmes, 2,000 scientists and 6,000 other employees. They boast 90+ research locations, including overseas laboratories and have an annual fiscal budget of \$1.1 billion.

In addition, they encourage diversity in their workforce, an attitude that encourages the ARS to be the best in terms of the excellent research work they carry out.

The vision of ARS is simply to, "lead America towards a better future through agricultural research and information"¹ according to their website. The organisation's mission statement is to conduct research to develop and transfer solutions to agricultural problems that are a high national priority. In addition, ARS sets out to supply information access and dissemination to:

- Ensure high-quality, safe food, and other agricultural products;
- Assess the nutritional needs of Americans;
- · Sustain a competitive agricultural economy;
- Enhance the natural resource base and the environment;
- Provide economic opportunities for rural citizens, communities, and society as a whole; and

• Provide the infrastructure necessary to create and maintain a diversified workplace.¹

One recent development is that the ARS recently launched a newly designed website which improves access to information about their research. The new site features mobile responsiveness, so that users can navigate and view information on both mobile and desktop devices with more ease. In addition, the ARS website has more than 300,000 dynamic pages, which is certainly a fantastic achievement.

"Measures to protect chickens from pathogens involves the use of antibiotics and other medications, sanitation, vaccination and biosecurity. Having said that, some chickens have a particularly efficient and robust immune response and as such, they can resist pathogens, underlines Swaggerty."

Commenting on the new design of the website, ARS Chief Information Officer, Paul Gibson said: "This new design better showcases the research generated by our scientists and allows us to better share ARS research findings that have impacted our nation and our world."

When visiting the new site, you can find out about ARS's role in mass-producing penicillin or developing new crops such as carrots, seedless grapes, watermelon and tomatoes. Other exciting subjects covered on the new site include preventing foodborne pathogens, developing low-fat cheese and countless other discoveries made by ARS.

Breeding pathogen-resistant chickens In other recent news from ARS, we find out about a

AGRICULTURE



new test developed by ARS scientists in College Station, Texas, which could make breeding pathogen-resistant chickens easier. The test identifies roosters whose blood contains naturally high levels of two key chemicals – chemokines and cytokines. These 2 chemicals mobilise the birds' innate immune response, in the view of ARS microbiologist Christi Swaggerty.

Using the new test, commercial poultry breeders can single out roosters with a strong immune response and use them to selectively breed a more robust flock. Such resistance, particularly during the birds' first week of life, could reduce costs around food safety and animal well-being.

Measures to protect chickens from pathogens involves the use of antibiotics and other medications, sanitation, vaccination and biosecurity. Having said that, some chickens have a particularly efficient and robust immune response and as such, they can resist pathogens, underlines Swaggerty.

In addition, the researchers also used the test to select roosters for breeding a line of resistant broilers. The researchers then exposed the resistant broilers to several pathogens, then they compared the resistant group to a group of susceptible broilers bred from roosters, with low cytokine and chemokine levels present.

Susceptible broilers had more signs of infection and pathogens than the resistant group, according to the published results. Ultimately, this resistance could mean that fewer pathogens remaining on birds at the processing plant, and an improvement in consumer safety, Swaggerty added.

It is also worth noting that Swaggerty and her colleagues study the genetics of chickens' resistance to foodborne disease-causing pathogens, such as Campylobacter and Salmonella. The ARS press release goes on to explain more around this compelling point.

"Some species of these two bacteria together cause 2 to 3 million U.S. cases of foodborne illness in consumers and 450-500 deaths annually.

Another poultry disease, coccidiosis, is caused by a single-celled parasite known as Eimeria. In the U.S., coccidiosis inflicts annual production losses of up to \$800 million, making this intestinal disease a significant threat to nearly 9 billion U.S. meat-type birds."²

In closing, the last word goes to the Director of the ARS's Office of Outreach, Diversity, and Equal Opportunity, Donald L. McLellan. Indeed, ARS strongly supports a diverse workforce, which will ultimately reflect the aim of the Agricultural Research Service (ARS) to reach their full potential. He says: "Let us all commit ourselves to a new conversation- one that celebrates our unique differences while acknowledging our common purpose- to becoming the best agency that we can be."³

- 1 https://www.ars.usda.gov/about-ars/
- 2 https://www.ars.usda.gov/news-events/news/research-news/2017/ breeding-resistant-chickens-for-improved-food-safety/
- 3 https://www.ars.usda.gov/office-of-outreach-diversity-and-equalopportunity/

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Vaccination a means of protection against infections in egg-laying hens

Dr David Peebles from the Poultry Science Department explains how Mycoplasma gallisepticum can effect egg-laying hens and available vaccination

ycoplasma gallisepticum (MG) is an economically important respiratory bacterial pathogen in commercial layers. It can colonise systemically, is insidious in nature, and displays resistance to its host's defence mechanisms. It is, therefore, difficult if not impossible to completely eliminate from the bodily tissues of egg-laying hens (Winner et al., 2000; Bradbury, 2005). Economic implications of MG infection in layers include reduced feed efficiency and egg production, and increased mortality (Mohammed et al., 1987; Branton et al., 1999; Ley, 2008).

The ramifications of these effects become pronounced on multi-age commercial layer operations where eradication of the disease is not feasible. Earlier estimates of annual financial losses to the table egg industry have been approximately \$150 million (Patterson, 1994). Live attenuated MG vaccines have been utilised to displace or exclude natural field strain MG infections that are of greater virulence. In accordance with producer preference and manufacturer recommendations, vaccination has been commonly administered by either drinking water, eye drop, or spray (Evans et al., 2013).

The F-strain Mycoplasma gallisepticum vaccine

In 1988, the F-strain of MG (FMG) was the first live attenuated vaccine approved by the United States Department of Agriculture (USDA)-Agricultural Research Service (ARS), for use in commercial egg-laying operations. However, because FMG is pathogenic to turkeys, its use is not allowed in some states and is approved for exclusive use in commercial layers. The use of FMG has proven effective as it has been observed to reduce virulent field strain MG populations (Levisohn and Dykstra, 1987; Kleven et al., 1998), induce a strong serological response (Roberts, 1969) and resistance to airsacculitis (Rodriguez and Kleven, 1980), and to have no adverse effects on subsequent egg production when administered to pullets before the onset of lay (Self, 2012, personal communication).

F-strain Mycoplasma gallisepticum vaccine research

The economic consequences of MG infections, in addition to concerns with animal health and welfare, have caused USDA-ARS to make funding for the control of this disease a major priority. An outcome of making MG-related research a priority of USDA-ARS has been the performance of a series of studies by the laboratory of Dr. E. David Peebles, of the Mississippi State University Poultry Science Department. His has conducted his work in collaboration with the USDA-ARS Poultry Research Unit in Starkville, MS.

The research that Dr. Peebles has conducted over the last 18 years in

collaboration with USDA-ARS, has concerned the timing and route of application of the FMG vaccine on the physiology and performance of commercial egg-laying hens. The goal of his research has been to determine optimal application regimens that are necessary to achieve improved bird health and egg-laying performance.

Recent innovation in F-strain Mycoplasma gallisepticum vaccine delivery

In 1992, in ovo, or "in the egg" injection technology was introduced to the poultry industry, and has replaced manual subcutaneous injection for the commercial administration of vaccines. This technology is now the primary means used to vaccinate broilers worldwide (Ricks et al., 1999).

Knowing the availability of this internationally established technology, Peebles and colleagues realised its potential use for the administration of the FMG vaccine to fertile hatching eggs in the subsequent production of commercial table egg-laying hens.

Recent research by Peebles and his collaborators has provided evidence, based on successful hatching rates at lower dosages, that this method exhibits excellent potential for the effective vaccination of layer embryos.

Further research is being conducted to establish the effects of in ovo FMG vaccination on the post-hatch immunity



and performance of commercial table egg-laying hens (Elliott et al., 2017). Considerable financial savings are anticipated upon adoption of in ovo FMG application methods by the table egg industry.

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Dr E. David Peebles Poultry Science Department Tel: +1 662 325 3379 d.peebles@msstate.edu http://www.poultry.msstate.edu/

AGRICULTURE

How communities are strengthening their food systems

Assistant vice president of programmes at American Farmland Trust, Julia Freedgood explains the challenges around the increasing demands to food systems

n the United States, as across the world, increasing demands to feed a growing population are challenged by urbanisation, climate change and an ageing farming population. While the U.S. is blessed with exceptional natural resources to support agriculture and food production, these are often taken for granted with little foresight or planning.

As the old adage goes, "a failure to plan is a plan to fail" and this is certainly true for food systems. Many communities have policies to protect farmland. But planning for the land base is not enough. It is also important to plan for local food economies and to support the people who produce our food.

A team of researchers and practitioners just completed Growing Food Connections, a 5-year USDA funded project to enhance community food security while ensuring sustainable agriculture and food production. Our approach included research, education and practice to increase local government capacity to strengthen community food systems by supporting small/mid-sized farmers and underserved residents through planning and policy.

A survey of planners at the start of the project found limited local government engagement in food systems. However, we did find inspiring examples, where local governments played a lead role developing plans and implementing food and farming policies. We identified 19 "Communities of Innovation" (COI) for further study. Many were big cities with active planning departments: New York, Baltimore, Minneapolis and Seattle. But we also found more rural examples including Marquette County, Michigan and Region 5 in central Minnesota.

The practice part of the project involved eight "Communities of Opportunity" (COO), which we selected



Julia Freedgood Assistant Vice President of Programmes

after a competitive application process, and supported as they developed their own visions, goals, strategies and plans. Urban, rural and in between, all the COOs were dealing with poverty and food insecurity, and most of their farms were small and struggling to survive.

Farm survey

We worked with the COOs over a 2½ year period to advance plans, policies and public investment. They were especially interested in creating food processing and distribution infrastructure, improving food access and increasing local food production. This included developing food hubs and mobile markets, supporting urban agriculture, and incentivising food insecure populations to shop at farmers markets.

These experiences led to Growing Local: A Community Guide to Planning for Agriculture and Food Systems, which showcases examples from COIs and COOs and includes the most comprehensive collection of local food system policies ever assembled. The practical guide highlights real life examples of ways communities can create connections between field and fork.

According to Susan Whitfield, director of operations for No More Empty Pots, the guide "Is an excellent resource

AGRICULTURE



because it pulls best practices from all regions across the country that have been battle-tested and successful. We will use it to assist us in working with local government entities in both urban and rural communities when recommending policy development and planning strategies to strengthen our regional food system."

Growing Food Connections was made possible with a grant from the USDA/NIFA AFRI Food Systems Program NIFA Award # 2012-68004-19894. Led by the University of Buffalo, American Farmland Trust, Cultivating Healthy Places, and Ohio State University, the core team partnered with American Planning Association and a National Advisory Committee to conduct research, advance graduate level planning education and to extend to communities through on-the-ground policy and practice.

American Farmland Trust is a national conservation organisation, dedicated to protecting farmland, promoting sound farming practices and keeping farmers on the land. Learn more at www.farmland.org.

Copies of Growing Local: A Community Guide to Planning for Agriculture and Food Systems are available for free download at: growingfoodconnections.org/wpcontent/uploads/sites/3/2013/06/AFT_GFC_Community-Guide_lo_res_04-2017.pdf

To learn more about Growing Food Connections and explore its many resources including case studies and policy briefs, visit growingfoodconnections.org/

Print versions of Growing Local also are available for sale. For information on purchasing, please contact Peggy McCabe at pmccabe@farmland.org.

Julia Freedgood Assistant Vice President of Programmes

American Farmland Trust Tel: +1 202 331 7300 jfreedgood@farmland.org https://www.farmland.org/ www.twitter.com/Farmland

ENERGY

Energy efficiency a win-win for Canada and industry

The Honourable Jim Carr, Canada's Minister of Natural Resources, looks at the potential of energy efficiency for the future

nergy efficiency has been called the "invisible fuel" – and for good reason. As the world makes the transition to a low-carbon economy, much of the focus has been on expanding our use of cleaner, renewable sources of energy and making traditional sources of energy greener. Both of those are worthy goals, but they overlook the most obvious starting point for lowering greenhouse gas emissions: using less energy, period.

The potential of energy efficiency cannot be overstated. According to the International Energy Agency, reducing our energy consumption through greater efficiencies could get us almost halfway to our Paris commitments for combatting climate change. That has caught our government's attention, which is why Budget 2017 included more than \$300 million in new investments for a wide range of energy-efficiency policies and programmes. Industry is a good case in point.

Making strides in industrial energy efficiency

In Canada, the industrial sector is the most energyintensive of our economy, accounting for approximately 37% of our country's greenhouse gas emissions. Unfortunately, industry investments in energy efficiency were once viewed primarily as an added expense, something that increased operating costs while producing only an ancillary benefit of lower energy bills.

In fact, between 1990 and 2014, energy use in the industrial sector jumped 33%. Some of that increase can be attributed to economic growth, but it also highlights the great, untapped potential that energy efficiency still holds for industry.

Many Canadian companies are discovering just how substantial the opportunities are. They are increasingly recognising that energy efficiency, the invisible fuel, can generate significant value through enhanced competitiveness, profitability, production and product quality – not to mention an improved environment for workers and lower operational costs.

Our government's investments build on this growing momentum for new ways to conserve energy.

Recognising top energy performance

In August, we launched the ENERGY STAR[®] for Industry programme to help Canadian factories and manufacturing plants reduce their energy needs and, in the process, improve their productivity, environmental performance and bottom line.

"The value of investing in energy efficiency is clear. By accelerating the adoption of energy management systems, such as ISO 50001, Canadian industry can play a leading role in helping us to realise regional and national climate and energy goals."

This new programme uses an Energy Performance Indicator – or EPI – to establish the benchmark for energy use in each industrial sector and allows individual companies to compare their energy efficiency against their competitors'. The top performing facilities will be ENERGY STAR[®] certified.

We've launched this new ENERGY STAR[®] programme with Canada's steel sector, but we are working to expand it quickly to other industries, such as commercial baking, automotive assembly, and cement and fertiliser manufacturing.

Partnering with industry

ENERGY STAR[®] for Industry is only the latest advancement in a long history of collaboration between the federal government and industry. The Canadian

ENERGY



The Honourable Jim Carr, Canada's Minister of Natural Resources

Industry Program for Energy Conservation (CIPEC) was established in 1975 to help organisations improve their energy efficiency. This voluntary partnership has played a key role in stabilising energy intensity in Canadian industry.

How? CIPEC supports a network of close to 2,400 facilities and more than 50 trade associations that work together to cut costs, improve energy efficiency and reduce industrial greenhouse gas emissions. It provides technical information and cost-sharing agreements to companies in more than 20 industrial sectors.

Without these types of efforts, that one-third jump in the industrial sector's consumption of energy between 1990 and 2014 would have been even higher, at an estimated 41%.

Managing what gets measured

CIPEC encourages Canadian industry to adopt integrated energy management systems such as ISO 50001, which is Canada's national energy management systems standard. By the end of last year, 31 organisations in Canada had achieved ISO 50001 certification. Canadian industrial facilities that have implemented the ISO 50001 standard have improved their energy performance by 10%, on average, in the first two years. This is consistent with available data showing that ISO 50001 can improve energy performance by 10%, or more, within the first 18 months, and that most of the improvement comes from low- or no-cost operational enhancements.

Investing in an energy efficient future

The value of investing in energy efficiency is clear. By accelerating the adoption of energy management systems, such as ISO 50001, Canadian industry can play a leading role in helping us to realise regional and national climate and energy goals.

"In Canada, the industrial sector is the most energy-intensive of our economy, accounting for approximately 37% of our country's greenhouse gas emissions. Unfortunately, industry investments in energy efficiency were once viewed primarily as an added expense, something that increased operating costs while producing only an ancillary benefit of lower energy bills."

Canadians expect no less. We've heard that, repeatedly, since we started a national conversation last spring to talk about Canada's energy future. Canadians want to see government and industry doing their part to enhance energy efficiency in this clean-growth century.

Working together, we can turn energy efficiency – today's invisible fuel – into tomorrow's obvious choice, setting the path for long-term clean growth and a more sustainable, low-carbon future.

The Honourable Jim Carr Canada's Minister of Natural Resources Government of Canada Tel: +1 343 292 6100 www.nrcan.gc.ca www.twitter.com/NRCan

Delivering flexible and secure energy solutions

Dom Barton, of Metropolitan Infrastructure Limited explores the national challenge to deliver sustainable, affordable and secure energy solutions

When the ating accounting for 40% of the UK's carbon emissions and over 2 million UK households in fuel poverty, the challenge to provide sustainable, affordable and secure energy supplies has never been greater. It directly affects the lives of individuals and their communities now and underpins the continued provision of their vital support services – including healthcare, social care, education and housing.

District energy and multi-utility solutions

Metropolitan is the leading independent district energy and multi-utility infrastructure provider in the UK. We are the only company combining all the traditional utility networks and future-proof district energy schemes as part of the complete solution for new build and regeneration sites nationwide.

We design, build, fund, own, and operate networks for decentralised and traditional energy and have delivered some of the UK's highest-profile, lowest-carbon new communities.

Our district energy networks provide sustainable, affordable and secure energy solutions for:

- High-density residential and mixed use commercial new developments;
- Urban regeneration areas;
- Combined regeneration and new development schemes;

• Retrofit of existing residential and commercial buildings.

We bring genuine choice in the delivery of district energy and multi-utility solutions, and their long-term economic operation, without the need for intervention from incumbent utility providers.

From network adoption to fully constructed and financed options, our investment models provide maximum flexibility with customers choosing the route that best suits their needs and objectives.

The only partner you need for all your energy and utility assets, Metropolitan provides solutions for:

- District energy;
- Electricity;
- Fibre-to-the-Home (FTTH);
- Water and wastewater;
- Gas.

What is district energy?

District energy reduces total carbon emissions and creates more affordable energy for all. Most importantly, it provides the opportunity to drive down fuel poverty. District energy networks allow different sources of low-carbon heating such as Combined Heat and Power (CHP), heat pumps, energy from Waste (EfW) or fuel cells



to supply heating through a network of insulated underground pipes to individual properties.

Scalable solutions

We provide solutions that are flexible, scalable and designed to evolve with the needs of the development serving the growing number of people living and working there. Once the initial part of a district energy network is operational, there are often opportunities to extend it into adjacent areas as a retrofit solution. This brings improved carbon performance to an entire area.

Transforming communities

Alongside energy networks, we deliver other enabling infrastructures, such as electric and fibre networks. These networks ensure that the provision and usage of energy are as efficient as possible while ultrafast Fibre-to-the-Home (FTTH) networks bring lifechanging benefits to consumers' personal and professional lives.

Heat Trust guarantee

Metropolitan was one of the first to register a scheme with the Heat Trust, and as members, we commit to abide by the scheme which serves to protect and safeguard the interests of all heat customers.

We are committed to obtaining Heat Trust status for all our networks, to offer independent reassurance to residents that our heat tariffs are always fair. Customers connected to our electric or fibre networks have complete freedom to choose their supplier and service package.

Public sector funding

Both the UK and Scottish governments have active strategies to promote the decarbonisation of heating for buildings, and have dedicated funding available to enable district energy projects. Funding is not limited to just local authorities and could be used to connect new loads to existing heat networks within other public sector organisations, such as NHS buildings and universities. We can incorporate such funding within our solution.

Models to reduce energy costs

Public sector organisations can choose to progress schemes themselves or look for partners in the private sector to realise their objectives. Metropolitan have proven and flexible Energy Services Company (ESCo) solutions and partnership models which allow for the separating of supply and distribution. We will also ensure scheme delivery is phased to match overall development investment timelines.

An ESCo is a commercial operation providing efficient and cost-effective energy to the development. We welcome the opportunity to share ownership of the ESCo to ensure community needs are being met both now and in the future.

With the option to sell any excess power generated back to the market, the ESCo model ultimately creates an efficient, secure and reliable communitybased energy solution with reduced energy costs for residents.



Dom Barton Metropolitan Infrastructure Limited Tel: 01359 758757 enquiries@met-i.co.uk www.met-i.co.uk

CASE STUDY

Kings Cross, London

Metropolitan is already delivering one of the largest regeneration projects in the UK, at Kings Cross in London. Eventually, there will be 2,000 new homes of which 330 are affordable housing alongside commercial premises, underpinning the creation of over 5,000 jobs in high-value knowledge sectors.

Our district energy network at King's Cross uses a Combined Heat and Power (CHP) plant with natural gas driving the engines, as well as plans to install a 1.4MW fuel cell to meet the increased heat demand for future phases.

The efficiency statistics speak for themselves:

- **Carbon:** 50% saving in carbon emissions based on traditional utility solutions.
- **Electric:** 80% efficient compared to 30% in the conventional UK electricity supply.
- **Heat:** An energy centre meets almost 100% of heat demand and 80% of power demand.

A fully managed ESCo is part of the solution for the local delivery of de-centralised energy, and this includes providing professional metering and billing services to the householder. The ESCo is a joint venture with Metropolitan and Argent, who maintain a stake in its long-term success and the ongoing interests of the King's Cross residents.

Let's be honest: gas and oil are not going anywhere, anytime soon

Danny Pay, Director of Maximus Green outlines energy efficiency towards gas and oil is a realistic approach over going 'green' for all applications

Renewable energy solutions, such as solar, tidal, wind, geothermal, etc. are all extremely useful alternatives. However, we are a society so dominated by gas and oil that we cannot simply stop using them. This isn't an article arguing the case for fossil fuels; this is an article stating the harsh truth that we are not going to stop using fossil fuels overnight, nor for a few years. We are talking decades. Instead, we must preserve what we do have by making it more efficient and economically viable.

The heating and boiler systems you have in your homes and businesses run on oil and gas. Even the most modern and fancy of these systems will use fossil fuels. We've made them more efficient over time. In 2015, the average annual energy bill for a dual-fuel household was £490 less than it would have been without such efficiencies. But the fact remains: they require fossil fuel sources.

According to the report, Unlocking Britain's First Fuel, the use of gas to power heating systems has dropped by 27% since 2004. The use of household electricity also fell by 13% in the same period. Certainly, we acknowledge the clear reduction in fossil fuel usage, but it's obvious that we won't eliminate fossil fuels by achieving a 100% reduction anytime soon. Thus, energy management and energy efficiency become priorities. Making these the focus of your "green" solutions will help you to not only meet your targets and save money, but alleviate the pressure as you wait for renewable solutions to replace your current systems.

Renewable energy

Ultimately, renewables are the only viable way to match our energy needs with environmental conservation but it is a long-term plan. Energy efficient use of current, fossil fuel reliant systems will bridge that gap between now and a renewable future. Many industrial systems were installed up to 50 years ago and designed to last 100 years. Expensive and awkward to



"THE BIGGEST SOURCE OF CLEAN ENERGY IN THE WORLD TODAY IS ENERGY EFFICIENCY"

ENERGY EFFICIENCY IS THE ANSWER



replace, they are not a feasible, longterm solution for businesses.

We are clearly aware of the necessity of energy efficiency and management; they have engendered an entire industry. Development in this sector has been rapid these past few years, with the increasing emergence of new technologies and consistent, environmental research. A report from Policy Exchange states that an energy efficiency policy upgrade could save businesses £1.3 billion a year. That's not with renewables, that's by making the systems we have more efficient.

"Improving energy efficiency is amongst the easiest and cheapest ways to decarbonise our energy system," said Joshua Burke, energy and environment research fellow at Policy Exchange. "Businesses and public sector organisations spend the equivalent of nearly 5% of GDP (£22bn) on energy every year but too many organisations still aren't investing enough in energy efficiency. It needs to be seen as a major strategic investment which is both good for the environment and good for profitability."

So what options are there? The Energy Managers Association (EMA) and the Carbon Trust both supply useful information to guide businesses but there is no one size fits all programme. Nonetheless, the importance of developing these guides should not be considered a low priority. As Brian Motherway, head of energy efficiency at the International Energy Agency (IEA), said: "People think about renewables and the supply side but the more mundane business of saving energy actually makes a bigger contribution. The biggest source of clean energy in the world today is energy efficiency because it allows you to do more without having to supply more energy."

Energy efficiency has never been more environmentally, nor economically critical. Energy and fuel costs are rising and budgets are getting smaller; in fact, many of these energy efficiency programmes were designed with the purpose of cutting business costs, rather than saving the planet. We should take every measure to decrease energy emissions by focusing not only on our energy systems, but also on the fuels we feed our systems.

Cleaner fossil fuels

The cleaner and purer the oil, gas or water that powers a system, the greater its efficiency and the less damage impurities cause to hardware. The system lasts longer and you save money. Improving the economy and efficiency of fuel must, unquestionably, become a part of your "green" strategy.

As Fabrice Leveque, an energy specialist at WWF, said: "This [increase in renewable energy] is yet more evidence that a zero-carbon future is in our grasp. However, at the present rate, it will take over 100 years for us to ensure our homes are carbon neutral."

Energy efficiency isn't going away anytime soon, nor should it. Even once renewables have fully taken over, there will still need to be effective power management and efficiency methods in place to ensure that we can continue to use this power unhindered, indefinitely.



Danny Pay Director

Maximus Green Tel: +44 (0)1843 572 574 dannyp@maximus-green.co.uk www.maximus-green.co.uk www.twitter.com/MaximusGreenLTD www.linkedin.com/company/maximus-green

ENERGY

A fusion future

Laban Coblentz, Head of Communication, ITER gives an absorbing insight into all things fusion and the future of fusion energy

rom its earliest history, the human animal, among all species, has been the most ambitious to dominate its environment: to conquer the earth, the seas, the skies, and – more than half a century ago – making its first forays into space. If Elon Musk and other visionaries have their way, humans will soon become an interplanetary species.

Harnessing nuclear fusion is an equally ambitious goal, but in reverse: bringing a star to Earth.

Fusion accounts for more than 99% of the energy of the universe. The fusion reaction powering our Sun at its core – 600 tons of hydrogen converted every second – is our engine of sustained light and heat: the source of all life on our planet. But the Sun accomplishes this feat using gravitation – 300,000 times that of Earth – and a temperature of 15 million degrees. The puzzle of how to replicate this phenomenon, how to "create a star on Earth" as a controlled energy source, has been a science and engineering quest for more than six decades. Many methods have been tried.

The front-runner, by a good measure, is the Tokamak: a toroidal or doughnut-shaped vacuum chamber encasing a second, invisible cage formed by magnetic fields. A gaseous soup made of two forms of hydrogen – deuterium and tritium – is injected into the chamber and heated until it becomes plasma: the fourth state of matter, with the electrons stripped away from their nuclei.

At a temperature of 150 million degrees, 10 times hotter than the core of the sun, the speed of these hydrogen nuclei overcomes their natural repulsion, allowing them to collide and fuse. Two new products result: helium and a neutron so energised that, in free space, it would reach the moon in less than 9 seconds. In a commercial Tokamak, these intense bursts of energy will heat water and drive a turbine to generate electricity.

Fusion energy is desirable because of its near-perfect characteristics. Fusion releases no carbon or other greenhouse gases. The fusion reaction, while difficult to create, is inherently safe; unlike nuclear fission, there is no possibility of a Chernobyl or Fukushimastyle meltdown. Nor does a fusion reactor produce any high-activity, long-lived radioactive waste.

And fusion energy is incredibly concentrated. Consider this: if the world were entirely powered by coal, at current consumption rates, it would require 24 billion tonnes per year; if powered by fusion, the same output would take a mere 867 tonnes of hydrogen.

Best of all, fusion fuel is abundant. Deuterium is easily extracted from seawater, and lithium, used in the Tokamak to breed tritium, is similarly plentiful. This translates to millions of years of supply. With this fuel accessible to every region and country, fusion visionaries foresee a transformed geopolitical landscape, an energy-rich global community unscarred by conflicts over access to petroleum resources.

Since the Russian invention of the Tokamak in the 1950s, hundreds of successively larger Tokamaks have been built and operated. The science and engineering challenges have largely been overcome, their solutions proven. What remains is to demonstrate and study a "burning plasma," meaning a plasma that is largely self-heated by fusion.

In fusion physics, the critical parameter is referred to as "Q": the ratio of thermal output from fusion power versus the thermal input power used to start up the plasma. With all other factors equal, Q is directly proportional to the size of the Tokamak vacuum chamber.



ITER

Which brings us to ITER: the first full-scale Tokamak, a project of 35 countries now taking shape in the picturesque heart of Provence in southern France. ITER will have a Q of 10 or greater: 50 megawatts of thermal power heating the plasma to produce, via fusion, a thermal output power of 500 megawatts or more. The ITER mission is to demonstrate the feasibility of fusion on a commercial scale through the production and study of this burning plasma.

Arguably, ITER is the most challenging science and engineering project humans have ever attempted. ITER's superconducting magnets, some as large as 24 metres in diameter, will be supercooled with liquid helium to -269°C, the temperature of interstellar space. A few metres away, the resulting magnetic cage will keep the superheated plasma - the hottest point in the universe - away from the walls.

"ITER," in Latin, means "the way"; and the complicated multinational collaboration at the heart of the ITER Agreement is seen by many as foreshadowing "the way" that future 'big science' must adopt to be successful. Each ITER Member supplies most of its financial support in the form of components: massive, delicate pieces of the Tokamak and support systems that must be shipped to Provence and assembled into this intricate, supersized fusion platform.

ITER's complexity demands extraordinary managerial and systems engineering performance; but the resulting benefits - new industrial expertise, spin-offs, and groundbreaking innovation in fields as diverse as materials science, robotics, electromagnetics, cryogenics, vacuum systems, and power electronics - accrue mutually to each of ITER's partners.

The ITER worksite is abuzz. Massive structures are emerging from the ground. Giant components are arriving weekly. Fast-paced construction has been proceeding for several years, and the assembly phase begins in 2019, with the operational machine – "First Plasma" – on schedule for December 2025. Stay tuned.

Laban Coblentz **Head of Communication** ITER Tel: +33 4 42 17 66 17 Laban.Coblentz@iter.org www.iter.org/whatsnew www.twitter.com/iterorg

Entrepreneurial opportunities in fusion energy development

Dr. Y. C. Francis Thio and Dr. F. Douglas Witherspoon turn the spotlight on how lower-cost pathways to fusion energy can be attractive to investors

n the first article in this series on fusion energy, Dr. Scott Hsu of Los Alamos National Laboratory explained why low-cost pathways to economical fusion power are needed to accelerate its development (1). Conventional wisdom has it that fusion-energy development necessarily involves tens of billions of dollars and thirty years or longer, and thus must be the domain of governmentsponsored "big science."

While that belief is valid within the framework of conventional magnetic confinement fusion (MCF) and laserdriven inertial confinement fusion (ICF), we argue in this article that the conventional wisdom is not necessarily valid due to the emergence of an entirely new class of fusion approaches called magneto-inertial fusion (MIF) (2,3), which could reduce the R&D cost by one to two orders of magnitude (3) and the timeline to perhaps twenty years or less.

The reduced cost of modern fusion approaches, the vast knowledge and technological base for fusion energy science, and the extraordinary potential market size of fusion power taken together make the risk and the potential returns on investment arguably commensurate for private development of fusion (e.g., the pharmaceutical industry, involving private development of new drugs, has similar costs, market potential, and time scales.)



The world is moving rapidly towards energy sources that are free from carbon emission. In principle, fusion can be a very attractive source of carbon-free energy because its fuel cost is near zero. A one-gigawatt fusion power plant uses annually only 200 lbs of deuterium (an isotope of hydrogen that occurs naturally in sea water) and 600 lbs of lithium.

Compared to renewables such as wind and solar, fusion can provide relatively compact, gigawatt-class, baseload power, and does not require expensive energy storage and complex load-balancing techniques. Compared with nuclear fission, fusion energy has reduced weapons-proliferation risk, produces manageable short-lived radioactivity, and is passively safe, i.e., in the case of equipment failure due to human or natural causes, the fusion reactor simply quenches. Fusion, together with wind, solar, and other clean-energy technologies, will maximise the probability that the global demand for carbon-free energy will be met.

Replacing existing power plants

By 2040, the world demand for electrical power is estimated to surpass 4,500 GW. A mere 2% replacement of this power annually by fusion power plants plus the annual growth in global energy demand will create a market size for fusion power plants of nearly half of a trillion dollars annually for decades.

Since the time that fusion reactions were dramatically demonstrated in thermonuclear weapons, the developed countries of the world have engaged themselves in developing controlled fusion energy. Over the last 60 years, this research has developed a broad and deep knowledge base of plasma science, as well as the engineering capabilities for generating, heating, compressing, confining and

manipulating plasma, powerful computational tools and diagnostic techniques. Building on these achievements, vectored and rapid progress towards developing an economical fusion approach suitable for commercialisation can be made. The technical challenges of fusion development are formidable and require creative innovations and patient funding to overcome them. These attributes can be met by privately funded enterprises.

The vast knowledge and technology base of fusion plasma science accumulated over the last 60 years was gained mainly by studying two diametrically opposite and extreme approaches to controlled thermonuclear fusion. At one extreme is MCF, which attempts to create a fusion burning plasma at extremely low densities (~10²⁰ ions per m³) and to confine it in steady state using magnetic fields. This approach is exemplified by the tokamak and stellarator configurations. At the other extreme is laser driven ICF, which attempts to create a fusion burning plasma at extremely high densities (~10³² ions per m³) in a pulsed mode on a nanosecond time scale, by compressing a frozen pellet of isotopes of hydrogen with high-intensity lasers, heavy ion beams, or other drivers.

It became clear by the mid-1990s that creating a burning plasma with either of these two extreme fusion approaches is prohibitively expensive, for reasons rooted in the fundamental principles of plasma physics and engineering. On the one hand, when the plasma density is low, the plasma volume needs to be large in order to keep the loss of thermal energy through its boundaries sufficiently low to create a burning plasma, leading to the use of large volumes of expensive magnetic fields to confine the plasma,



as well as costly hardware to heat the plasma. On the other hand, when the plasma density is very high, the heat loss from the plasma is very rapid, and a very high implosion velocity is required, thus demanding nanosecond-scale drivers of very high-power density which again is extremely expensive.

Integration of energy forms

It gradually became clear that the potential lowest-cost pathway for practical fusion energy based on thermonuclear fusion reactions is to combine the best features of MCF and ICF in a new class of fusion approaches called MIF, by exploiting the intermediate-density regime (10²⁴ to 10²⁹ ions per m³); see figure showing the cost of a fusion breakeven facility versus the burning plasma density³ and for two different qualities of thermal insulation (energy confinement) of the burning plasma configuration. Better energy confinement generally leads to lower cost of the reactor. MIF uses a heavy material shell (called a liner, which could be initially plasma, liquid, or solid) to compress a magnetised target plasma to achieve fusion conditions. It combines the effectiveness of magnetic thermal insulation of MCF with the pulsed, compressional heating of ICF. The heavy liner in MIF provides enhanced inertial containment of the burning plasma pressure more effectively than conventional ICF without such a heavy liner. MIF is indeed a super hybrid of MCF and ICF. Using a much higherdensity plasma than MCF, MIF reduces the size of the fusing plasma from meter scale to centimetre scale. Furthermore, by using a magnetic field in its target plasma and a much-lower density than ICF, MIF can be implemented with low-cost, pulsed-power drivers (microsecond-to-millisecond timescales), potentially lowering the R&D cost and the reactor cost by up to two orders of magnitude compared to MCF and ICF.

Different target and liner formation schemes and their integration are possible, giving rise to a number of embodiments of MIF being currently pursued, presenting a number of opportunities for private investment. In future articles, we will report on a few of these opportunities and the private ventures already underway, and discuss the role of governments in facilitating and accelerating these privately funded fusion ventures.

- (1) Scott C. Hsu, Open Access Government, August 4, 2017. https://www.openaccessgovernment.org/exploring-lowercost-pathways-economical-fusion-power/35785/
- (2) Y. C. Francis Thio, "Magneto-inertial Fusion: An Emerging Concept for Inertial Fusion and Dense Plasmas in Ultrahigh Magnetic Fields," http://www.osti.gov/scitech/biblio/1159661.



Dr. Y. C. Francis Thio and Dr. F. Douglas Witherspoon HyperJet Fusion Corporation Tel: +1 (703) 378 4882 francis.thio@hyperjetfusion.com www.hyperjetfusion.com

⁽³⁾ Lindemuth, I. R. and Siemon, R. E. The fundamental parameter space of controlled thermonuclear fusion. Am. J. Phys. 77, 407, 2009

Time to support 'non-statutory' economic development practitioners

The Institute of Economic Development (IED) puts forward the case for supporting economic development practitioners in local government

Any economic development practitioners in local government who are tasked with the delivery of critical agendas, such as growth and regeneration, say they lack general knowledge about the profession. They are also concerned that they have insufficient local knowledge and skills needed to make a difference to their communities.

This is the key finding of new research from the Institute of Economic Development (IED), the UK's independent professional body for economic development and regeneration practitioners serving local and regional communities.

"In our survey of practitioner challenges, resourcing was cited as the single biggest concern by over a quarter of local government respondents."

In our survey of practitioner challenges, resourcing (especially in terms of department capacity) was cited as the single biggest concern by over a quarter of local government respondents. Others reported challenges in relation to the political environment, policy, funding, organisational culture and their ability to directly support businesses. However, more than a third of respondents (35%) specifically identified gaps in their local knowledge and skills and general knowledge of economic development as the biggest barrier to effective practice.

I must stress this is no fault of, nor should it be interpreted as a negative reflection of, practitioners. The painful reality is that economic development remains a non-statutory function in local government and this is not helpful for improving the UK's prosperity, productivity and competitiveness – this must surely change.

It also shines a light on a more complex challenge, with economic development being such a broad sector and

discipline it can be hard to define. But what I'm seeing, and what I'm hearing by talking to others in the sector, is that many professionals working 'on the ground' are being thrown into roles in local authorities without necessarily having the required comprehension, knowledge and skills-set for being an effective economic development officer.

The apparent lack of general knowledge about economic development can, in part, be explained by many individuals being new to the profession and an acknowledgement of the learning required on an individual basis. The issue around local knowledge and skills, particularly around local initiatives and funding programmes, is more surprising. This suggests the need for improved communication at a local level. What we should all be in no doubt about is that the recognition of a lack of knowledge and skills is a major issue for the effectiveness and success of economic development interventions.

The changing economic climate

In a climate of shrinking budgets, continually limited resources and the delivery of an arguably critical but non-statutory service, staff must not only be equipped with the appropriate tools to deliver economic development but must also have confidence that their colleagues and those partners they rely on are equally well equipped. What I'm hearing is that staff are not always being given the tools to do their job effectively.

So, what be done about it? Well, firstly we need to act on this feedback. Respondents to our research reported that a lack of formal learning and knowledge sharing with peers creates further barriers to gaining sufficient knowledge. Yet 46% said that professional development was 'very important' to them and a further 37% said it was 'somewhat important'. Our



Economic Development Skills and Demand survey, published last November, also highlighted issues around training and development not always being provided due to lack of budget and we called for this to be "higher up the priority list".

So, we are taking the bull by the horns ourselves and are now developing new bespoke training opportunities for economic development professionals. Aligned to our flagship Excellence in Economic Development standard, which is available to public and private sector organisations, we are creating a professional development offering for economic development practitioners that will directly address their issues.

Specific knowledge gaps that were identified around alternative funding models, inclusive growth and place competitiveness are top of our agenda – and we hope this will meet some immediate development needs. We're keen on partnership, and welcome approaches from organisations that want to get involved in sharing their training needs for us to respond to or to work with us to create effective training programmes.



Suzanne Malcolm, Director

The issue around economic development being a nonstatutory function in local government is a longer-term challenge. However, this is something we urgently need to address and the IED will be campaigning for over the next 12 months.

Suzanne Malcolm Director

Institute of Economic Development Tel: +44 (0)1925 730 484 info@ied.co.uk www.ied.co.uk www.twitter.com/theIED



Adapting defence technology to business enterprise

Paddy Bradley, Director, Swindon and Wiltshire Local Enterprise Partnership

n the 23 January 2017, the Government released for consultation its Green Paper, "Building our Industrial Strategy". The consultation sought responses on a range of issues including views on industrial sectors and the structures and processes necessary to enable the UK to be a competitive and successful global innovator and trader. In addition, areas of the country were asked to identify what made them special and distinctive, which would warrant investment to produce world class product and process performance. The 38 local enterprise partnerships in England singularly and in some cases collaboratively, responded with enthusiasm to describe their versions of potential local industrial strategies.

In its response, the Swindon and Wiltshire Local Enterprise Partnership (LEP) identified the outstanding features of the area's economy and focussed on those future-oriented opportunities with excellent scope for expansion. Amongst those economically powerful combinations was the location of major defence technology expertise and the increasingly productive routes to commercially successful enterprises.

The Swindon and Wiltshire LEP is at the heart of a thriving defence science and security technology cluster in central southern England and is home to a range of leading companies including QinetiQ, Porton Biopharma, and Chemring Countermeasures, and major research led organisations such as Defence Science and Technology Laboratory (DSTL) and Public Health England (PHE). Wiltshire is home to a quarter of the British Army and has

Contact details:

Paddy Bradley, Director Swindon and Wiltshire LEP E paddy.bradley@swlep.co.uk W: www.swlep.co.uk major assets in defence and security technologies including; the Chemical Biological and Radiological research and development capability at Porton and through DSTL and the Ministry of Defence (MoD) site at Lyneham, which hosts the Defence College of Technical Training (DCTT), which includes the Defence School of Electronic and Mechanical Engineering. The MoD site at Boscombe Down is an established centre of excellence for aerospace defence and security technology, hosting 2000+ staff.

DSTL manages £380 million per annum of UK Government funding on science and technology projects. The new Porton Science Park, forming part of a wider campus is a unique opportunity offering a state of the art 10 hectare defence and security research and development facility. Porton carries out research to ensure that the UK's military and wider public benefit from the latest technical and scientific developments. The UK Government is investing £115 million in developing new facilities at Porton, which will bring 650 new jobs to the area. Porton has close links to PHE, world leaders in high quality microbiological research and testing, and DSTL, specialising in development of effective countermeasures against chemical and biological events, and Porton Biopharma Limited, established in 2015 to commercialise research outputs into pharmaceutical development and manufacturing. Recently, Boeing Defence UK (BDUK) selected Boscombe Down as its preferred choice for its new UK headquarters delivering 1,500 jobs and a multimillion pound investment. It will work with OinetiO on defence-related aerospace activity. The LEP sees this as the first step in the development of a commercial defence technology site in the south of Wiltshire.

Advanced engineering companies

Swindon and Wiltshire is already home to a wide range of world class advanced



engineering companies including Honda which has recently invested £250m in its plant at Swindon and has employment levels back above precrash numbers. Dyson, one of the UK's leading high technology engineering companies and the country's largest investor in robotics, is creating a new campus at the Hullavington Airfield, near Malmesbury, increasing its footprint in the UK by ten-fold. This is in addition to its £560m commitment to its existing campus at Malmesbury and is a significant vote of confidence in the Swindon and Wiltshire area and the UK. Dyson already employs 3,500 people in the UK, half of which are scientists and engineers.

Swindon and Wiltshire has a range of education and skills facilities to support the expansion of the advanced engineering sector including: the Defence School of Electronic and Mechanical Engineering at Lyneham; QinetiQ Apprentice Training School at Boscombe Down; the Empire Test Pilots School also at Boscombe Down and apprenticeship opportunities at DSTL at Porton.

The combination of these assets and their supply chains lays a firm

foundation for additional skills development in defence engineering and aerospace across central southern England. This will require teaching and research work across a range of colleges and Universities and will support other private sector businesses operating in the advanced manufacturing and aerospace sectors. In the future, these assets will be enhanced by the co-location of defence and public-private defencerelated activity as an unique feature of Swindon and Wiltshire, which has the potential to transform not only the local economy but that of neighbouring areas linking activity in Swindon and Wiltshire with Bristol and Bournemouth and beyond. However, the advanced engineering workforce at higher levels is mobile. This means that the challenge to any area with this type of sector clustering is to cultivate home grown talent to deliver the technical and higher level skills needed to support accelerated developments in this field.

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dstl

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Dstl at Porton © Dstl 2017

UK set to improve in funding research and development

Warwick Business School's Professor Stephen Roper reveals the UK Government's exciting plans for funding research and development in business

istorically, the UK has fallen short in funding research and development compared to its leading international competitors. This may be about to change, however, at least as far as public support for research and innovation is concerned.

The UK Government's Industrial Strategy Green Paper published this spring contained an eye-catching promise, to increase public spending on supporting R&D and innovation by around €2.2bn per annum by 2021. This amounts to increasing public support for business R&D and innovation in the UK by around two-thirds over the next four years. How (and where) should this new spending be allocated? Should we invest in basic R&D which may lead to commercial benefits in many years' time? Or, are we better investing in more applied R&D which is closer to market, and which may do more in the short-term to address the UK's productivity challenges?

Individual scientists and innovators in the UK will have their own priorities, of course, and there is probably a good case to be made for more investment in many areas of scientific and innovation activity. But what does the evidence say? And, what can we say about where the returns from investment are greatest?

New data

A new study recently published by the UK Enterprise Research Centre provides at least some of the answers. This study, the first comprehensive assessment of the business benefits of grants from the Research Councils and Innovate UK, examined the impact on business growth and productivity of all Research Council and Innovate UK grants for research and innovation provided between 2004 and 2016. It looked at around 10,000 companies which participated in publicly funded research or innovation projects over this period, and compared their performance to a closely matched control group drawn from the one million or so other UK businesses (with employees).

The findings are encouraging. Firms which participated in publicly funded projects – and these were primarily funded by EPSRC and InnovateUK – grew their turnover and employment 5.8-6.0% faster in the three years after the project, and 22.5-28.0% faster in the six years after the project, than similar non-participating firms. There were also productivity gains of around 6% over six years.

Increased spending

So, the UK might anticipate significant positive benefits from the new Challenge Fund spending. Patience will be necessary, however. Challenge Fund investments in 2018 -2020 will not have their greatest effects on business performance until 2024- 2026. Whether this is before or after post-Brexit trade deals are concluded between the UK and other countries remains to be seen, but investments such as the Challenge Fund will contribute to the future international competitiveness of UK firms.

The new research also provides an indication of what types of firms benefit most from participating in publicly funded science, research and innovation projects. Figure 1 illustrates this in terms of the impact on turnover growth over the six-year period following the start of the project. For all firms (the top bar) being part of a project adds 28% to turnover growth. This effect is larger for manufacturing firms, particularly in high-tech industries. It is also larger where firms are smaller. Larger firms benefit less in proportional terms.

Plausible explanations for these results relate to larger firms' stronger financial resources, and the higher cost



Figure 1: Turnover growth impact of participating in publicly funded science, research and innovation projects after 6 years (%)

of manufacturing v service sector innovation. For those seeking to maximise the returns to future Challenge Fund investments, however, the messages are clear: think smaller firms, think high-tech manufacturing.

Looking forwards there is significant anxiety within the UK research and innovation community about the effects of Brexit. The extent to which leaving the EU will undermine existing research networks, reduce available funding and make the UK a less attractive place to do science remains uncertain despite reassuring noises from politicians. This is not just a funding question. Restrictions on researcher mobility – and a perceived climate of hostility – also have the potential to reduce the flow of scientific talent to the UK.

In 'normal' times, the boost to public support for research and innovation which the Challenge Fund represents would be a significant boost for UK innovation. The anticipation of Brexit and its potential implications changes a bold policy initiative into what may turn out to be an insurance policy for UK innovation. The author is director of the Enterprise Research Centre (<u>www.enter-</u><u>priseresearch.ac.uk</u>) and professor of enterprise at Warwick Business School.

The link for the research referred to in the article is: <u>www.enterprisere-</u> <u>search.ac.uk/publications/accessing-business-performance-effects-re-</u> <u>ceiving-publicly-funded-science-research-innovation-grants-research-p</u> <u>aper-no-61/</u>

Professor Stephen Roper Director, Enterprise Research Centre

Warwick Business School Tel: +44 24 7652 2501 Stephen.roper@wbs.ac.uk www.wbs.ac.uk www.twitter.com/SteveRop

Backing innovation for commercial success

Dr David Wilkes, Innovate UK's Deputy Director – Connect Portfolio explores the importance of driving UK productivity and economic growth by supporting businesses to realise the potential of new technologies

nnovate UK is the UK's innovation agency. We are government funded, but business focused, and innovation and business led. Since 2007, Innovate UK has been driving UK productivity and economic growth by supporting businesses of all sizes to realise the potential of new technologies, develop ideas and make them a commercial success.

The impact of innovation on the productivity and performance of businesses is clear. We know that businesses that innovate grow faster and export more than those that do not innovate. We also know that innovation accounts for between 25-50% of productivity, and firms that innovate are more productive than their competitors. The robust <u>programme evaluations</u> that we carry out prove what Innovate UK does works – significantly boosting jobs, turnover and productivity – and, as we look to the future, we have a strong foundation to build on in the years ahead.

Our work is also backed up by independent research. A recently study done by the Enterprise Research Council – 'Assessing the business performance effects of engagement with publicly-funded science' – looked into research and development grants over a 13-year period. It tracked the impact of grants totalling £8 billion, which went to nearly 15,000 firms. Included in this number were grants from Innovate UK.

The findings showed, across all grant recipients, employment grew by 6% in the short-term and 23% in the longer-term (after 6 years), turnover grew by 6% in the short term, and 28% in the longer term, productivity grew by 6% in the longer term and an estimated 150,000 new jobs were created, many in highly-skilled sectors such as biotechnology, medical equipment, engineering, life sciences and high-tech manufacturing. Innovate UK can help companies overcome some of the most significant barriers which businesses report, from lack of finance to access to markets. Our grant funding helps to de-risk innovation projects sufficiently to bring in private sector investors. It also helps to support collaborations within supply chains, between sectors and, critically, enables businesses to work closely with the research base. Without the incentive and support of the government, many of these collaborations would never get off the ground.

In the past ten years, Innovate UK has invested around $\pounds 2.2$ billion in businesses right across the country, matched by $\pounds 1.6$ billion from those businesses. We've helped more than 8,000 organisations and created around 70,000 new jobs; with a return on investment of more than $\pounds 7$ for every $\pounds 1$ of government money.

We have also established the world-class <u>Catapult net-</u><u>work</u>, which ensures that UK businesses have access to state-of-the-art facilities wherever they are in the UK. They provide a perfect environment for university and business collaboration.

Connectivity and competition

Innovate UK currently runs funding competitions across four broad sectors (emerging and enabling technologies; health and life sciences; infrastructure systems; and manufacturing and materials) as well as an open category for projects regardless of their technology or sector.

We also help companies by connecting them to the partners they need to innovate, whether they are researchers, suppliers, customers, or collaborators. This is primarily through our two business facing networks – the <u>Knowledge Transfer Network</u> and the



Dr David Wilkes, Innovate UK's Deputy Director

Enterprise Europe Network. We can help businesses to find the right expertise, facilities, financiers and influencers that can help them bring their ideas to market.

We are also innovating ourselves, in the way that we finance innovation, including through innovation loans (with a £50 million pilot programme from April 2018) and engaging with the Venture Capitalist community to provide the match funding for small businesses under-taking early stage feasibility projects (<u>www.gov.uk/gov-ernment/news/accelerating-innovation-with-public-and</u>-private-investment-apply).

Looking forward, Innovate UK has a vital role to play as the government continues to develop its Industrial Strategy. To support this ambition, the government has committed an extra £4.7 billion over the next 4 years.

We are transforming existing industries and helping to create completely new ones through the new Industrial Strategy Challenge Fund, delivered by Innovate UK and our colleagues in the UK's Research Councils. It aims to tackle the biggest societal challenges and technology opportunities facing the UK such as efficient medicines manufacturing, robotics and artificial intelligence (AI) and better batteries for electric vehicles. It is important we are developing UK industries that are fit for the future, driving progress in technologies where the UK can become a world-leader in their research and commercialisation.

This significant commitment and confidence from the UK government enables Innovate UK to identify opportunities across our economy so that we can support businesses to grow, create more highly-skilled jobs and spread the benefits of our economic success right across the country.

For further information and to stay updated on our latest news visit <u>www.gov.uk/innovateuk</u>, follow us on Twitter at <u>@innovateuk</u> or subscribe to our YouTube channel at <u>www.youtube.com/InnovateUK</u>.

Link to the ERC study – '<u>Assessing the business per-</u> formance effects of engagement with publicly-funded <u>science</u>'.

Innovate UK's funding reports data overview: https://innovateuk.blog.gov.uk/2017/08/29/innovate-uks-201617-fundingreports-what-do-they-tell-us/

https://www.gov.uk/government/publications/innovate-uk-funded-projects

https://datavis.innovateuk.gov.uk/

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Innovate UK

Dr David Wilkes Deputy Director – Connect Portfolio Innovate UK Tel: +44 (0)300 321 4357 support@innovateuk.gov.uk www.gov.uk/innovateuk www.twitter.com/innovateuk

Priorities for rail transport in Denmark

Ove Holm, from the Danish Transport and Logistics Association (DTL) reveals his opinion on the challenges around rail transport in Denmark, including ERTMS

The Danish Transport and Logistics Association is the trade organisation for the Danish road and rail transport sector. DTL represents its members on political issues at local, national and EU level, as well as helping its members with everything from legislation to specific problems within the companies. DTL is also an employers' association for the Danish transport sector. This allows us to cover the needs of the entire sector.

DTL has 2,000 transport companies as members. They oversee 10,000 lorries, 59 locomotives and a total payroll of DKK 5.3 billion. In this interview, Ove Holm, deputy director and policy affairs manager at Danish Transport and Logistics Association (DTL) outlines the priorities for rail transport Denmark, including rail safety and interoperability.

Electrification is a major priority for the rail industry in Denmark, Holm explains as the interview begins. The country is still running diesel locomotives and this makes it expensive to buy new locomotives with diesel engines he tells us. Holm calls for full electrification of the country's rail system and says it is very important that this is rolled out. He then tells us more about Denmark's ERTMS (The European Railway Traffic Management System system) – in his own words.

"DTL thought it might be an advantage in terms of safety and operation, but we have seen that it is not positive for Denmark right now as it is very expensive and we are running into problems in that we are using three different versions of ERTMS (Swedish, Danish and German). We therefore think it is an important priority to get ahead with this – but we have recently received a report from the European Court of Auditors on ERTMS and they even visited us here at DTL." Overall, the European Court of Auditors found that the deployment of ERTMS was based on a strategic political choice and had been launched with no overall cost estimate, or appropriate planning for a project worth up to €190 billion by 2050. Even though the ERTMS concept and the vision of enhancing interoperability are not generally questioned by the rail sector, so far ERTMS deployment has been low and patchy they found. Even if EU funding could be better managed and targeted, it can only cover a limited amount of the costly investment.

The Court made several recommendations including: the assessment of ERTMS deployment costs; decommissioning of national signalling systems; compatibility and stability of the system; alignment of national deployment plans, monitoring and enforcement as well as the absorption of EU funds for ERTMS projects¹.

Holm then turns our attention to how DTL is looking to Norway, which means looking at the tracks and there are some issues on that stretch, between the two countries. Holm tells us more.

"There are some infrastructure challenges on that track, which we would like to fix, but it costs money. Getting the goods from the western part of Norway to Denmark and other parts of the Europe is important to us. Now, the freight trains are passing the Great Belt Fixed Link between East and West Denmark, but it was decided that a fixed link across Fehmarnbelt between south-eastern part of Denmark and Germany should be built (the project will consist of a four-lane motorway and a double-track electrified railway, in an immersed tunnel, to open in 2028), to get between and Sweden, Denmark and Germany, so we will have a 200km short cut" Holm explains².

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Holm then highlights the message he would like to convey to the current Minister for Transport, Building, and Housing, Ole Birk Olesen. Investment in the northern part of Jutland and getting to grips with ETMRS would be brought into any conversation between DTL and the Ministry of Transport, Building and Housing, Holm explains.

Holm goes on to suggest that the Ministry should slow down the introduction of ETMRS in Denmark, to work towards one harmonised system, as opposed to using 3 different types. He suggests that investment by the government should be made in one type of system – that works for Sweden, Norway and Denmark – so that trains can easily cross over borders.

Signalling systems

The Ministry is currently committed to the implementation of delivering two new signalling systems: the common European Rail Traffic Management System (ERTMS) level 2 on the Main Line along with a Communication Based Train Control (CBTC) system on the suburban network, in the Greater Copenhagen area (the S-train network). We read of the Ministry's website that: "In most cases, the current signalling systems on the Danish railway network are more than 30 years old and a mixture of different technologies that are not able to function well together."³

In terms of the Ministry's support for rail, it is worth pointing out that earlier this year; they announced that private operators will be able to bid for more railway routes in Denmark. This is due to an agreement concerning the tendering of Danish rail traffic, which was entered into by a broad majority in the Danish Parliament in June this year. Minister of Transport, Building and Housing, Ole Birk Olesen, comments:

"Providing Denmark with significantly more rail transport is part of the Government's manifesto and...we are taking an important step along the way. At the same time, we will ensure the future of direct rail connection between Copenhagen and Struer, via Herning, which has long been a strong local desire."

"It is important that we develop a modern, effective and market-oriented railway network. The extended tender for Central and West Jutland is a step along the way. But our work doesn't stop here", the Minister added³. Holm at DTL then brings in an environmental flavour to the conversation, in terms of rail freight. He says we need to have a fully electrified railway and that if DTL could have a bigger market share of rail freight, that would help matters enormously.

"It would make more sense to have heavy and long-distance goods on rail, but of course Denmark is a small country so in this vein we are thinking more about exporting goods that can make a difference. Added to that, we have a regulation on how to calculate environmental impacts of transport which only count on the global, but not on the Danish level."

On the challenges and opportunities that lie ahead for the rail industry in Denmark, Holm reveals that the government have supported the Great Belt Fixed Link and have proposed to lower the toll by 25%, but this does not apply to freight trains. Holm explains more on this, as the interview ends.

"It's counter-productive to do this if you want to get more goods on to rail, so DTL have asked the government why they don't include rail freight in the overall equation. The Ministry of Finance said they have scare capacity on Funen (Fyn in Danish, Denmark's second largest island) than on the bridge itself. We suggested a possible night time rebate or other slots during the day – where there isn't scarce capacity.

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Ove Holm Deputy director Policy affairs manager

Danish Transport and Logistics Association (DTL) Tel: +45 70 15 95 00 oho@dtl.eu

Research project on railway switches and crossings: INTELLISWITCH

Professor Dorte Juul Jensen project leader of INTELLISWITCH provides insight into the world of railway switches and crossings in Denmark

"By

using

an

approach, a reliable, intelligent quality

assessment with one or more Mainte-

nance Performance Indicators (MPIs)

witches and Crossings (S&Cs) are an essential part of any railway network, as they enable trains to be directed from one track onto another at railway junctions, allowing for necessary flexibility during train operations. At the same time, they are also one of the most vulnerable parts of the railway network, suffering from moving parts and from peak stresses because of their greater geometric complexity, compared to normal tracks. As a critical part of the railway, poorly maintained S&Cs have a detrimental impact on railway operations.

In Denmark, 3000 trains run every day on the 2000 km of the railway network, annually transporting 170 million passengers and 15 million tonnes of freight. In this network, there are roughly 3500 S&Cs, which are currently inspected manually, in a regular schedule by staff from the infrastructure provider Rail Net Denmark, who determine the condition of each S&C. Their work is supplemented by automated inspections with measuring vehicles. Rail Net Denmark has an excellent track record in this respect.

With the aims of reducing inspection and maintenance costs, getting detailed know-how on the degradation process and developing new prognosis tools, the INTELLISWITCH research project was therefore formulated with the following hypothesis:



Figure 1. The project organisation

Funding and organisation

To achieve our goals, it was clear from the start that a multidisciplinary approach would be needed, and that substantial funding should be available. Added to this, a close collaboration between Rail Net Denmark and academia would be critical. The funding was assured through the Innovation Fund Denmark, who support the project with 12.7 MDKK (approx. 1.7 MEUR).

for individual S&Cs can be integrated with existing fault prediction tools (such as measuring vehicles). It can also be used to predict the appropriate maintenance operations in advance, thereby significantly decreasing the number of regular manual inspections."

interdisciplinary

STARTING POINT



The project partners are Rail Net Denmark and three departments at the Technical University of Denmark; namely the Departments of Electrical Engineering, Mechanical Engineering as well as Applied Mathematics and Computer Science. To take advantage of the broader knowledge within the field, 4 European partners are affiliated to INTELLISWITCH, namely from Chalmers University of Technology, Norwegian University of Science and Technology, University of Birmingham and Graz University of Technology.

Each work package has a leader from the Technical University of Denmark, as well as a "business owner" from Rail Net Denmark. This is to ensure that those of us at the university are always aligned with the practical needs of the project and remain grounded in what we do. In our opinion, this organisational model functions extremely well. An overview of the project organisation into work packages (WPs) is given in fig 1.

Progress so far and the priorities moving forward

The first task of INTELLISWITCH in WP1 was to acquire a sensor system to be mounted in a selected S&C, which could continuously capture data of the right type, format and quality from designated measurement points on the S&C. As a requirement, the installation should not involve any modification of existing track components and the sensors should be mounted either in sleeper drilling zones, or on rail pieces. Based on a limited tender process, a measuring system consisting of several 2-axel accelerometers (vertical and lateral measurements), vertical displacement sensors and wheel sensors was delivered and mounted on an S&C in Funen, where 80-100 passenger and freight trains pass daily.

After various challenges, including connection and mounting issues as well as problems with the tough environment, the system has now been delivering data for about a year, which is being used in the other work packages for identification of changes over time in both the superstructure and substructure of the S&C.

The next focal point for the INTEL-LISWITCH, is the development of a robust signal-based condition monitoring system for both the diagnosis and prognosis of the health state of the S&C (in WP2). Towards this end, research has been conducted to identify a low-complexity behavioural model of the turnout, which can be used to predict the vibration levels associated with trains. In particular, the identified model is tuned to closely capture the contributions of the ballast layer and rail pad to the overall infrastructure vibration. The predictive capability of the model is tested against the measured vibration data, when trains at different speeds pass the selected S&C on Funen. An excellent agreement between experimental and modelling data has certainly been achieved.

In WP3, a novel methodology to carry out track degradation assessment in the S&C is implemented, by using a commercial multibody dynamic software. The process is divided into two different phases. In the first one, a train/track interaction analysis is developed and assessed by evaluating the contact forces between the train and the track. In the second phase, the forces at each particular support element, beneath the rail, are taken out and transformed by applying a degradation law, into vertical displacements that in turn are applied as longitudinal level irregularities in the corresponding rail nodes. The process is completed by including the updated geometry, enabling the continuation of the calculations, in a loop mode



(see figure 2), considering as many cycles as required.

In the metallurgical work package (WP4), the damage and degradation of Hadfield type manganese steel crossings have been investigated, using metallographic techniques such as 3D X-ray tomography and microscopy. A detailed characterisation has been made with reference to the measured hardness profiles, microstructure of plastically deformed material, strain distribution, as well as nature of the crack network. It is observed that the deformation hardening at the running surface, where there is wheel-rail contact, of the crossing nose as well as the wing rails extends deep within the material to depths up to several millimetres. Upon wheel transitions between the wing rail and crossing nose, an impact will occur which causes cracks to form. These cracks networks have been characterised non-destructively, using X-ray tomography, an example of a 3D reconstruction from a crossing nose is shown in figure 3.

Whereas each of the above-mentioned WPs (2-4) will develop MPIs focusing on their specific discipline, e.g. the metallurgical degradation, WP5 will try to take advantage of all these, plus relate the new data from the sensor measuring system to existing Rail Net Denmark data. The latter are both manually measured data on unloaded S&Cs, as well as loaded data obtained by the measuring vehicles passing the S&Cs.

Earlier investigations have relied on using just one value to characterise the S&C. This is not recommended, due to the complexity of the S&C. The S&C is therefore split into three different regions, (a) the switch panel, (b) the closure panel, and (c) the crossing panel. Thereby the unique mechanical behaviour of the three regions can be investigated. Now the MPIs can be defined based on the local values. Finally, we aim to extract important features, by lowering the dimensionality of the data taking advantage of the correlation structure among the variables.

Conclusion

In short, the progress so far is very positive – indeed several models for the response of the S&C to train passage, including degradation, are in place, deformation mechanisms of the metallic parts have been identified and the various measurement data are in the process of being aligned.

We are therefore confident that a series of MPIs can be deduced, to create a basis for more intelligent data-driven decision support to both the maintenance and renewal of S&Cs. This will reduce life cycle costs and ultimately increase future reliability, punctuality and the safety of the railway infrastructure. Improving passenger comfort and travel experience will make rail travelling more attractive, as well as being a major step towards ensuring a more sustainable transport sector.

INTELLISWITCH

Dorte Juul Jensen

Professor Section of Manufacturing Engineering DTU Mechanical Engineering Tel: +45 452 547 77 Mobile: +45 222 646 57 doje@mek.dtu.dk www.intelliswitch.dk



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Right on track – the future of European rail

Nicolas Furio from Unife explores the latest developments in the all-important European rail industry and what they mean for the future

n April 2016, the European Parliament overwhelmingly approved the Council Common Position on the Technical Pillar of the Fourth Railway Package. Hailed as the single most significant achievement in European rail legislation to date, it aims to remove remaining administrative and technical barriers in the sector, harmonise and accelerate the processes of vehicle authorisation and safety certification and harmonise the implementation of ERTMS.

It is in fact estimated that the technical pillar of the fourth railway package will bring a 20% reduction in the time to market for new railway undertakings and a 20% reduction in the cost and duration of the authorisation of rolling stock, leading to a saving for companies of €500 million by 2025.

However, while this was a major step towards the achievement of a Single European Railway Area and increasing the competitiveness of the railway sector, it was only the starting point of what will be a long journey. In fact, the Technical Pillar of the Fourth Railway Package, which comprises the recast Interoperability and Safety Directives and the revised Regulation on the European Union Agency for Railways, gives the latter and the sector three years to prepare and implement the new regime.

Already one year into the three-year implementation phase, the technical pillar is entering a critical stage for the adoption of the necessary implementing regulations, setting out the practical arrangements for vehicle authorisation and safety certification, amongst others.
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Once adopted, the European Union Agency for Railways is scheduled to be part of a shadow running phase from June 2018, before becoming fully operational a year later.

"With the right financial support, the rail industry will maintain its position at the top of the world market, continue to thrive in research and innovation, and further its role as a key lever for social inclusion, economic growth and environmental sustainability."

The 'Implementing Regulation on practical arrangements for the railway vehicle authorisation and railway vehicle type authorisation process, pursuant to Directive (EU) 2016/797' is due for vote in the November RISC (Railway Interoperability and Safety Committee) by Member States. This is a critical document regarding the impact and benefit of the Fourth Railway Package.

Future innovation

Meanwhile, and more specifically regarding interoperability, DG Move's ERTMS Deployment Action Plan will be officially adopted at the ERA CCRC2017 conference during November 2017. This Action Plan identifies barriers to achieving interoperability and incorporates significant steps that have already been taken so far, while recognising that the basic regulatory framework is in place and focusing on the concrete actions and defined deadlines. A co-ordinated deployment will drive down costs and deliver significant benefits, to help the rail industry be more competitive.

Between policy advances and continued innovation, Europe is on track towards a more efficient and more competitive rail industry, despite the challenges.

We need, however, to make sure that that the post-2020 Multiannual Financial Framework adequately funds rail research and innovation – and that other innovative financing sources are tapped as well. European rail supply companies have been partners in Public Private Partnerships (PPPs), and there is rich know-how on structured finance within the industry.

The European Fund for Strategic Investments (EFSI) should also play a key role in fostering private investment in important long-term transport infrastructure projects – to date the number of these types of projects in the rail sector is far too low. Finally, Connecting Europe Facility (CEF) Transport grants should continue to be the cornerstone of the EU Investment Policy in the transport sector.

With the right financial support, the rail industry will maintain its position at the top of the world market, continue to thrive in research and innovation, and further its role as a key lever for social inclusion, economic growth and environmental sustainability.

Nicolas Furio Head of technical affairs Unife Tel: +32 2 626 12 60 general@unife.org www.unife.org www.twitter.com/UNIFE

Asset management in rail: cognitive computing

CEO of ZNAPZ, Marcel Van Velthoven provides a compelling perspective on how cognitive computing can assist asset management in rail

he variables in the rail industry, especially in rail infra are numerous. Asset management in rail with all the variables in a reliable way is a challenge. However cognitive computing which has recently become available, can make a big difference. In the article below is described what kind of questions can be asked and what answers and reliable information can be obtained.

Assets just don't break or fail as a coincidence. Something has happened that has started or accelerated the deterioration process. Identifying what has happened or is happening becomes one of the standard possibilities with today's assets. This information can be obtained and with cognitive computing, a realistic prediction becomes possible. The challenge is to combine many different data sources and to develop a realistic pattern of the ageing of the asset.

Some examples

It is well known that the rail and the rail system, switches, power lines are affected by the traffic. What was the speed of the train, what was the load of the train, what was the weather condition and what was the quality of the bogies that contacted the rail? Getting this data together, preferably in real time was, until recently absolutely impossible, however it is becoming standard today.



On today's tracks, the temperature of the track is permanently measured, as well as the vibration. This varies of course when a train passes. A train passing gives the first pattern of vibration and temperature of the track. This can be combined with the train speed and load and the weather conditions. This combination gives a good first impression of the effect of the passing train, on the quality of the track.

Taking it, a step further can per bogie be identified what the quality of the wheels, the roundness, is. Even a non-significant deviation does already have a significant effect on the rail track quality and life expectation. All this data can easily be send to a central computer which makes profiles of the train journey, speed and load and the quality of the relevant assets in the train affecting the asset life of the track.

Looking ahead, when it comes to cognitive computing and Internet of things (IoT), real-time information can be interpreted and analysed. Taking in account all factors, e.g. customer delay minutes, asset life, maintenance cost and capabilities, we can generate a real-time signal identifying what the train speed should be along the trajectory that the train should take. It will become a dynamic journey, taking in account the trains time schedule and physical status of the train and the track.

Firstly, we can focus on asset life and deterioration, but soon we can identify



how special conditions lead to a shorter or longer asset life and how this can be optimised, taking in account the specific speed of the train under these specific circumstances.

Watson can make these predictioczlns today. Even better with all the variables, even variables we may not think of today, Watson, the cognitive computer from IBM will be able to recognise patterns over time and dynamically adjust the recommended driving conditions for the train. A combination from trains driving close after each other may have an effect that currently isn't taken in account and also a passing train could have an effect.

With the dynamic guidance of Watson and the recommended speed, the train could be guided to pass the other train at the best-chosen area. This demonstrates how artificial intelligence will make its entree in the rail infra world enabling the rail infra company to take appropriate actions, to generate the highest value from its rail assets over the lifetime, while managing risk and cost.

The non-standard deviations of the track can be identified using modern technology, such as drones or also measurement trains. The data gathered from these inspections can be interpreted by Watson, after a learning period, where Watson has been thought what is the right condition of the track and what is an abnormal condition. Bends, curves, corrosion, corrosion frequency and acoustic information can be analysed to create the most accurate profile of the status of the track.

Watson will support the asset operator to optimise rail performance, while minimising risk and cost in a real-time fashion. This dynamically against all the measurable variable conditions that can occur. The first step is the asset operator should identify how Watson will be educated. Watson is the next step in rail asset performance.



Marcel Van Velthoven CEO ZNAPZ Tel: +31 402 668636 info@znapz.com www.znapz.com

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The key role of the aviation sector in the UK economy

Graham Bolton, Chairman of the British Aviation Group provides an insight into the role of the aviation sector within the UK economy

The aviation sector plays a key role in the UK economy, contributing some £20 billion per annum to the economy and directly supporting around 230,000 jobs. The national and international connectivity it provides supports trade in goods and services; enables inward and outward tourism; whilst connecting friends and families around the world.

With one of the world's largest and most competitive aviation markets, the UK aviation sector is of global significance, setting standards for operational performance and promoting innovation. We are home to one of the world's top ten airports for passenger satisfaction, the world's busiest single runway, and we lead in adoption of new technologies for aviation security and passenger processing.

Building on the experience gained at UK airports, the British Aviation supply chain supports development and operation at airports of all sizes around the world – with UK businesses providing goods and services to all the world's largest 50 airports, and a wide cross section of the balance.

Despite the significance of the aviation sector, the development of our airport infrastructure has at times lacked strategic direction from national government – whether in planning for new capacity or in the integration of airports with the wider transport network. Perhaps, with a draft National Policy Statement on expansion in the South East, and development of a national strategy in progress, we can hope for a clearer and more consistent direction in the future.

So how then can government support the sustained development of this sector, in both its planning for post Brexit trade, and in development of the Aviation Strategy?

Ensuring the market stays open

Firstly, and perhaps most urgently, it is essential that arrangements are made to maintain market access for when the UK leaves the European Union. Our membership of the European Common Aviation Area (ECAA) and bilateral agreements between the EU and 3rd countries currently govern air access to 44 countries, accounting for around 85% of the UKs international connections. With airline tickets typically going on sale up to a year in advance, a plan for spring 2019 is urgently needed to protect connectivity both within Europe and globally.

Secondly, we need the development of a national strategy for aviation that allows all airports to plan with confidence the capacity required for sustainable traffic growth. The first step in this process should be adoption of the National Policy Statement for capacity in the South East in early 2018, but this needs to be complemented by wider consideration of capacity needs across the nations and regions of the UK.

Growth in airport capacity will need to be aligned with modernisation of UK airspace – delivering greater capacity, and thereby reducing cancellations and delays, and minimising the impact of aviation on communities and the environment. The implementation of changes already outlined in the 2017 consultation will require continued government commitment and resourcing by the CAA.

Likewise, airport expansion will need to be coordinated with a strategy for ground transport that achieves a more sustainable and passenger centric integrated transport solution. Surface access to Heathrow is already considered in the draft NPS, with the wider importance of connectivity to airports such as Stansted highlighted by the earlier work of the Airports Commission. Improved rail

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connectivity to all main UK airports should be a national priority – to be achieved through a combination of new physical infrastructure and updated operating models.

"Despite the significance of the aviation sector, the development of our airport infrastructure has at times lacked strategic direction from national government – whether in planning for new capacity or in the integration of airports with the wider transport network. Perhaps, with a draft National Policy Statement on expansion in the South East, and development of a national strategy in progress, we can hope for a clearer and more consistent direction in the future."

Maintaining the UK's influence

Finally, we should take the opportunity to ensure that the UK remains at the forefront of innovation to improve safety, environmental performance and passenger experience. Our aviation sector currently leads the world in areas such as air traffic management, passenger processing and screening, and sustainable building design – based on collaboration between regulators, operators, and supply chain.

Cross governmental support for investment in and application of new technology and process – such as

roll out of biometrics for identify management or autonomous vehicles for airside operations – will help us maintain this position. This should be underpinned by our continued involvement in multi-national agencies and initiatives, including the European Aviation Safety Agency (EASA) and single European sky (SESAR) programme.

So then, as the UK government develops future domestic transport and international trade policy, there is a clear challenge: are we prepared to recognise the value that the aviation sector brings to Britain as a global trading nation, and provide a policy environment under which it can continue to thrive?

Graham Bolton

Chairman of the British Aviation Group Market director for aviation, Atkins Graham.Bolton@atkinsglobal.com

www.britishaviationgroup.co.uk www.twitter.com/BritishAviation

Reducing the effects of turbulence on aircraft

Professor Jonathan Cooper at University of Bristol's Faculty of Engineering describes how reducing the effects of turbulence can also benefit the environment

e are all familiar with airline pilots telling us to put our seat-belts on due to the possibility of turbulence occurring during a flight. All aircraft are subject to sudden motion in the atmosphere causing turbulence, sometimes referred to as gusts, when they fly which can cause sudden motions in flight. "Bumpy air" not only causes discomfort to the passengers, but also causes stresses and strains to occur throughout the aircraft. Designers ensure that the structure is strong enough to deal with the loads¹ occurring due to turbulence, but this results in heavier aircraft which are less fuel efficient².

One solution to reduce the effect of gusts acting on an aircraft, sometimes referred to as "gust load alleviation", and consequently reduce the aircraft weight by requiring less structure to deal with the loads, is to make use of a Gust Alleviation System. Modern commercial jets are often equipped with computer controlled "fly-by-wire" systems – that couple motion sensors in the fuselage with the ailerons (control surfaces at the trailing edge of the wings).

When the aircraft enters turbulent air, the resulting motion is sensed and the control surfaces are automatically moved in such a way to reduce the movement and the loads. It is usual when an aircraft enters a longer patch of turbulence that the spoilers (flap type devices on the wings that are



Glamour Model in the Politecnico di Milano Wind Tunnel



mostly used on landing) are deployed so that the loads are reduced. Such technologies have been available for the past 20 or so years, but they are continually being improved.

Schematic of the GLAMOUR Wind Tunnel Model

Research into reducing the effects of turbulence

The European Community's "Flightpath 2050" initiative has many goals focussed upon the European aerospace industry, primarily aiming to develop significantly improved environmental aircraft performance (less emissions and less noise) and enabling vastly more efficient design and certification processes. One of the key instruments for funding research to achieve these goals is the Clean Sky programme,



Model in the Wind Tunnel Showing Gust Vanes

now on its second phase, which has developed a large number of technology demonstrators to validate advances in a wide range of different technical disciplines (e.g. aerodynamics, structures, control, etc.)

The GLAMOUR³ (Gust Loads Alleviation Techniques Assessment on Wind Tunnel Model of Advanced Regional Aircraft) project was funded under the Clean Sky Joint Technology Initiative and involved the Politecico di Milano (Lead - Italy), IBK (Germany), University of Bristol (UK), Technion (Israel) and Re Fraschini (Italy). The project aimed to develop novel control algorithms for the control of gust loads on a representative regional aircraft (~100 passengers), in particular investigating the use of both control surfaces on the wings and aircraft tail, and the effect of different means of sensing the turbulent air flow.

The most promising techniques were then demonstrated upon a unique wind tunnel model which was designed and manufactured specially for this project. The model consisted of half of a scaled aircraft with a wing of 2m length and a fuselage that was 4.5m long. Control surfaces were included on the wing and the horizontal tail surfaces. Special attachments were designed so that the model could behave in heave (up and down) and pitch (aircraft nose up and down) in the wind tunnel, in the same way as the aircraft would in flight. Gust vanes were also designed so that controlled turbulent airflow could be input onto the model. The response of the model at different wind airspeeds and levels of turbulence was measured using 3D cameras and accelerometers, and the capabilities of the different control algorithms to reduce the motions and loads was explored in a dedicated wind tunnel test campaign.

It was shown that it is possible to make significant reductions in the motions and loads resulting from the turbulent flows, through the use of the active gust loads alleviation schemes, and that it is particularly beneficial to make use both the ailerons and elevators simultaneously.

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Professor Jonathan Cooper Faculty of Engineering, University of Bristol Tel: +44 (0)117 33 15819 j.e.cooper@bristol.ac.uk www.bristol.ac.uk/engineering/

The Education Policy Institute and education performance in England

Executive Director of the Education Policy Institute, Natalie Perera shares her reflections on education performance in England today

n August this year, the Education Policy Institute published new research which considered the extent to which education performance in England would need to improve, to match the top performing nations. 'English Education: World Class?' analysed the latest PISA data from 2015 and, using the grades of pupils in England who then went on to take their GCSEs in 2016, the report provided an estimate of how well pupils in many of the top performing countries would have performed if they had taken GCSE exams.

We presented our findings using the new numerical scale for GCSEs (9-1, with 9 being equivalent to the top end of an A*) for maths and English. While a grade 4 is considered a standard pass under this new system, the Department for Education has confirmed that a grade 5 is a 'strong pass', with many universities already stating that they will consider a grade 5 as their benchmark.

The results were striking. As we might expect, the top 5 performing nations in mathematics are all in East Asia (Singapore, Hong Kong, Macao, Taiwan, and Japan). We estimate that their average GCSE grade in maths would be 5.4. The average grade in England in 2016 was 4.7. This means that the average grade in England will need to improve by around two-thirds, to match the highest performing nations.

The challenge is not quite so significant in reading. The top performing countries in reading are more varied than in maths and consist of Singapore, Hong Kong, Canada, Finland, and the Republic of Ireland. The average grade amongst these countries is 4.9 and pupils in England are already achieving an average grade of 4.7. Nevertheless, this still requires us to get an additional 42,000 pupils into the 9 – 5 points bracket (or A* - C in old money). Our research therefore confirms that the



Department for Education has set the new 'strong pass' at the right grade – a grade 5.

So, what now? Clearly there needs to be overall improvement in grades if we want to be amongst the world leaders but we need a better understanding of what might be holding us back. We don't have all the answers but recent research by EPI, as well as by the OECD, sheds some light on where we might improve.

Firstly, there is significant variation in England. If we translate our grade 5 pass mark across all 8 GCSE subjects taken (typically) by a year 11 pupil, then we would expect that pupil to achieve an overall score of at least 50 points to achieve a 'world class' standard – and we'd expect at least 50% of the population to reach

EDUCATION & YOUNG PEOPLE



this. While there were 14 local authorities in England that exceeded this benchmark, there were 8 others that were more than 20 percentage points below it. The system it seems then is working well for some, but it's failing others.

Teacher's work conditions

Another factor could be the workload and pay of teachers in England. A study by the EPI last year found that teachers in England work some of the longest hours across the OECD, report some of the highest levels of workload and have fewer opportunities for Continuous Professional Development than most other participating nations.

In addition, a recent report by the OECD also found that teacher's pay in England declined by 12% in real terms, between 2005 and 2015 (for those with 15 years or more experience). While teacher pay in England remains like that in Finland, we should ask ourselves whether these overall trends are enough to recruit, retain and motivate the profession.

England also fares badly in relation to early years education. We estimate that 40% of the socio-economic gap that is present at age 16, emerges by or around age 5. Despite this, total expenditure on the early years represents only 0.5% of GDP (in the UK), compared to an OECD average of 0.8%. Even then, unlike most of our international counter-parts, most of funding comes from the private purse, rather than the public. Given that another OECD study found that children who attended pre-school for two years or longer performed better (by around half a year) at age 15 than those who didn't, this area is ripe for further investment in both access and quality.

These are only three areas which merit further investigation, when considering how to raise standards in England. The list could go on, not least to include pedagogical solutions as well as structural. And we also need to look beyond raw attainment. Young people in the UK score below the OECD average on life satisfaction, with many reporting bullying and exam anxiety as key concerns. As we've discovered, international comparisons are immensely useful in helping to benchmark our own performance – but they must also be used carefully, without simply 'cherry picking' the things we like or those that seem easiest to adopt.

Natalie Perera Executive Director Education Policy Institute Tel: +44 (0)20 7340 1160 info@epi.org.uk epi.org.uk

Bercow: children's communication skills ten years on

Mary Hartshorne, Head of Evidence at I CAN, the children's communication charity writes about the importance of good language and communication skills

ur ability to read, to learn, to develop and sustain relationships, manage our emotions and mental well-being all rely on good speech, language and communication skills. There is good evidence to show the links between spoken language and these life skills, and when most people think about it, it is obvious.

What is less obvious to many is the significant numbers of children and young people without good language and communication skills. 7.6% of children have a developmental language disorder that persists throughout school and impacts on learning, and on their social and emotional development; at least two pupils in every classroom. In some deprived areas of the UK this figure is much higher – as many as 50% of children start school without the language they need to learn, learn to read or make friends.

"There is still a need for a strong business case to be made for prioritising identifying and supporting language disorder; early identification and intervention can save money in the short and long-term."

The impact of this is well evidenced. Without support, children and young people with a language disorder risk poor life choices and chances. They are four times less likely to achieve a good level at the end of primary school, and four times less likely to get good GCSEs.

There are also wider impacts; two thirds of excluded children from school have language disorder, along with 45% of young people referred to mental services and 60% of young offenders.

And yet with support, these children and young people can do well.



Ten years ago, John Bercow MP led a cross government review of services for children and young people with speech, language and communication needs (SLCN). At that time, he found huge variability in services across local areas. The joint commissioning needed across health and education just wasn't happening.

He also found a significant need for the children's workforce to understand about the importance of speech, language and communication, how to identify problems as early as possible and put effective intervention in place.

The government backed action plan that followed the review really set the scene for change, with local authority pathfinders trialling new approaches to commissioning, and a national year of communication led by the government's communication champion.

However, since then, there has been widespread change to the political, economic and social landscape; the whole system for supporting children and young people with special educational needs and disability has been transformed, driven by the need to give more power and choice to parents.

EDUCATION & YOUNG PEOPLE

New research

Now a decade later, I CAN and the Royal College of Speech and Language Therapists are conducting an inquiry, Bercow: Ten Years On, to find out exactly how the situation has changed for children and young people with SLCN and their families. The inquiry heard evidence from over 2,500 practitioners, parents, commissioners of services – and from young people themselves. It also draws from a raft of relevant reports and recent research.

Throughout analysis of this evidence there have been consistent themes: The commissioning landscape has matured, and where it happens joint commissioning is effective – but it is rare. Financial cuts in local authorities have meant shrinking specialist services such as speech and language therapy, but although much more is known about the most effective models, cuts do not reflect this.

As a result, provision is fragmented and not 'joined up' leaving parents frustrated, with difficulty accessing support, which is unacceptable. A national programme of research into children and young people's SLCN, which followed the 2008 review left a 'what works' database of effective interventions as a legacy; more recently a national centre of research into young children's speech and language has given us robust evidence about the very early signs of SLCN.

Difficulties can be identified as early as two years of age, and yet we do not have robust enough screening tools to do this. Over the last ten years, there has been a positive trajectory of change across the workforce; more people are confident in their knowledge and skill in identifying and supporting SLCN. But still this is not enough and as many as half of children and young people with language disorder are missed, or misidentified.

In 2008, the vision was that children's speech, language and communication and services to support SLCN would be mainstreamed. We are still a way off this, but in our recommendations, we are keen to pinpoint exactly what will make a difference and to identify the levers, which will help to make change happen. At a strategic level integration of services is an aim both in health services, through the move to accountable case systems, and in education through the implementation of the special educational needs reforms. The risk is that SLCN services fall between the two. Examples of effective joint commissioning need to be considered, modelled and shared as part of these processes.

In the most effective services, children's SLCN is integrated in local strategy: children are routinely screened for language difficulties as early as 18 months; early years settings use early years pupil premium funding to train practitioners in early language; schools analyse their data knowing that poor progress in literacy, exclusion, mental health issues are red flags for language disorder; youth offending services know the prevalence of SLCN and screen in, not out; services regularly collect and analyse outcome data not just numbers of children seen or assessments carried out.

Clearly, for many people there is still a need for a strong business case to be made for prioritising identifying and supporting language disorder; early identification and intervention can save money in the short and long-term. We have the evidence we need to make this and the evidence from our review to identify the key features of good, effective practice.

Over the next few months we will be building and testing emerging recommendations for a range of stakeholders, based on our evidence analysis, with the aim of achieving systems change. Publication of the report in spring 2018 will provide the evidence and platform for discussion, influencing and review with the aim of improving services for children and young people with SLCN.



Mary Hartshorne Head of Evidence info@ican.org.uk I CAN Tel: +44 (0)20 7843 2510 www.ican.org.uk www.twitter.com/ICANcharity

What causes specific language impairment?

Mabel L Rice from the University of Kansas describes how nonverbal cognitive impairments are neither necessary nor sufficient

'hildren's language starts out very simply and grows with age. Yet some children do not keep up with their age peers. This is a developmental condition known as "language impairments," which sometimes but not always exists when children have other developmental disorders, such as hearing loss or cognitive impairments. The cause of children's language impairments is not known. People often draw upon the observed overlap with other obvious developmental disorders such as hearing loss, intellectual impairments, autism spectrum disorder (ASD), Down syndrome, or Fragile X to conclude that language impairments share the same underlying cause. This assumption, although widespread, is off the mark in important ways and can create misleading impressions of children with language impairments and their families.

Instead, the acquisition of language follows a distinct pathway. This is evident in documentation of selective sparing of language in children with cognitive impairments and selective impairment of language in children's development, most notably in children with Specific Language Impairment (SLI). This is the most common, but unrecognized, developmental disorder of childhood, which most likely persists into adulthood for many of the affected children. Best estimates are that 7-10% of children who have no hearing loss or other developmental delays show language impairments at school entry, around 5 years of age^{1,2}.

The language of children with SLI is not the same as unaffected children, yet also shows many of the same strengths³. Important features of SLI are that children are not likely to outgrow it, are likely to encounter difficulties in learning to read and likely to struggle in other academic endeavors. People can assume the children may not be very bright, or are simply poorly motivated, assumptions that only add to the frustration of children with undiagnosed SLI.

Selective sparing of language acquisition in cases of very limited cognitive abilities

To unpack the relationship between general cognitive ability and language ability, let us begin with cases of selective sparing of language in persons with very limited cognitive abilities. Such children have been documented in the literature for a long time and are of interest to scholars of the origins of human language abilities. For example, one well documented phenomenon is the "cocktail party syndrome" for some patients (adults or children) with spina bifida and/or hydrocephalus, in which subnormal intelligence co-exists with excessive talking comprised of superficial content but well-formed and sometimes quite complex grammar⁴. A detailed case study is reported of an adolescent female referred to as "D.H." She functioned in everyday life situations at the level of significant cognitive impairments. Yet in her spontaneous conversation her language appeared to be normal, with appropriate syntax, vocabulary and interactive topic maintenance. The conclusion of the linguists who studied her was that she had skillful use of all aspects of language, in spite of her cognitive impairment, posing a puzzle that persists to the present⁴.

"The cause of children's language impairments is not known. People often draw upon the observed overlap with other obvious developmental disorders such as hearing loss, intellectual impairments, autism spectrum disorder (ASD), Down syndrome, or Fragile X to conclude that language impairments share the same underlying cause."

Another well documented case history describes a young man with limited cognitive abilities who had extraordinary linguistic prowess. He was a native speaker of English, with a diagnosis of brain damage of an unknown kind. His performance IQ scores were between 42 and 75 (100 is expected) and his verbal IQ scores were between 89 and 102 (also with 100 as expected). As a young adult, he lived in a sheltered community with assistance with daily living activities. He had a remarkable ability to translate from and communicate in a large number of languages, with some knowledge of Danish, Dutch,



Finnish, French, German, Modern Greek, Hindi, Italian, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, Turkish and Welsh. His linguistic abilities were studied in great detail by linguists hoping to capture the underlying properties of universal grammar that were spared in his condition⁵.

Children with ASD are often thought of as having language impairments and limited cognitive abilities. Yet the recent revision of the Diagnostic and Statistical Manual of Mental Disorders: DSM-5⁶ revised the diagnostic criteria for ASD to demote language impairments from a centrally defining characteristic to a "specifier" condition. This means that ASD can be officially diagnosed in children with or without language impairments, and with or without intellectual impairments. Instead, deficits in social communication and social behavior are crucial to diagnosis, as are restrictive, repetitive patterns of behavior, interests, or activity. In other words, the DSM-5 criteria recognize that classic language impairments are not intrinsically interconnected with social communication deficits or repetitive behaviors, and are not diagnostic of ASD.

Documentation of independence of language impairments and cognitive impairments in population-based samples of children

Population-based studies recruit a large sample of children representative of the full range of children in the population. When all children in the sample are measured, it is possible to identify children with SLI and children who have low nonverbal IQ but do not have language impairments. Either of these groups are likely to be unidentified by educators or other special service providers if there is a strong assumption of causal overlap for cognitive impairments and language impairments in children without other obvious developmental disabilities indicative of brain damage or other syndromic conditions. The evidence required to evaluate this possibility is expensive to obtain because assessments should be individually administered to each child for domains of language and nonverbal cognitive abilities. This is time-consuming and requires well trained data collectors, in addition to experts in experimental design and quantitative analyses. One such study^{2,7} is of interest here because measures from the same 5-year-old children are reported for general language assessment, nonverbal IQ, a grammar marker⁸, and speech disorders9. Children were excluded from the sample if they had neurological disorders, clinical syndromes, and/or hearing loss. The outcomes can be presented as percentages of children who fall into four groups based on levels of language ability and nonverbal IQ: 1) Typical or above in both language and nonverbal IQ; 2) Low levels of both language and nonverbal IQ; 3) Typical language and low nonverbal IQ; and 4) Low language and typical or above nonverbal IQ (i.e., a profile consistent with SLI). See another paper¹⁰ for more details about the assessments in the study.

The results are displayed in Figure 1. Two cells, indicated in red and pink, are expected to collect all the children if language and nonverbal IQ are tightly associated in a shared causal pathway. Instead, we see nontrivial exceptions in the off cells: Children with low nonverbal IQ but nevertheless typical or above language scores (~12%) (shown in yellow cell), and children with SLI (low language with typical or above nonverbal IQ) (~8%)



(green cell). The expected red cell of "typical children" captures 75% of the sample; the expected pink cell of low language and nonverbal IQ captures 5% in this sample which excluded children with neurological disorders. So roughly 20% of the children show a profile inconsistent with the assumption that low nonverbal abilities cause SLI. The conclusion is that low nonverbal IQ levels are neither necessary nor sufficient for language impairments in children.

On a more detailed level, there is evidence in support of selective sparing of certain properties of the grammar. English sentences have a requirement for grammatical tense marking (also called "finiteness marking") for a full clause. This is especially evident in questions with DO, such as "Where does he go?" The form of DO is required to mark tense and agreement with the subject, without any contribution to the meaning of the sentence. Other indicators of grammatical tense marking are copula and auxiliary forms of BE, third person singular -s, regular and irregular forms of past tense¹¹. Young English-speaking children are likely to use these forms optionally where they are required in sentences for some time before they consistently use them, a period that persists for children with SLI^{12,13}. Thus, there is reason to think of this grammatical requirement as "weak" in some children. The results are shown in Figure 2, which reports the mean percentage correct for grammatical tense marking. Five years of age is when typically developing children are reaching full mastery, with a group mean of .90 or 90% use in obligatory contexts as shown in the red bar of the figure. The Low Cognition group is not statistically significantly different,

with a mean of .86 (yellow bar). On the other hand, the SLI group scores statistically significantly lower, with a mean of .78 (green bar), and the Low/Low group is lowest, with a mean of .71 (pink bar). The pattern across the groups provides further support to the possibility of selective sparing of grammar in children with low nonverbal IQ even when they do not have classic clinical syndromes associated with developmental disorder, as documented in the cases above. Thus, the grammar marker of SLI is not diagnostic of low nonverbal IQ.

The assumption that low nonverbal IQ causes SLI could be related to the ways in which children who do not match our expectations can remain undetected. The cases of selective sparing of language can cause people to assume a child has robust nonverbal IQ when this is not true, thereby



leading to frustration for the child in school where a lack of nonverbal ability can be attributed to low motivation or poor study habits. On the other hand, children with SLI often go undetected in part because they develop compensatory ways of avoiding situations that call for more language ability than they have. This can be apparent in their avoidance of advocating for themselves in childhood disputes with peers, or avoiding verbal participation in class activities. Another way they remain invisible is that most children with SLI do not have clinically significant speech disorders, even at school entry. In the study reported in Figures 1 and 2, 98.2% of the children had developmentally appropriate speech in a measure adjusted for mild misarticulations, such as a frontal lisp, that may be evident at 5 years but are likely to be outgrown by 7 years of age. The rate of speech impairments in children with SLI was estimated at 0.51%, suggesting that speech disorders and language impairments are likely to appear independently in young children. The rate of speech impairments in the low/low group was 0.77%; in the low nonverbal/typical or above language group the rate was 0.5%. A recent population study also reported

high levels of speech ability in children with language disorders¹ although the groupings were not defined out in the same ways as the study reported here, i.e., the prevalence estimates for the low nonverbal IQ group included children who did not have language impairments.

The conclusion is that the common assumption that children with SLI are not very bright is not warranted. Instead, children with SLI can have normal or above nonverbal IQ levels and children with low nonverbal IQ levels can have language abilities as expected for their age. Further, these non-confirming conditions/cells are not rare, comprising about 20% of the population. Language can be selectively impaired or selectively spared. This means scientists need to search for two possible causal pathways that sometimes intersect, instead of one common cause. It also means the common assumption needs to be suspended when encountering children likely to have SLI.

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Mabel L Rice University of Kansas Tel: +1 785 864 4570 mabel@ku.edu www.ku.edu

INDEX

Aalto University – Business School	248-249
Agile Business Consortium.	258-259
ALKENoNE Project	. 304-305
Ambrosus Technologies.	. 236-238
Biobank Graz	24-25
Biochemical Technology Research Division.	. 312-313
Bouygues Energies and Services FM UK Ltd	. 290-291
Brock University – Faculty of Social Sciences	284-285
Bull s.a.s Atos Technologies – MONT BLANC Project	. 270-271
CARDIS Project.	88-89
Climate Service Center	. 330-331
CRHEA-CNRS	226-227
Department of Animal Biology, University of Illinoi	. 324-325
Department of Biological Sciences, The George Washington University	190-191
Department of Biology & UF Genetics Institute	. 194-196
Department of Biology New Mexico State University	188-189
Department of Biomedicine	. 118-121
Department of Cell Biology & Histology, Faculty of Biology	. 164-165
Department of Chemistry – Washington State Univers	200-201
Department of Clinical Medicine – Department of Haematology	60-61
Department of Emergency Medicine – BRIPPED Project	76-77
Department of Entomology	. 364-365
Department of Geosciences.	320-321
Department of Industrial & Manufacturing Engineering	. 166-167
Department of Nuclear Medicine	. 102-103
Department of Orthopaedics.	72-73
Department of Pharmacotherapy and Translational Research	32-34
Department of Psychiatry, University of Utah.	30-31
Department of Zoology	346-347
Division of Biostatistics & Research Support.	98-99
Dole Human Development Center	. 408-411
DTU CEN – Center For Electron Nanoscopy	42-44
Dublin City University.	. 170-171
Eindhoven University of Technology – Department of	
Biomedical Engineering	84-85
Faculty of Geosciences	C, 340-34 1
FCIÊNCIAS.ID.	218-219
FEAM	14-15
Fujitsu Scanners	0-261, IBC
Fujitsu Services LTD.	252-253
Hard Winter Wheat Genetics Research Unit	. 360-361
HealthyMinorCereals Project.	. 350-351
Hewlett Packard.	266-267
Hygiena International LTD.	. 148-149
HyperJet Fusion Corporation.	. 380-381
IBM Research Zurich.	. 230-231
imec.istart business accelerator program	. 254-255

Institut National de la Sante et de la Recherche Medicale	68-69
Institute for Energy Technology	308-309
Institute of Pathology – University of Lausanne	56-57
INTELLISWITCH Project	392-394
Laboratoire de Tribologie et Dynamique des Systemes	162-163
Lloyds Register Quality Assurance LTD.	274-275
Ludwig Maximilians University Munich	174-175
Marshalls PLC	278-279
MASTERCARD	264-265
MAXIMUS GREEN LIMITED	376-377
Medical and Pharmaceutical Research Unit	112-113
Natural History Institute	192-193
New York University School of Medicine	64-65
Nordic Built Active Roof & Facades	334-335
Norwegian Polar Institute	316-317
On Target Laboratories (OTL).	52-53
Pfalzklinkum fur Psychiatrie und Neurologie Ador	36-37
PLACEmaking	288-289
Portland State University	142-143
Poultry Science Department.	368-369
Power on Connections Ltd	374-375
Professor Colin J Suckling	114-115
ROBUST Project	224-225
Safetell	280-281
School of Chemical Science and Engineering	208-209
Scientific Institute of Public Health	16-17
Swindon Wiltshire LEP	384-385
Swiss Re	230-231
TAURA Project – Universite Clermont Auvergne	154-155
Technische Universitat Chemnitz.	176-177
The City of Varberg	338-339, OBC
The Connecticut Agricultural Experiment Station	362-363
The Lin Brain Lab	138-139
Tieto	246-247
TOMRA Systems ASA	300-301
UC Davis Department of Molecular Biosciences	212-213
UCB	132-133
UCL	126-127
University of Bristol – Faculty of Engineering	402-403
University of California.	45-47
University of Coimbra	92-93
University of Florence – Physics Department	80-81
University of Florida	328-329
University of Luxembourg – Laboratory of Solid Structures	182-183
University of Missouri, Columbia.	358-359
Van't Hoff Institute for Molecular Sciences (HIMS)	204-205
Znapz BV	398-399

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With responsibility towards the Swindon and Wiltshire community, its people and the environment

Swindon and Wiltshire is an area of major economic significance; attracting substantial overseas and UK investment. Its pivotal location in central southern England offers direct links to London, Heathrow, Oxford, Bristol, Cardiff, the Midlands and beyond.
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The Swindon and Wiltshire Local Enterprise Partnership (SWLEP) is a business-led partnership between Swindon Borough Council, Wiltshire Council, local businesses, the military and the education sector. The SWLEP is making over £518m investments to drive local economic growth. To know more about the SWLEP and the Swindon and Wiltshire area, please visit <u>https://www.swlep.co.uk/why-swindon-wiltshire</u>



www.swlep.co.uk



REINVENTING THE COMMUNITY

building on creativity

reativity, innovation and a strong focus on social and cultural aspects of sustainability are at the very heart of developing the Municipality of Varberg to become the Swedish West Coast's Creative Hot Spot by 2025.

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