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NORTH AMERICA ANALYSIS

THE ROLE OF RESEARCH IN THE FUTURE OF AGEING

DR YVES JOANETTE, SCIENTIFIC DIRECTOR AT THE CIHR INSTITUTE OF AGING EXPLORES HOW CANADA'S RESEARCHERS ARE MEETING THE NEEDS OF AN AGEING POPULATION

IN THIS ISSUE

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Gene expression and Huntington's disease

Naoko Tanese from New York University explores how monitoring gene expression can be used to treat neurodegenerative diseases such as Huntington's.

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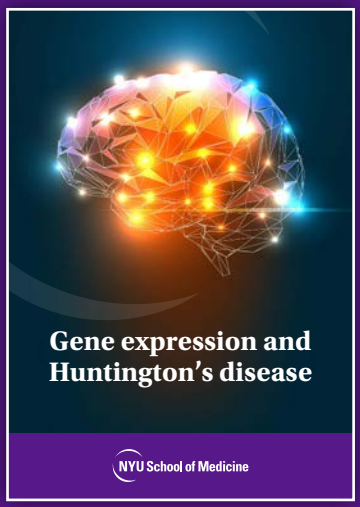

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INTRODUCTION

Welcome to the packed July 2018 edition of North America Analysis. One of the many insights in this edition comes from Leora Fox, Jennifer Simpson and George Yohrling from the Huntington's Disease Society of America. In their article, they explore the sources of funding in the development of therapies for Huntington's disease (HD) in the U.S. today.

We also include a fascinating piece from Dr Yves Joanette, Scientific Director at the CIHR Institute of Aging. In his insightful comment piece, he explores how Canada's researchers are meeting the needs of an ageing population, now and in the future.

A further health insight comes from David Bearman, M.D., Executive VP of the American Academy of Cannabinoid Medicine. In his analysis, he details the research priorities for cannabis, one of the most thoroughly studied plants of all time.

Heading up the research & innovation focus, we are thrilled to feature a compelling article by Dr Juan C. Meza, Division Director for the Division of Mathematical Sciences (DMS) at the National Science

Foundation (NSF). This article reveals exactly why mathematics is such a powerful tool for understanding the world around us, we find out.

Also, in this summer edition, we are pleased to feature an article on advancing open access and open data in higher education. This comes from Jaime Adams at the U.S. Department of Agriculture and Anne Mims Adrian, PhD at Auburn University.

Finally, one guest article worth mentioning here is from Marta Pierkarska, Director of Developer Ecosystem at Hyperledger who reveals her thoughts on the current status of blockchain technologies in the world today.

I trust that you find this publication useful and insightful. Please do reach out if you have any ideas for compelling content for the future, or perhaps you'd like to provide comments on this edition. ■

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Nanomedicines: Depicting human health risks hindering clinical translation

Cecilia Van Cauwenberghe from Frost & Sullivan shares her expertise on the world of nanomedicines, with a special focus on depicting human health risks hindering clinical translation

By way of background, although nanomedicines hold the promise of contributing to provide therapeutically efficient and early-stage diagnostics accuracy, the clinical translation of nanomedicines face numerous challenges. Reproducible manufacturing, efficient scaling-up, appropriate formulation, accurate characterisation, in vivo instability and bioavailability, disease heterogeneity, epigenomic impact, potential toxicity, immune response, regulatory barriers, safety issues and ethical concerns, represent some of the multiple hurdles hindering the clinical translation of nanomedicines.

Furthermore, despite the vast number of opportunities in treating complex and rare diseases, including cancer, derived from the advent of nanomedicines development, the dichotomy between nanotechnology and nanotoxicology remains unresolved. Novel methods attempting to address this concern are emerging driven by the advent of new paradigm-shift approaches.

Nanomedicines overview: The nanoscale effect

Singular features and industry impact

Engineered at an unparalleled small scale, nanomaterials display distinct chemical, physical and biological properties in comparison to those observed in the same compounds at a larger scale. Consequently, it is these features that make nanomaterials extremely versatile and potentially applicable to all industries impacting upon modern lifestyle, including biomedicine. Nevertheless, the same properties could make nanomaterials increasingly unpredictable once interacting with other agents, especially where cells and tissues are concerned.

Nanomedicine constitutes a field of molecular medicine that exploits the ability to control individual properties and combined behaviour of atoms and molecules to build complex functional medicines, ranging from drug delivery vehicles, diagnostic and imaging technologies, analytical tools and theranostic platforms, among many other products, for their application in medicine (Vance et al., 2015; Sharma et al., 2017).

Regarding basic design, a nanomedicines library comprises of a combinatorial approach based on: 1) size, ranging from 1 to 100 nanometers (nm); 2) shape, usually sheet, tube, fibre, sphere, cube; 3) surface, varying charge, crystalline structure, coatings, defects, impurities; and 4) functionality, related to optical, electrical, mechanical, or chemical behaviour. Regarding targeting design, nanomedicines can be structurally, chemically and thermodynamically built to carry small molecules, genes, antibodies, peptides, or radioactive materials, either inside or at their functionalised surface. Among the most commonly used nanomedicines, liposomes, polymers, metals and metal oxides and composites, can be cited. Ideally, nanomedicines respond to certain parameters, such as pH, temperature, or light, to trigger a controlled release of their payload. This controlled action also helps to protect both the host from unintended exposure to an active drug or compound and the drug or agent from being detected by the host's surveillance system or being disintegrated by an adverse microenvironment. Therefore, a great specificity and fine-tuning control must be guaranteed (Etheridge et al., 2013).

Clinical validation: The nanotoxicity potential

Understanding complex biology

Overall, biological effects induced by nanomedicines are associated with their fluctuating, random and sometimes unstable physicochemical behaviour within tissue microenvironments. Naturally, through the complete past decade, notable efforts have been

devoted to developing suitable in vivo, in vitro and in silico toxicity testing assays, intending to assess nanotoxicity. One of the first impediments found is related to nanomaterials insolubility and tendency to aggregate, which derives from all types of test sensitivity failures and significant interference with optical measurements, hence remarkably challenging test validation methods.

Furthermore, the extremely high degree of variables because of a potentially unlimited set of nanomedicines constructions, along with the multiple biological functions and pathways impacted by each nanomedicine, make conventional test validation obsolete (Hare et al., 2017).

Accordingly, while the development and expectations of nanomedicines generally increase, a standard methodology for safety testing of nanomedicines and human health risk assessment is yet to be instituted. Meanwhile, in vitro human cell culture models and in silico approaches combining molecular biology, artificial intelligence and adaptive omics data analytics, more oriented to mimic complex biology, are gaining attention.

Concerning epigenetic regulation

An aspect that cannot be ignored when analysing the human health risks of nanomedicines pertains to their interaction with the genetic material and potential induction of genotoxicity and mutagenicity. By mediating inflammatory responses and oxidative stress process, nanomedicines may trigger epigenetic modifications related to the onset of cancer. DNA methylation, histone modifications and interacting regulative non-coding RNAs, constitute the epigenetic mechanisms strictly regulating gene expression in both the normal and disease microenvironment (Van Cauwenberghe, 2018a).

Consequently, nanomedicines validation requires a solid demonstration of null nanomaterial-induced genotoxicity, that is, nanomedicines must not impair the expression of genes involved in DNA methylation reactions, methylation or acetylation of histones and/or expression of micro RNA (Smolkova et al., 2017).

Meeting artificial intelligence (AI)

Cellular functions are controlled by sophisticated communication routes and signalling pathways between cells, driven by knotty networks of genes, peptides, proteins and metabolites that interact with each other operating as messengers, sensors, regulators, promoters and/or inhibitors of internal and external signals (Halappanava et al., 2017).

Due to their size and ability to interact at tissue microenvironment levels, nanomedicines studies demand an in-depth knowledge of systems biology complexity to carry out sensitive toxicity testing approaches and drug safety evaluation strategies (Agrahari and Agrahari, 2018). Artificial intelligence (AI), including machine learning and deep learning approaches, among many other developments, is prone to improve the complete nanomedicines development process by exploiting large sets, multisource data, to transform them into usable and actionable knowledge and decision-making tools, while leaving behind years of trial-and-error drug development. By allowing the assessment of dozens of trillion data points in a single tissue sample, the building of multi-physics modelling and simulation and the correlation of thousands of sources, AI platforms can be optimally suited to identify new drug targets and to design novel nanomedicines, while minimising screening time and enhancing patterns identification, among many other applications. The necessary step is a strong combination of AI-based technology with biological sciences, especially metabolomics.

This branch of science allows carrying out the quantitative and qualitative scrutiny of all metabolites present in the human body because of both normal and disease processes in diverse organs and tissues. Hence, technologies based on metabolomics approaches, enable the translation of biological outputs to therapeutic candidates. Moreover, the assessment of drug efficacy and safety can be carried out by detecting changes in metabolite profiles, which can be measured significantly faster and simpler than genetic or protein responses (Van Cauwenberghe, 2018b).

In addition, the smart synergy between omics science and AI technologies may outstandingly help to maximise the benefits of the unique combination of adaptive, omics-based biological data and advanced AI machine learning algorithms to build accurate predictive models for nanomedicines clinical validation.

Final remarks

The clinical translation of nanomedicines presents several hurdles. Indeed, at the very early stages of discovery and development, nanotoxicity, including nanomaterial-induced genotoxicity, constitutes one of the principal challenges to overcome in the future.

Systems-level approaches appear highly promising, especially due to their capability to evaluate individual parts of the system, such as the tissue microenvironment, very precisely, accurately, promptly, systematically and exhaustively. Leveraging terabytes of data generated by a single experiment by high-content omics technologies, the industry is focusing its attention on artificial intelligence (AI) learning approaches allowing assessing, interpreting, organising and controlling the quality and reproducibility of big data generated by each of these systems. Hence, the impact of nanomedicines on the genome, proteome, lipidome and metabolome can be smartly assessed thanks to the development of AI-based intelligent frames for data mining, model curation, statistics visualisation and pattern correlation.

Although still in progress, this technology convergence is expected to significantly impact upon the healthcare sector soon, enabling the emergence of programmable nanomaterials, highly appropriate to precision medicine approaches.

Acknowledgements

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Further reading

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CD33-directed therapy: Current and future perspectives on targeted therapy in acute myeloid leukaemia (AML)

Mohammed Gbadamosi and Jatinder K Lamba from Department of Pharmacotherapy and Translational Research at the University of Florida explain CD33-directed therapy for acute myeloid leukaemia (AML), focussing on current and future perspectives

Acute myeloid leukaemia (AML) is a complex heterogeneous disease characterised by a variety of cytogenetic abnormalities and recurrent molecular mutations and aberrant expression patterns. As the most common and second most common leukaemia in adults and children respectively, many strides and efforts using new technologies and personalised treatment approaches are being undertaken to address and improve therapy surrounding the disease.

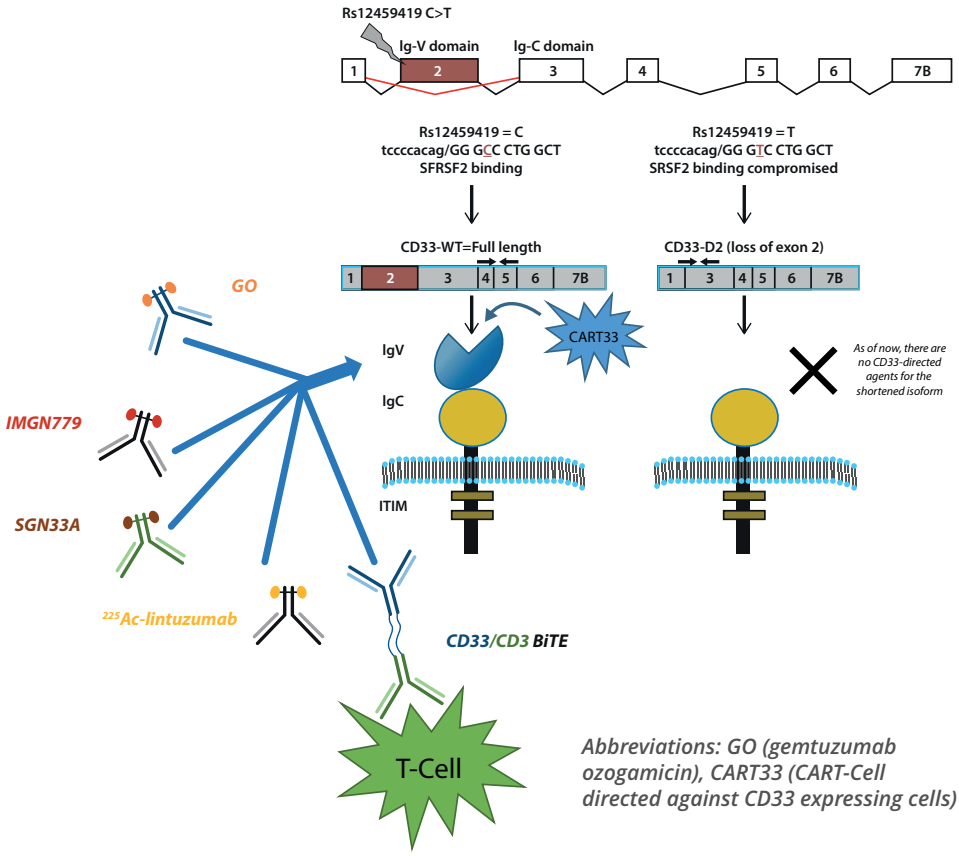
However, despite these efforts, outcomes surrounding the disease remain abysmal. In particular, for younger patients, complete remission (CR) rates of greater than 80% are achievable, however, the 5-year overall survival (OS) still remains relatively low at ~40% in comparison to other cancers due to high relapse rates. The outcome is even worse for older patients with five-year overall survival at less than 25%.[2] To address these poor outcomes, several targeted therapeutics have become popular additions to the mainstay 7+3 induction therapy.

Among these promising options are CD33-directed immunotherapeutics including antibody drug conjugates, as well as other CD33-directed therapies using newer technology like bispecific T cell engaging antibodies (BiTE) and chimeric antigen receptor T-cell (CART) therapy. The efficacy of these CD33-directed therapies is rooted in the ubiquitous nature of CD33 as an antigen marker present on AML blasts in 90% patients making it a potent distinguisher of AML blasts.[3] While its specific biological function is yet to be elucidated, CD33 is a known regulator of various cell processes related to calcium mobilisation, cytokine release and transcriptional activation.[4] Additionally, CD33 is internalised when engaged with antibodies thus making it an ideal vehicle for antibody-based therapies.

Emergent CD33-directed therapies

The recognition of this internalisation mechanism is the inspiration behind many of the ADCs targeting CD33 such as gemtuzumab ozogamicin (GO; Mylotarg™) which recently received reapproval by the FDA in September 2017. GO is structurally composed of hP67.6, a CD33-directed monoclonal antibody, covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin.[5] The story of GO in AML has been remarkable, starting with accelerated approval in 2000 based on promising results from phase II studies, voluntarily withdrawn in 2010 due to increased induction death and no observed survival benefit in the post approval phase III study. Despite these setbacks, much has been and still remains to be learned from the story of GO and results from multiple subsequent phase III clinical trials have allowed recent breakthrough re-approval of GO as a low fractionated dose for treatment of AML.[6-8]

Following GO, several other ADCs directed to CD33 were designed and are currently undergoing development. Vadastuximab talirine (SGN33A) is generated through conjugation the CD33-directed antibody lintuzumab and a pyrolobenzodiazepine dimer.[9] Early clinical trials in relapsed AML have shown encouraging results, but unfortunately, due to a higher rate of deaths in phase III clinical trials, all SGN33A studies have been placed on hold. At this time, the cause of these early deaths is not clear, further work will be required before the potential of SGN33A can be re-evaluated for treatment of AML. IMGN779 is another ADC directed to CD33 using a humanised anti-CD33 antibody



Abbreviations: GO (gemtuzumab ozogamicin), CART33 (CART-Cell directed against CD33 expressing cells)

Z4681A and contains DGN462, a novel DNA-interacting IGN molecule. [10] With encouraging results from *in vitro* studies, phase I trials are for IMGN779 currently underway. Newer approaches using alpha particle therapy and other radioimmunology-based strategies have also shown encouraging results. ^{225}Ac-lintuzumab, the premiere the therapeutic of this drug class for AML uses ^{225}Ac to generate α-emitting isotopes, which induces a cytotoxic dose of alpha radiation killing AML blasts.[11] Promising preliminary results from a first-in-man safety and pharmacology study, as well as preliminary data on the feasibility of combinatorial treatment regimen are currently available.[12]

CD33 has also been explored for use in the realm of T-cell therapy. AMG330, a CD33/CD3 Bi-specific T-cell engager (BiTE), contains two fused single-chain monoclonal antibodies, which allows AMG330 to simultaneously take advantage of the pervasive nature of CD33 as an antigen in AML and the activation pathway of T-cells through CD3 binding.[13] In essence, AMG330 works by recognising CD33^{+} AML blasts and forming a link to neighbouring T-cells. The connected T-cell then releases proteins, which induce apoptosis of the AML blast. *Ex vivo* and *in vivo* studies using patient samples and immunodeficient xenograph mice models respectively have demonstrated effective recruitment of T-cells by AMG330 and significant inhibition of tumour growth. Chimeric antigen receptor T-cell (CART) therapy, using CD33 as a target, is being investigated as well. CART cells targeted to CD33 (CART33) are developed by using a disarmed virus to engineer the T-cells to produce receptors for CD33 on their surface.[14] Preclinical experiments have demonstrated potent anti-leukemic activity of CART33, with much excitement surrounding the development of next-generation CART cells targeted to CD33 as well as other strategies surrounding the use of CD33 in CART therapy.

How can we improve CD33-directed therapy?

With a growing catalogue of CD33-directed therapeutics, interest surrounding treatment paradigms utilising CD33 have been piqued (Figure 1). Specifically, factors influencing crucial steps related to internalisation processes, release and activation of a therapeutic warhead, the intracellular levels and DNA binding capabilities of cytotoxic agents, as well as the efficiency of downstream DNA damage repair pathways and apoptotic pathways can play a critical role in defining the therapeutic efficacy of CD33-directed agents.

Expression levels of CD33 have been evaluated from multiple phase II and phase III clinical trials of GO. Previously, *in vitro* data have shown CD33 expression to be associated with greater GO efficacy; however, results from initial clinical trials in adult AML patients have shown conflicting results with CD33 expression with clinical response. Overall, the relationship between CD33 blast expression levels is inconclusive with follow-up studies needed, however, this information can be used to determine patients should receive CD33-directed agents based on the potential benefit to be gained.

In our group, we have described genetic polymorphisms in CD33 that may be related to the response of GO.[15] Through our studies, we have identified rs12459419 (C<T; Ala14Val) as a critical regulator of response. Located in exon 2, rs12459419 is a coding SNP present within four base pairs of the intron/exon junction and impacts the exonic splicing enhancer binding site for SRSF2 resulting in skipping of exon 2. The shorter CD33-isoform (D2-CD33) lacks the IgV-domain due to alternate splicing. Loss

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of the V-set antibody binding domain has two significant implications: it appears that most (perhaps all) available diagnostic antibodies are directed at the V-set domain, thus carriers of the T allele for rs12459419, would appear to be CD33 negative due to the lack of inclusion of the V-set domain. More importantly, loss of the V-set domain would directly affect the binding, internalisation and clinical efficacy of CD33-directed therapeutics. Altogether, these results suggest that loss of IgV domain due to presence of the splicing SNP compromises GO efficacy and, similar to expression levels, CD33 genotype can be used as a means of stratification to decide patients who will benefit from regimens including CD33-directed therapeutics.

While targeted immunotherapy is still relatively young in the realm of AML treatment, their potential in changing the field forever is palptiable. Ultimately, much more additional research is needed to understand the capacity of these therapeutics, the factors affecting efficacy and the potential limitations that may arise, however, the future for the role of immunotherapy in AML treatment remains bright and propitious.

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Sources of funding in the development of therapies for Huntington's disease

Leora Fox, Jennifer Simpson and George Yohrling from the Huntington's Disease Society of America explore the sources of funding in the development of therapies for Huntington's disease (HD)

Huntington's Disease (HD) is an inherited brain disorder affecting approximately 1 in 10,000 people in the United States.[1,2] HD patients suffer from a triad of debilitating cognitive, emotional and movement symptoms that usually strike during a person's prime working years but can sometimes appear as young as early childhood. Huntington's disease is defined as a rare disorder because of its prevalence of fewer than 200,000 affected individuals in the United States.[3] An estimated 30,000 people in the US are symptomatic, with an additional 200,000 at risk.[4,5] In comparison, 5.7 million Americans are affected by Alzheimer's disease and 14 million are projected to be diagnosed by 2050.[6] Given this disparity in medical and social impact, the development of treatments for rare and debilitating disorders like HD requires the collective efforts of public and private entities.

The management of Huntington's disease relies on conventional, non-specific medications to address individual psychiatric symptoms like anxiety and psychosis and to calm the characteristic involuntary movements known as chorea. These approaches can temporarily mask the signs of a deteriorating brain, but they are not reparative or restorative. Designing therapies aimed at the genetic and biological causes of HD requires an in-depth understanding of its underlying biology and pathology. Traditionally, such research has been the realm of government entities like the National Science Foundation (NSF) and the National Institutes of Health (NIH). As the largest public funder of biomedical research worldwide,[7] the NIH dedicated more than $2 billion to neurodegenerative disease research in 2016, with $37 million devoted to HD-specific projects, comprising just under 2% of the spending on neurological diseases.[8] Funding of studies that look at the biology and pathology of rare neurodegenerative diseases like HD are essential to furthering our understanding of rare and complex diseases, paving the way for novel therapies in humans.

Limited funding in the HD field leaves little space for high-risk, high-reward projects and creates intense competition that can discourage a young scientist's commitment to a rare disease like HD. As a result, research funding through private entities like non-profit foundations must be present to foster medical progress. The HD field is extremely fortunate to have dedicated sources of non-government funding; the largest, CHDI Foundation, a privately-funded, not-for-profit biomedical research foundation, is focused solely on the development of therapeutics for Huntington's disease. CHDI has an estimated annual budget of $100 million,[9] nearly three times the reported NIH contribution to HD research in 2016. To avoid duplicate efforts and maintain collaborative relationships, other HD organisations carve out complementary niches in their research focus or grant funding programmes. The Huntington's Disease Society of America, for example, funds HD research initiatives that focus on human-centric projects, engaging promising young scientists, promoting opportunities for community engagement in trials and providing support to researchers with strong mentorship who are committed to becoming independent and devoting their professional lives to HD.

Ultimately the goal of government and non-profit investments in HD research is to bring effective treatments to market. This is greatly expedited by public-private partnerships and requires investment from industry, especially as novel potential therapies enter the clinical phases of the research pipeline. In the HD field, the efforts of researchers supported by the government, the not-for-profit sector and industry funding, combined with the tenacity and dedication of

affected families, culminated recently in a clinical trial to test the safety of a novel gene therapy designed with the underlying biology of HD in mind. Its success, announced in December 2017 and detailed at the 2018 CHDI HD Therapeutics Conference, has led to a significant investment from Roche Pharmaceuticals to plan and execute a critical Phase 3 trial.[10] Beyond supporting and contributing to the medical research itself, public-private partnerships help to speed the regulatory processes behind drug development and approval. In March 2018, the Critical Path Institute (C-Path) and CHDI announced the official launch of the Huntington's Disease Regulatory Science Consortium (HD-RSC), which will include representatives from various sectors and will focus on cost reduction and efficiency in HD drug development.[11]

With the field poised on the brink of several promising trials, diverse funding sources and collaborative initiatives between government, the not-for-profit sector and industry remain critical to expand our knowledge of HD biology and hasten the progress of medicine. The rarity of Huntington's disease does not lessen the needs of affected families, and additional resources serve to solidify a collaborative research community and power faster medical innovations both inside and outside of the HD field. Therefore, we need to be vigilant in ensuring increased access to funding for rare disease projects. This includes working to increase the visibility of rare disease research in such a way that both public and private entities recognise the potential of their investments to inform broader medical applications, pave the way for novel methodologies, and shape policy for the Huntington's disease community and beyond. ■

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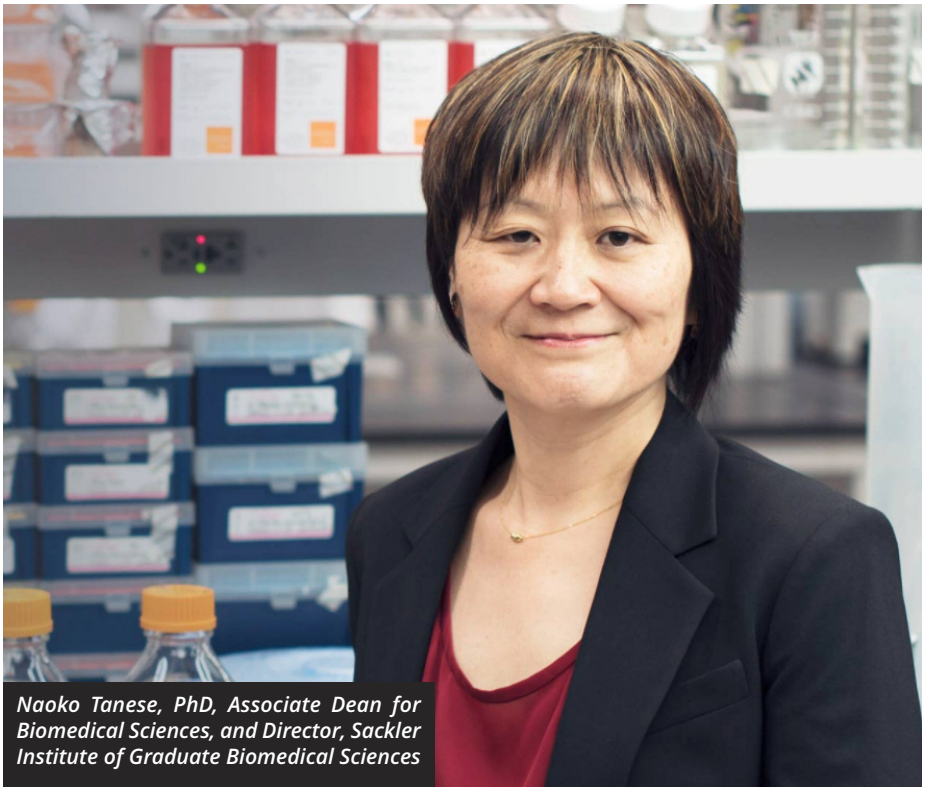
What's in an aggregate? Therapeutic intervention in Huntington's

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

Huntington'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.



Naoko Tanese, PhD, Associate Dean for Biomedical Sciences, and Director, Sackler Institute of Graduate Biomedical Sciences

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.

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The diagnosis and treatment of cancer in the United States

The vital work of the National Cancer Institute, part of the National Institutes of Health, is placed under the spotlight here by Open Access Government, including the dissemination of new findings on the diagnosis and treatment of cancer

The National Cancer Institute, part of the National Institutes of Health, is the U.S. federal government's lead agency in coordinating research, providing training and disseminating new findings on the diagnosis and treatment of cancer.

In 1937, President Franklin D Roosevelt signed the National Cancer Act to support cancer research – the first time Congress had appropriated funds for a non-communicable disease.

The act established the National Cancer Institute as the federal government's primary agency in coordinating grant funding for cancer research, providing training in diagnosis and treatment and disseminating the findings of research carried out in the U.S. and other countries.

Thirty-four years later, the National Cancer Act of 1971 greatly expanded the role of the NCI, giving its director the broad authority to plan and develop an intensified and coordinated National Cancer Programme that included NCI and related initiatives, other research institutes, federal and non-federal programmes "in order to more effectively carry out the national effort against cancer".

The act also granted the NCI director access to the president of the United States and required them to submit an annual budget directly to the Oval Office. Furthermore, it established the National Cancer Advisory Board, made up of 18 distinguished scientists, members of the public and ex-officio members of other government agencies, to advise the NCI on its programmes, along with the President's Cancer Panel to provide annual reports.

On top of this, the act provided additional funding to establish 15 new cancer research centres, local control programmes and an international cancer research data bank.

Over the years, the NCI has established several major programmes to tackle cancer, including the Cancer Information Service (1976), the Office of Cancer Survivorship (1996) to study ways to enhance the length and quality of life for cancer survivors and the TARGET Initiative (2006) to identify the molecular characteristics of childhood cancers in order to design better treatments.

It has also worked with the National Human Genome Institute to launch the Cancer Genome Atlas, a project to systematically examine the genomic changes involved in human cancer.

There has been tremendous progress made. Over the past two decades, research has led to a 25% decline in the rate of deaths from cancer.

However, there is still much to do. Nearly 40% of Americans will be diagnosed with cancer in their lifetimes. Around 600,000 adults and 2,000 children die from cancer in the US every year.

The NCI is pushing ahead with a broad portfolio of research. In 2017-18, the institute's total budget stood at $5.67 billion, around 40% of which goes towards research grants.

Current key initiatives include the Cancer Moonshot, an ambitious plan to accelerate a decade's worth of

research into five years through targeted grant funding, supplements and where appropriate, partnerships with foundations, academia and the private sector. In 2016, Congress approved $1.8 billion over seven years to support the Cancer Moonshot.

The NCI also runs the Precision Medicine Initiative, which focuses on four broad areas – new and expanded precision medicine clinical trials; overcoming drug resistance to cancer treatments; developing new laboratory models for cancer research; and building and sharing a digital repository of data resulting from NCI-sponsored precision medicine clinical trials – with the aim of bringing precision medicine into everyday clinical practice.

Meanwhile, the National Clinical Trials Network (NCTN), the cornerstone of NCI's clinical trials programme, brings together organisations and clinicians to conduct large-scale trials across the U.S. and Canada. These help to establish new standards of care, move new therapies toward FDA approval, test new approaches to radiation therapy and surgery and validate new biomarkers. The NCTN provides the infrastructure for NCI-funded treatment, screening and diagnosis treatments at over 3,000 sites.

NCI-backed research has made headlines in recent months. In June, it was reported that a novel approach to immunotherapy developed by NCI researchers had led to the complete regression of breast cancer in a patient who had been unresponsive to all other treatments.

> "Nearly 40% of Americans will be diagnosed with cancer in their lifetimes. Around 600,000 adults and 2,000 children die from cancer in the US every year."

The findings of the clinical trial, which was led by Dr Stephen A Rosenberg, chief of the surgery branch at the NCI's Center for Cancer Research, were published in Nature Medicine.

"We've developed a high-throughput method to identify mutations present in a cancer that are recognised by the immune system," Dr Rosenberg says.

"This research is experimental right now. But because this new approach to immunotherapy is dependent on mutations, not on cancer type, it is in a sense a blueprint we can use for the treatment of many types of cancer.

"All cancers have mutations, and that's what we're attacking with this immunotherapy. It is ironic that the very mutations that cause the cancer may prove to be the best targets to treat the cancer."

The Center for Cancer Research is the largest division of the NCI intramural research programme and comprises nearly 250 groups conducting basic, translational and clinical research. The CCR's clinical programme is housed at the National Institutes of Health's Clinical Center, the world's largest hospital dedicated to clinical research. ■

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Cancer immunotherapy therapy is here and now

Stephanie K. Watkins PhD from Loyola University Chicago shares her views on cancer immunotherapy therapy – the concept of using the immune system to fight and destroy cancer cells

The concept of using the immune system to fight and destroy cancer cells has been a dream of clinicians since 1891 when Dr William Coley first injected a patient with an inoperable bone cancer with streptococcal organisms and observed the regression of an aggressive, malignant tumour. These first attempts were quite extraordinary, given how little was known or understood about the immune system at that time. Unfortunately, because of this lack of understanding, many clinicians ignored the potential that these immune therapies carried to cure cancer and the strategy fell by the wayside for many years.

Now that the field of immunology has exploded and is accepted as a critical component across all areas of medicine, scientists and clinicians are once again focused on utilising the power of the immune system to eradicate cancers of all origins. Immunotherapies today are highly technologically advanced and target an array of properties of the immune system. In this review, we will briefly cover the main types of therapy used in the clinic.

Monoclonal antibodies are one class of immune therapies designed to target specific antigen (Ag) expressed by tumour cells. Different types of monoclonal antibodies include: naked, conjugated and bispecific. The naked monoclonal antibodies consist of popular drugs, such as alemtuzumab, trastuzumab and pembrolizumab. The naked monoclonal antibody sticks to the target Ag on the surface of tumour cells and generates an immune response by recruiting immune cells to destroy the cell harbouring the antibody. A second mechanism uses the antibody to block Ags on cells in the tumour microenvironment.

> "The major advantage of immune-based therapies is that they are very individualised for each patient and tailored to "natural" protection against tumours."

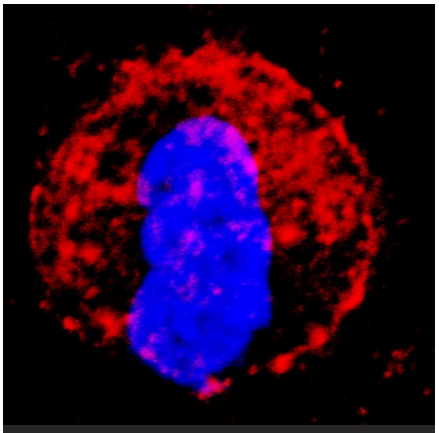
The blockage prevents tumours from growing or spreading by denying activation of the blocked Ag. The conjugated monoclonal antibodies are joined to a chemotherapy drug or sometimes a radioactive particle. This type of monoclonal antibody is often used to deliver a cytotoxic drug (the chemotherapy or radioisotope agent) directly to a tumour cell that is bearing the target antigen. The directed delivery lessens the destruction of normal healthy cells during the destruction of tumour cells.

The bispecific monoclonal antibodies are drugs designed to target two different antigens, one on the tumour cell and one on the T cell, an immune cell capable of killing tumour cells and the antibody brings the two cells together, allowing the T cell to destroy the cancer cell. The largest hurdle to overcome with monoclonal antibody therapy is that cancer cells constantly mutate or lose expression of the antigen – that antibody was designed to target and frequently become resistant to the therapy. Therefore, the key to this therapy is choosing the appropriate target and monitoring desensitisation.

Similar to monoclonal antibody strategies, one of the most successful therapies across a spectrum of cancers currently, is the use of immune checkpoint inhibitors. T lymphocytes or T cells are a critical cell in the immune system and are the primary cell responsible for targeting and destroying cells that are harmful to the body, including virus-infected cells and tumour cells. In normal immune responses, it is important to keep T cells under control and prevent them from destroying healthy tissues, therefore, when they are activated they upregulate receptors on the cell surface that allows their functions to be quickly turned subdued. These regulatory receptors include PD-1 and CTLA-4.

In cancer, when activated T cells infiltrate a tumour, many tumours express the ligands that bind to the regulatory receptors and can turn T cells "off". Therefore, the checkpoint inhibitors are designed to bind to either the receptors or the ligand and prevent the interaction from eliminating the T cells anti-tumour functions.

Commonly used drugs are the PD-1



Dendritic cell coated with prostate specific antigen

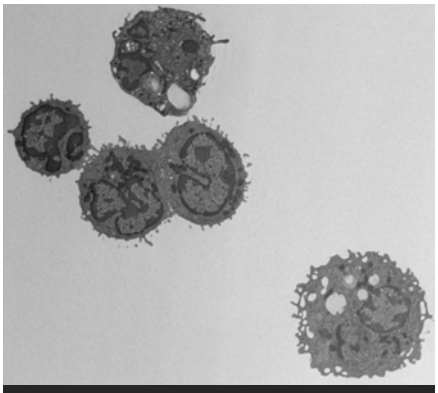
inhibitors pembrolizumab and nivolumab, PD-L1 inhibitors atezolizumab, avelumab and durvalumab and CTLA-4 inhibitor ipilimumab. Ipilimumab was the first FDA approved immune-checkpoint drug for the treatment of melanoma and kidney cancers. Within the last year, six more drugs in this class have made approval and the list continues to grow. Current strategies are now working to combine these checkpoint inhibitors with the use of small molecule drugs that can also prevent T cell exhaustion, which happens in during chronic antigen stimulation, such as within a tumour.

> "Now that the field of immunology has exploded and is accepted as a critical component across all areas of medicine, scientists and clinicians are once again focused on utilising the power of the immune system to eradicate cancers of all origins."

The third class of therapies making tremendous strides in the clinic today are the cancer vaccines or adoptive T cell transfer therapies. This therapy is the direct transfer of immune cells into a patient that is capable of either directly destroying cancer cells or boosting the internal immune response to fight cancer. The first vaccine of this type was called sipuleucel-T (Provenge) and was approved by the FDA in 2010 for the treatment of metastatic prostate cancer. Provenge was a vaccine using dendritic cells (DC). DC is responsible for presenting antigen to T cells that are then stimulated to attack cancer cells bearing similar antigen. The original trial was conducted in 512 randomised patients and the vaccine was found to extend the median survival time 4.1 months. Again, this was a small but important step, paving the way for more advanced immune cell vaccines.

In recent years, researchers have identified ways to make more effective and potent immune cells for patient delivery. The CAR T-cell therapy was FDA approved for treatment of children with acute lymphoblastic leukaemia (ALL) and adults with other lymphomas in 2017. CAR T-cell stands for chimeric antigen receptor T cell. These T cells are the patient's own T cells that are genetically modified to add an artificial receptor to their cell surface that targets the CD-19 molecule by cancer cells. The genetic modifications promote the T cell to produce an abundance of inflammatory proteins, called cytokines and often resulting in a "cytokine storm" shortly after patient administration. It's approximated that 70-90% of patient experience this short-term event due to the robust immune response. Originally, the cytokine storm was somewhat feared as a negative result of stimulating the immune system, but now with drugs, such as tocilizumab, the duration and intensity can be controlled, and the cytokine storm may be observed as a positive event indicating the initiation of an effective therapy.

The major advantage of immune-based therapies is that they are very



Electron microscopy image of immune cells, T cell, neutrophil, monocytes

individualised for each patient and tailored to "natural" protection against tumours. Many immune bases therapies, especially the adoptive T cell transfer therapies consist of a single infusion with only a few weeks of follow up care, compared to traditional chemotherapy approaches which often last six months or more. Cancer continues to evolve, but research and ongoing clinical trials are making successful strides to employ new technologies to harness the power of nature's best medicine, the immune system.

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Muscular dystrophy: Present concerns and foreseen opportunities

Cecilia Van Cauwenberghe from the TechVision Group at Frost & Sullivan provides a detailed analysis of the present concerns and foreseen opportunities around muscular dystrophy (MD)

Muscular dystrophies constitute a group of genetically dissimilar diseases related to the weakening and breakdown of skeletal muscle. At present, nine main categories and over thirty subtypes of muscular dystrophy have been recognised, based on alterations in the structure and/or function of the dystrophin protein caused by mutations in certain genes specifically impacting muscle function *(Saada et al., 2016)*.

Despite the prevalence and the estimated economic burden of over $795 billion associated with the whole set of types and subtypes of muscular dystrophy, the underlying biology and pathogenesis remains poorly understood (Gumucio, 2017). Nevertheless, recent advances in omics-based science, including the advent of artificial intelligence (AI) learning methods contributing to the analysis and the correlation of genome, proteome, epigenome, metabolome and lipidome data, are significantly accelerating disease pattern identification under a precision medicine framework. An in-depth knowledge of the mechanisms involved in both normal physiological functioning and disease status is becoming crucial for the development of efficient treatment strategies for muscular dystrophy.

Muscular dystrophies: A brief overview

Disease implications and collateral effects

Myopenia, a clinically relevant muscle wasting condition associated with the impairment of muscle function due to congenital or acquired causes including cachexia and sarcopenia, may represent a life-threatening disorder.

Cachexia is a multifactorial syndrome related to a variety of conditions leading to inflammatory muscle mass loss, hence potentially resulting from multiple different disease causes and genetic variability. Cancer patients are commonly affected by cachexia. Most immune checkpoint inhibitors utilised in cancer therapy involve the release of a cascade of immune systems that accelerates muscle loss. Moreover, nutritional support results are generally ineffective in these patients due to the fundamental molecular processes governing cancer-associated muscle metabolism and the epigenetic processes conducting muscle wasting phenotype *(Carr et al., 2017)*.

Sarcopenia is defined as low muscle function in the presence of low muscle mass. Sarcopenia is mostly associated with endocrine causes such as diabetes mellitus and insufficient insulin-like growth factor 1, as well as, decreased growth hormone and male hypogonadism, conveniently treated with insulin, testosterone and selective androgen and anti-myostatin activin II receptor molecules *(McKee et al., 2017)*.

Additional factors leading to sarcopenia are decreased physical activity, sudden weight loss, reduced blood flow to muscles, loss of motor neuron units and lack of vitamin D, generally treated with leucine-enriched essential amino acids and vitamin D, while increasing aerobic exercise.

A collateral effect associated with muscular dystrophy is myosteatosis, that is, the accumulation of pathological ectopic lipid with concomitant atrophy and fibrosis. Myosteatosis mostly follows chronic rotator cuff injuries. Scleraxis, a basic helix-loop-helix transcription factor required for the embryonic formation of tendon and the differentiation of tendon progenitor cells, is supposed to play an important role in adult tendon adaptation as well, along with the progression and consequences of myosteatosis on muscle metabolism and function. Although the pathways activated by excess lipid are poorly understood, the myosteatosis process starts with an initial acute inflammatory phase

due to a dysfunctional mitochondrial functioning unable to oxidise lipid. As a result, a lipid is accumulated over time, leading to a chronic, persistent inflammatory condition causing increased oxidative stress, tissue atrophy and muscle dysfunction.

Clinical approaches: The precision medicine era

Diagnosis and treatment opportunities in modern medicine

A recent focus in the field has centered on the ability to recognise the genetic mutations related to each subtype of muscular dystrophy, followed by the prospect of gene manipulation intending to reverse the disease progression. Indeed, genetic modulation via DNA and oligonucleotides and gene editing technologies including clustered regularly interspaced short palendronic repeats (CRISPR) are expected to hold the great promise of a cure for muscular dystrophy (Morley and Anker, 2017). The advent of precision medicine is significantly paving the way for the development of novel genomics-based early preventive strategies and potential treatments for a plethora of severely underserved conditions, such as those associated with some type of muscular dystrophy.

Breakthrough genetic therapies targeting muscular dystrophy

The estimated prevalence of Duchenne's and Becker's muscular dystrophy (DBMD) in the United States is 1 in every 7,250 males aged 5-24 years (Romitti et al., 2015). Both diseases involve the loss of function of the dystrophin gene, generally due to a disruption in the dystrophin protein reading frame. Therefore, an accurate correction of the dystrophin gene via gene editing, gene therapy or cell regeneration approaches would constitute a noteworthy therapeutic solution. In fact, recent approaches have been made intending to use recombinant adeno-associated viral (rAAVs) vectors and lentiviral vectors, as well as, sleeping beauty non-viral transposons to host truncated highly functional microdystrophin or microutrophin genes into the genome aiming to improve the dystrophin function.

Additional advances have been made with the development of DNA and RNA-based therapies, including smart oligonucleotides capable of interfering the splicing process to restore the dystrophin protein reading frame (Van Cauwenberghe, 2018). Indeed, the U.S. Food and Drug Administration (FDA) approved eteplirsen for the treatment of Duchene's muscular

Continued on page 25 →

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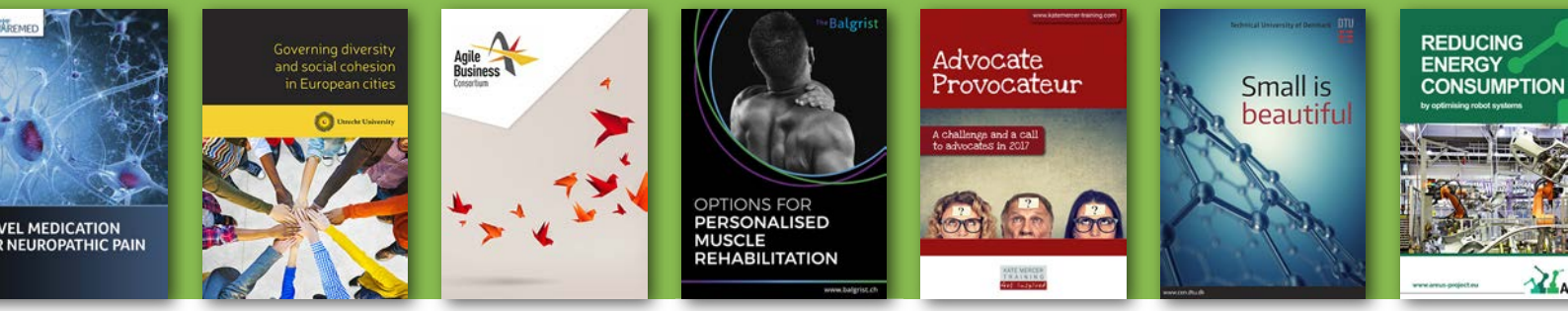

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dystrophy (DMD). Gene editing approaches, more precisely CRISPR techniques, have been tested to genetically alter, enhance or inhibit specific genes related to muscular dystrophy in human stem cells (Iyer, 2017). Although most results achieved via gene editing approaches have led to unintended mutations, the synergy of this technology with human induced pluripotent stem cell (iPSC) therapies is still highly promising.

> "Myopenia, a clinically relevant muscle wasting condition associated with the impairment of muscle function due to congenital or acquired causes including cachexia and sarcopenia, may represent a life-threatening disorder."

Final remarks

Gene and cell therapies, including gene editing and stem cells technologies, synergistically combined with data analytics and AI-based learning processes, constitute a powerful potential approach to efficiently treat muscular dystrophy. Associated with a deficient structure or function of the dystrophin gene protein, myopenia represents a therapeutic area that can be powerfully addressed under a precision medicine approach. Although further efforts remain to be made, the use of a patient's own genome, proteome, epigenome, metabolome and lipidome outputs as predictive and prognostic biomarkers for the adequate treatment and management of muscular dystrophy is making precision medicine a reality, propelling therapeutics discovery pathways through notable innovations in microRNA-based platforms, self-delivered RNA interference-based liposomes, anti-code therapeutics, therapeutic ribonucleases, antisense drugs, RNA splicing modulation, exon skipping treatments and microRNA programming, among many other disruptive approaches. ■

Acknowledgements

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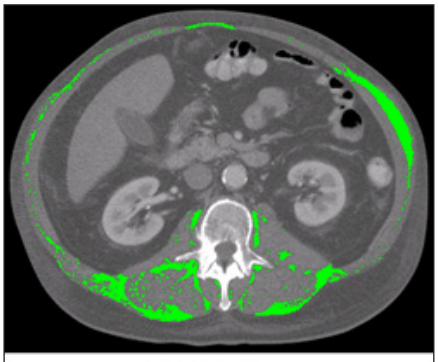
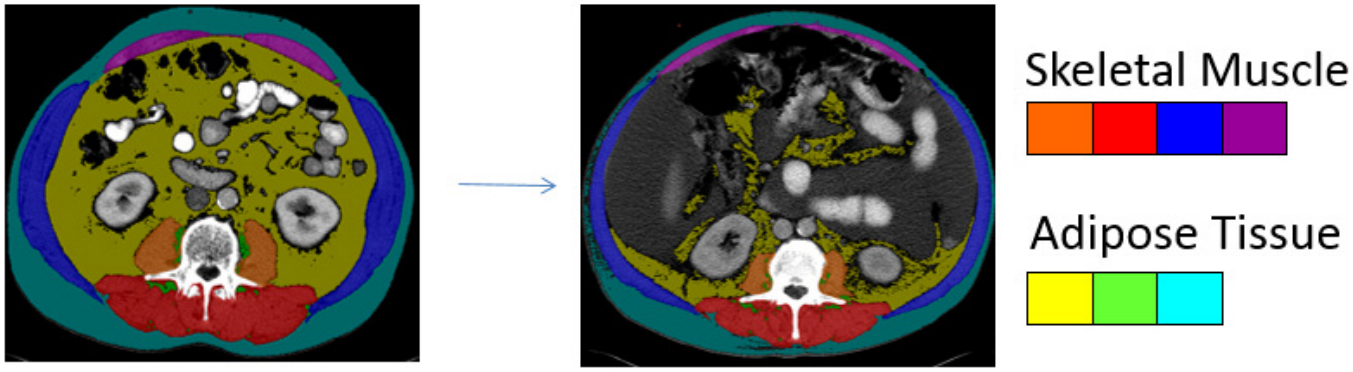
Disease-associated myosteatosis in people with cancer: Can it be treated?

Pathological fat infiltration into muscle is a feature of disease-induced muscle loss that significantly associates with shorter survival in people with cancer. Fat is associated with skeletal muscles in the form of intra-myocellular lipid droplets within the cytoplasm of myocytes as well as intermuscular adipocytes. These lipid stores are thought to provide fuels for skeletal muscle contraction, however, excess deposition of triglycerides within cells and organs that normally contain only small amounts of fat (such as liver, pancreas, skeletal and cardiac muscle) is defined as steatosis. Myosteatosis (steatosis of the muscle) is a pathological phenomenon reflecting an impairment of synthesis and elimination of triglyceride.

Myosteatosis is revealed in vivo by computed tomography (CT) imaging as muscle with low radiodensity combined with presence of intermuscular adipose tissue. The evidence for a relationship between low muscle radiodensity and shorter survival in people with cancer is building. Loss of skeletal muscle mass appears to generally occur with accumulation of adipose tissue into muscle. We reported that patients undergoing treatment for lung cancer lost muscle mass and concurrently gained intermuscular adipose tissue during treatment for cancer, whereas patients who supplemented their daily intake with fish oil containing eicosapentaenoic acid and docosahexaenoic acid [EPA+DHA (2.2 g/day)] maintained or gained muscle mass and experienced a decline in intermuscular adipose tissue over the same time period. This intervention also resulted in a greater response by the tumor to the drugs being used to

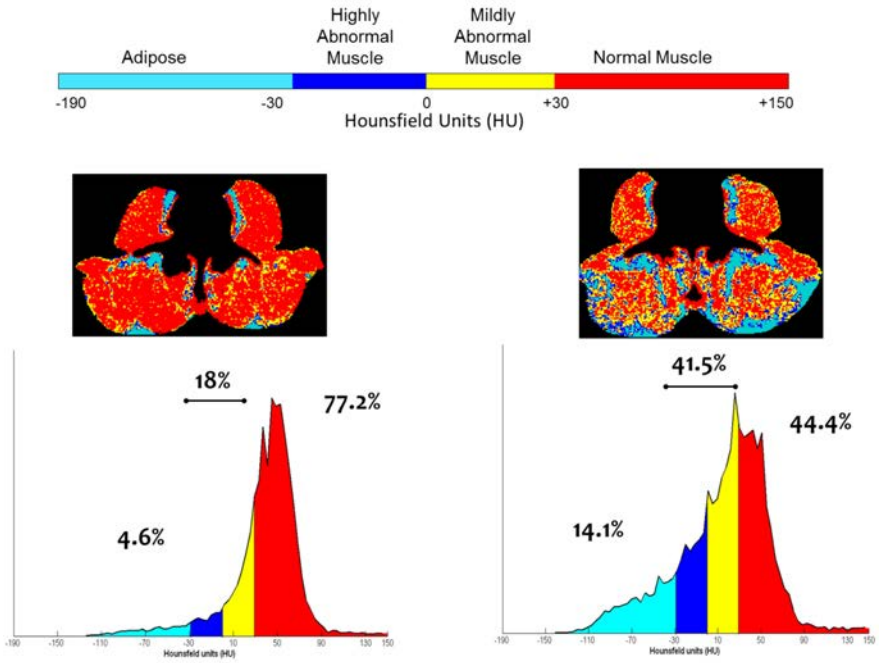


This slide shows a CT image from a cancer patient who underwent 16 weeks of first line platinum doublet chemotherapy for lung cancer. Only the intramuscular adipose tissue is shown in color



To quantify different tissues for body composition analysis using computed tomography imaging, a bony landmark is used to consistently measure the same region of the body across patients. The 3rd lumbar vertebrae is an established landmark in body composition analysis that correlates with amount of whole body muscle and fat. Each tissue attenuates radiation in a specific way which is recognised by a software program to enable skeletal muscles and different types of adipose tissues to be identified. Each tissue of interest is then color coded (see legend). When more than one CT image exists in the patient record, tissue changes over the trajectory of the disease can be determined. This image presents 2 scans taken approx 6 months apart at the same region within the same patient. The marked decline in muscle and adipose tissue is evident, concurrent with deposition of adipose tissue into muscle

Illustration of Variation in Muscle Radiodensity



An illustration of annotated CT images, and accompanying histograms of radiation attenuation showing the percentages of total tissue cross-sectional area within the ranges of adipose tissue in paraspinal/psoas muscles is useful to understand the problem of myosteatosis. This illustration shows the percentages of total tissue cross-sectional area within the typical attenuation ranges determined for the respective tissues for 2 subjects. Subject 1 is a 63 year old male with muscle characteristics at the median values for male cancer patients with a diagnosis of solid tumor at our centre. For Subject 2 there is extensive macroscopic adipose tissue and less than half of the cross sectional area of his muscles falls within the normal attenuation range. Overall, Patient I has a greater proportion of fat and low attenuation muscle, than muscle with normal characteristics. Patient II is remarkable in several respects, including extensive visible fatty infiltration and extremely high proportion of total muscle area falling within a range of attenuation values generally recognized to be abnormally low (adapted from Aubrey et al 2014)

treat the cancer. Therefore there may be multiple benefits of dietary fish oil to the cancer patient undergoing treatment.

To explore these observations that cancer patients supplementing with EPA+DHA experience an improvement in myosteatosis, we established a pre-clinical model to enable intervention with EPA+DHA at various time points in the cancer trajectory. We used an rat model bearing the Ward colorectal tumor and treated in a manner that mimics standard clinical care for this disease in humans with respect to the types of drugs used and the toxicities they evoke. Using this model we have demonstrated that the results align with our human data suggesting an improvement in muscle condition concurrent with a better response by the tumor to the anti-cancer drugs. Using this as the rationale for the next step of this line of questioning, we have planned a clinical trial upon which to text the biological efficacy of fish oil to reverse cancer- associated myosteatosis in a cancer population known to exhibit myosteatosis, verified by in vivo imaging of muscle features by CT scan. At the time of diagnosis and treatment planning, patients will be randomized and consented to consume EPA+DHA (2.2 g per day) until day of surgery (at least a 4 week period) or receive standard of care (no intervention). Muscle from the subjects will be collected at the time of surgery and prepared for analysis. Analysis of the muscle tissue will enable determination of differences in Triglyceride-fatty acid content (a hallmark of myosteatosis). We expect that this research will verify the tantalizing evidence we have in hand that suggests an improvement in pathological features of myosteatosis by dietary EPA and DHA. If so demonstrated, this work will provide critical translational knowledge required to effectively plan treatment interventions that have significant potential to impact the lives of people diagnosed with cancer, a major cause of death globally.

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Duchenne muscular dystrophy (DMD): Correcting the dystrophin gene

Dr Ahlke Heydemann, Associate Professor and Director of Medical School Curriculum at University of Illinois, Chicago explains Duchenne muscular dystrophy (DMD), focussing on the issue of correcting the dystrophin gene

Duchenne muscular dystrophy (DMD) is an inherited progressive disease that affects skeletal, diaphragm and cardiac muscles. The pathology initiates with muscle weakness, particularly noticeable on the leg muscles of the young – two to three-year-old – boys. The dystrophin gene is located on the X-chromosome; therefore, it is sex-linked and only boys get the full disease. Women are carriers and can develop cardiomyopathy much later in life. As time goes on, the skeletal muscles continue to weaken, and corticosteroid treatments are initiated, usually at around six years of age.

A few years later, night-time assisted ventilation and then prophylactic ACE inhibitors for the maintenance of respiratory and cardiac function, respectively, are added to the treatment regimen. These combined treatments have extended the quality and quantity of the patients' lives, but more effective treatments or even cures are still urgently required. Within MD, there is some relationship between the specific mutation in the dystrophin gene and the protein levels of dystrophin and the severity of the disease.

The mildest cases are classified as Becker MD (BMD). These mild cases reveal that a relatively low expression level of dystrophin – only 20 to 40 % of normal levels – is required to establish a mild disease course. This very important trait can be utilised to set a reasonably achievable goal for a highly beneficial and successful therapy.

Treatments in the preclinical and clinical trial pipeline

There are many promising treatments in the preclinical and clinical trial pipeline. These can be subdivided into overlapping categories.

- Inflammation/immune inhibitors.
- Modulators of metabolism.
- The reestablishment of the dystrophin glycoprotein complex without dystrophin and
- Gene correction.

The gene correction strategy can be further subdivided as shown below.

Gene correction

1. Cell transplantation.
   a. Stem cells
      i. Embryonic.
      ii. Induced.
         1. From normal donors.
         2. From the patient, corrected in vitro
   b. Muscle satellite cells.
      i. From normal donors.
      ii. From the patient, corrected in vitro.
2. Premature stop codon read-through.
3. Exon skipping.
4. CRISPR/Cas.

Utilising cells to reintroduce a wild-type dystrophin gene into diseased muscle has been investigated for many years. Recent progress has given new hope to this particular therapy for MD. Stem cells (SC) can be harvested from a number of sources: embryonic (ESC) tissues or induced (induced pluripotent stem cells) (iPSC) from adult tissues. These SCs have the potential to become permanently engrafted into the host muscles, proliferate, express dystrophin and respond to injury. ESCs have the benefit of being immune privileged, meaning the host tissue will not reject the cells as foreign. However, obtaining the number of ESCs required to treat a patient has been difficult. Proliferating the ESCs in culture causes functional changes that impede their effectiveness in establishing themselves in the host tissue.

One of the benefits of iPSCs is that scientists can produce large numbers without changing their effectiveness for transplant. ESCs are usually derived from normal donors and therefore, contain and deliver the intact dystrophin gene to all muscles that the cells populate. iPSCs can be derived from a normal donor or the patient themselves. If derived from the patient, the genetic defect will have to be corrected while the cells are in culture. An additional step, but a highly effective one, and using the patient's cells ensures that a large immune response will not be

mounted upon transplantation. One of the most positive aspects of this stem cell transplantation approach is that it can be a true cure. If the cells engraft and repopulate the muscles appropriately, they could survive and provide sufficient dystrophin for the life of the patient.

Muscle satellite cells (muscle resident stem cells) are another source of cells that could potentially engraft all muscle groups and be a true cure. These cells are derived from adults and are, therefore, more plentiful and tolerate proliferation in cell culture very well and their use has fewer ethical ramifications. The donor is a normal volunteer or the patient themselves, with the same considerations as mentioned above for the iPSCc. Recent work identifies a procedure that fuses normal donor satellite cells with the patient's satellite cells. This results in cells which express dystrophin and are immune privileged. And, as mentioned above, the cells tolerate proliferation, so the clinicians can have a large number of cells available for transplantation.

Clinical trials are also being conducted upon premature stop codon read-through strategies. This approach is based upon a fortuitous discovery that some antibiotics impede bacterial proliferation by causing the protein-making machinery to ignore the bacterial stop codons, thereby, making longer and less functional proteins. A subset of dystrophin mutations in patients causes a premature stop codon, by the selective use of antibiotic-like pharmaceuticals, the mammalian ribosomes will ignore the stop codon and continue making the remainder of the dystrophin protein, with just one amino acid change, instead of no protein at all. In addition, advanced generation read-through pharmaceuticals have a much higher efficiency of ignoring the stop codon then the original antibiotics, providing higher levels of dystrophin expression.

Recent news has highlighted the success of exon-skipping strategies. This strategy is based upon aligning two synthetic nucleotide strands, with specific sites of the native DNA which causes the normal mRNA processing machinery to skip exons which contain the mutation. So far, this strategy has caused almost normal dystrophin protein to be expressed at close to therapeutically beneficial levels. Researchers are still perfecting this technique to produce more protein.

The CRISPR system is also being investigated for gene correction in isolated cells from DMD patients and for gene correction within the patient. The final stages of preclinical testing will soon be completed. The exon-skipping and CRISPR systems are largely patient specific. Therefore, each patient will require specific chemistries to guide the editing machinery.

The further good news is that these genetic correction strategies can be utilised with other strategies that treat the symptoms to provide the most patient benefit with the lowest side-effects. Very importantly, transplantation, read-through and exon skipping studies are currently being tested in patients for efficacy. In the near future, multiple options will be available for clinicians and their patients to combat this disease.

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Cannabis: One of the most thoroughly studied plants ever

David Bearman, M.D., Executive VP of the American Academy of Cannabinoid Medicine details the research priorities for cannabis, one of the most thoroughly studied plants of all time

Cannabis is one of the most thoroughly studied plants of all time. Its documented medical use goes back to the first known materia medical, the Ping Ts'ao Ching, dated by Chinese oral tradition to be written in 2637 BC. At the turn of the 19th to the 20th century, cannabis was the third most common ingredient in physician prescriptions and over-the-counter (OTC) medications, after opium and alcohol. Cannabis was in the USP (United States Pharmacopeia) from the 1850s to 1942.

In more contemporary times, there have been more than 25,000 articles printed in peer-reviewed medical journals on cannabis, cannabinoids and the endo-cannabinoid system, since 1995. Numerous human studies have been performed at four UC medical schools under the administration of the California Medical Cannabis Research Center at UCSD Medical School. Many human studies were done on whole plant alcohol extracted cannabis in the UK from GW Pharmaceuticals. Their tincture of cannabis product, Nabixol, is approved for use in 24 countries including Canada, the UK and the European Union.

Studies

The combination of historical medical use, modern research and clinical experience have demonstrated many of cannabis' therapeutic effects, including analgesic, anti-inflammatory, anti-epileptic and migraine relief. Because of government interference, whole cannabis plant studies in the U.S. are few. We are however beginning to see state and private money supplanting federal government funding of medical cannabis research. Two new academic-based research centres have opened in California, one at UCI School of Medicine and another at UCLA School of Medicine. This is in addition to the Medical Cannabis Research Center at UCSD School of Medicine.

Cannabinoids and terpenes

Over the past three decades, we have been moving into an ever more sophisticated understanding of both the endocannabinoid system (ECS) and the therapeutic constituents of the cannabis (aka hemp) plant. An increased focus is being placed on many of the other 113 cannabinoids found in the plant beside THC and CBD. Research is being done on THCa, CBDa, THCV, CBC, CBN, CBG and other cannabinoids. For instance, the existing research shows CBC has anti-inflammatory and anti-cancer properties.

Terpenes are the most common molecule in nature. There are more than 200 terpenes in the plant and they have got the attention of researchers. Cannabis terpenes include B Caryophylin, Pinene, Humulene, Myrcene, Linalool, Limonene and Nerolidol. Not only will more research be done on the role of these cannabinoids and terpenes, but studies have and will look at not only the THC/CBD ratios but also the therapeutic contribution of many of the other constituents of the plant, such as those mentioned above.

Health

Allopathic physicians are experts in disease not health. Cannabis has been called a food, a vegetable and a nutraceutical. The seeds are high in Omega 3 and Omega 6 fatty acids and cannabis may decrease the risk of certain cancers. We need to study what the daily minimum dose of cannabis should be recommended.

Medical conditions and cannabis treatment

As to looking at cannabis' therapeutic utility for specific disease entities, we have over 4,000 years of clinical use to suggest what conditions to look at. To date, most of the modern studies have looked at the low hanging fruit; treating nausea, epilepsy, pain and for appetite stimulation. A ground-breaking study on

cannabis for post-traumatic stress disorder (PTSD) is being carried out in Arizona right now with 76 military veterans by Dr Susan Sisely. With 22 American military veterans committing suicide each day and the VA ignoring the potential benefit of cannabis for treating PTSD, this is an enormously important study.

"As to looking at cannabis' therapeutic utility for specific disease entities, we have over 4,000 years of clinical use to suggest what conditions to look at. To date, most of the studies have looked at the low hanging fruit; treating nausea, epilepsy, pain and for appetite stimulation. A ground-breaking study on cannabis for post-traumatic stress disorder (PTSD) is being carried out in Arizona right now with 76 military veterans by Dr Susan Sisely."

Another related area is ADD (attention deficit disorder) /ADHD (attention deficit hyperactivity disorder). ADD/ADHD often has a genetic component however it can also be a co-morbid condition with PTSD. There have been well over 75 studies done on cannabis and cannabinoids for the treatment of the symptoms of ADD/ADHD. Prominent researchers, such as Dr Danielle Piomelli at UC Irvine have done ground-breaking work on the benefits of cannabis and cannabinoids for treating this condition and more work continues.

Does cannabis "cure" cancer?

The most important question to answer is, does cannabis cure cancer? Donald Abrams, MD, oncologist and professor at UCSF School of Medicine, has said that there is more than enough basic scientific evidence and anecdotal reports to justify doing double-blind studies to see if cannabis cures cancer. The first such human study was completed last year in the UK on glioblastoma (GBM). With a very low dose of a whole cannabis plant alcohol extract (25 mg. THC, 25 mg. CBD administered three times a day), the study documented a 40% increase in lifespan from diagnosis to death for those receiving conventional treatment plus tincture of cannabis as opposed to conventional treatment alone (330 days compared to 510 days). Clearly, more studies with higher doses of THC and CBD need to be done not only on glioblastoma but also on multiple types of cancer.

Dose and THC/CBD ratio

Researchers and clinicians are still trying to determine what the appropriate dose of THC and CBD is, as well as what role, if any, other plant constituents play in treating the many medical conditions that respond favourably to cannabis. With the federal government sitting on their hands, it is important for state governments and private interests to fund cannabis research that could prove to be critical to potentially life-extending discoveries.

Endocannabinoid system (ECS)

Lastly, we need another article to cover the studies required to learn more about the ECS. As a clinician, I leave that article to basic science researchers. The ECS plays a key role in neuromodulation and homeostasis. Because of the ECS's impact on most organ systems, there are an enormous number of disease types which are ripe for more research on cannabis' therapeutic value. These conditions include but are not limited to, neurodegenerative disease, autism spectrum disorder, bipolar disorder, autoimmune diseases, connective tissue disorders, gastrointestinal disorders, as well as the well-known conditions of migraine treatment, seizure disorder, analgesia PTSD, ADD/ADHD and cancer. A better understanding of the ECS is giving us new insight into the functioning of the human brain and immune system.

I invite state, federal and private resources to help us better understand the human body to develop better, more effective prevention and treatment of disease. ■

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Acute respiratory distress syndrome – diagnostics and therapeutics

Cecilia Van Cauwenberghe, from TechVision Group, Frost & Sullivan provides a detailed analysis of acute respiratory distress syndrome, focussing on the evolving diagnostics and therapeutics in the precision era of medicine

Rezoagli et al., 2017, investigated acute respiratory distress syndrome (ARDS) epidemiology and etiology, concluding that ARDS can be triggered by a broad spectrum of local and systemic factors. Pneumonia, extrapulmonary sepsis and aspiration are the most critical risk factors for ARDS, along with additional demographic and environmental risk factors.

The acute lung injury prediction score (LIPS) is a model that introduces a series of risk factors and risk modifiers to predict patients' predisposition to develop ARDS by using routinely available clinical data even before they are admitted to the intensive care unit (ICU). Bauman et al., 2015, validated the use of LIPS for early recognition of ventilated patients at high risk for developing ARDS and mortality in ventilated surgical critical care patients. According to the researchers, early identification enables ventilator and fluid management optimisation strategies, thereby reducing the risk of developing ARDS and overall mortality.

Life-threatening interaction – pulmonary vascular dysfunction

Strongly characterised by diffuse alveolar and endothelial damage, ARDS is indeed the most severe form of acute respiratory failure. Wohlrab et al., 2018, emphasise in the impact of an increased pulmonary vascular permeability and a loss of aerated lung tissue that lead to bilateral opacity, pulmonary edema, hypoxemia, increased venous admixture and decreased lung compliance. As a result, patients with ARDS need supportive care in the ICU to maintain oxygenation and prevent even more adverse consequences.

Sipmann et al., 2018, focuses their investigations on the heart-lung interactions present in ARDS because of the critical pathophysiological alterations in lung parenchyma and pulmonary circulation accentuating the effects of positive pressure ventilation. This affection is designated as pulmonary vascular dysfunction (PVD) and it denotes the specific alteration of the vascular system in ARDS leading to an increase in pulmonary arterial (PA) pressure and pulmonary vascular resistance (PVR) and right ventricular (RV) distress and potential death due to heart failure. This interaction involves a series of factors that contribute to an inefficient ventricular ejection, which along with impaired pulmonary vascular mechanics, increases both arterial elastance and wave-reflection, additionally leading to RV afterload.

Therapeutic intervention broadly recurs to selective pulmonary vasodilators, lung protective mechanical ventilation strategies involving prone positioning and the open lung approach (OLA), to amend PVD by enhancing functional lung volume. Nevertheless, ARDS holds a high mortality rate mostly driven by pulmonary vascular interaction and RV afterload.

Advanced diagnostics and potential therapeutics

Next generation biomarkers

In the precision medicine era, discovery and validation of biomarkers constitute an essential need to help ARDS patients to prevent lung injury severity by directly conducting effective therapies. García-Laorden et al., 2017, have investigated the trajectory of many candidate biomarkers.

Unfortunately, specific biomarkers for ARDS are difficult to find due to the complex and heterogeneous pathophysiology of the disease. Therefore, scientists are more focused on recognising combinations of biomarkers and clinical predictors reflecting different aspects of diffuse alveolar damage (DAD) such as

epithelial damage, endothelial injury and/or inflammation, more prone to be identified.

Lin et al., 2018, have deeply analysed the metabolomics of patients with ARDS between healthy people, aiming to find metabolic markers with potential diagnostic values and prognosis. The authors found that caprylic acid, azetidine, iminodiacetic acid and ornithine had a positive correlation with the ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2). The researchers also uncovered near a hundred of new metabolic pathways linked to these metabolites exhibiting significant statistical references to ARDS, which can be potentially used to judge the acuteness and envisage the prognosis of ARDS.

Receptor for advanced glycation end-products (RAGE) has been reported as a promising biomarker of lung epithelium injury as a pattern recognition receptor. Angiopoietin-2 (Ang-2) and surfactant protein D (SP-D) play a key role in endothelial junctional integrity. Due to their levels are significantly altered in patients with ARDS, they can be used for diagnostics. Similarly, interleukin-8 (IL-8) regulates neutrophils and monocytes chemotaxis in the lung, so that higher IL-8 concentrations have predictive value in high-risk patients for developing ARDS.

Therapeutic pipeline

Despite promising ongoing clinical trials being undergone, presently, there are no specific and effective pharmacotherapies to address the ARDS challenge. Principal attempts are based on a combination of therapies leveraging the advent of several adjacent technologies including small molecules agonists and inhibitors, interferons, nano-peptides, stem cells and microRNAs (miRNAs), among other innovations.

Aerosolised beta2-adrenergic agonists (β2-agonists) have been suggested to prevent the development of ARDS. SB-681323 is a selective p38 alpha inhibitor that may potentially inhibit the inflammatory response by interfering with the mitogen-activated protein kinase (MAPK) pathway, hence preventing inflammatory cascade events. As responsible for the well-functioning of the endothelial barrier function, interferon beta-1a may prevent vascular leakage. Nano-peptides, such as AP301, which activates the pulmonary epithelial and endothelial amiloride-sensitive sodium channel (ENaC) to facilitate alveolar liquid clearance, have been receiving increasing attention over the past decade.

Stem cell technology has also been proposed to regenerate lung tissue while modulating inflammation via secrete growth factors and cytokines. A further approach can be carried out by implementing miRNAs, small non-coding RNAs involved in the post-transcriptional regulation of various genes' expression, as both biomarkers therapeutics, due to miRNAs may control several signalling pathways associated with the onset of ARDS.

Acknowledgements

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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

Patients 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 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.

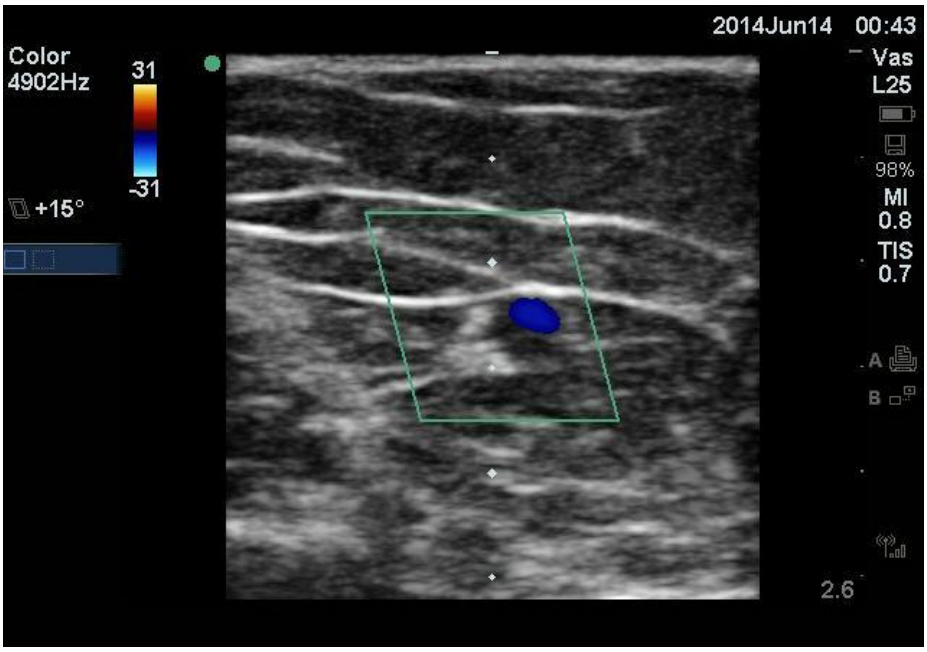

Figure 1: Short axis view of a peripheral vessel visualised with Colour Doppler (blue). The scale on the right of the screen demonstrates a total depth of 2.6 cm. A guide (white dots) in the centre of the screen marks each 0.5cm of depth. Therefore the depth of the vessel is between 1-1.5cm deep to the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

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

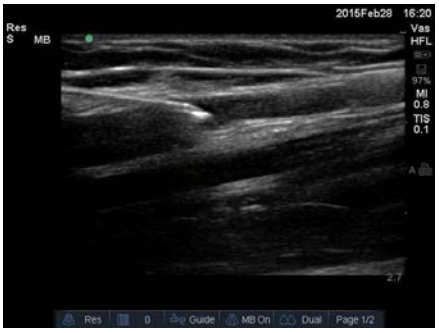

Figure 2: Long axis view of a peripheral vessel. The hyperechoic needle is visualized approaching from the top left of the screen into the vessel lumen.

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 thinner-walled 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

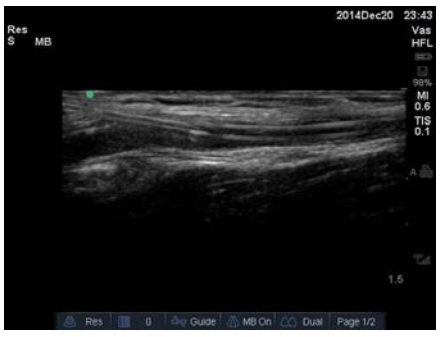

Figure 3: In this long axis view of a peripheral vessel the catheter has been threaded and is seen within the lumen of the vessel.

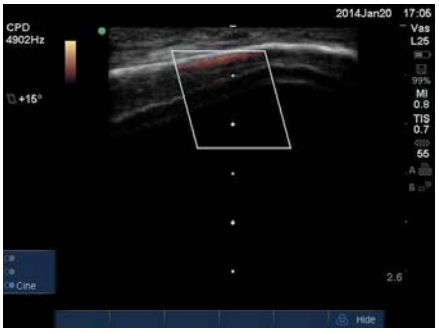

Figure 4: Power Doppler (orange) confirms placement of an intraosseus line within the distal tibia. The bright white line of the tibia cortex (in long axis view) is visualised at the top of the screen, with flow confirmation from a 10cc saline flush immediately distal (below) to the hyperechoic cortex.

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: http://rmgultrasound.com/piv-access/

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Mathematics: A powerful tool for understanding the world

Dr Juan C. Meza, Division Director for the Division of Mathematical Sciences (DMS) at the National Science Foundation (NSF) reveals why mathematics is such a powerful tool for understanding the world around us

In the article, "The Unreasonable Effectiveness of Mathematics in the Natural Sciences", the well-known physicist Eugene Wigner once wrote about the wide applicability of mathematics even beyond its own field. So, why is it that mathematics has proven such a powerful tool for understanding the world around us?

For many people, mathematics research often seems esoteric, but the results inspire new ways of thinking and commonly lead to novel applications. Here at the National Science Foundation's (NSF) Division of Mathematical Sciences (DMS), we support research in mathematics and statistics, the research training of the next generation of mathematical scientists and a portfolio of national research institutes.

An unexpected outcome

One of the goals of DMS is to develop new mathematical theories, models and tools to help solve some of the most challenging problems in the physical, biological and life sciences. This research ultimately has a significant impact on the United States' health, security and economy.

A clear example emerged last year. In 2017, the U.S. Food and Drug Administration approved two new magnetic resonance imaging (MRI) devices that dramatically speed up scanning of the body – between eight and 16 times faster than conventional methods. Siemens' technology (CS Cardiac Cine) reveals movies of the beating heart and GE's technology (HyperSense) allows rapid 3-D imaging of the brain.

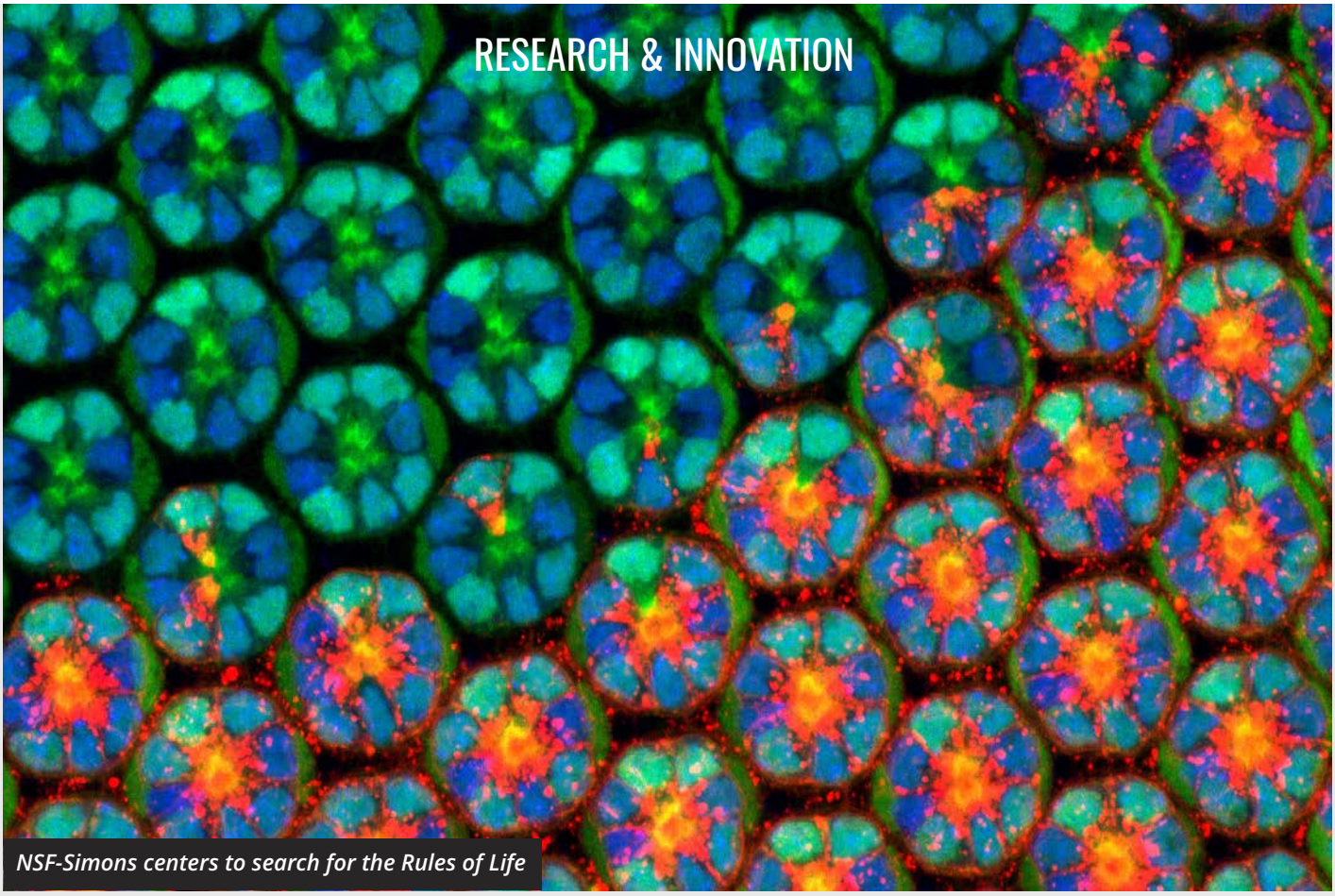
Both products make use of a mathematical technique known as compressed sensing, a breakthrough developed ten years earlier by NSF-supported mathematicians. While the underlying mathematics can be daunting, the idea is actually quite simple. The basis for this technique relies on the idea that many signals (audio, video, images) have a structure that we can take advantage of when they are first measured and then stored. By using mathematical algorithms, we can reconstruct images based on far fewer measurements than we had previously thought possible. One simple analogy is when we recognise a whole song by hearing just a few bars of the melody or recognise a picture from a few well-chosen features.

Using this technique, scanning is strikingly faster, resulting in patients spending much less time inside MRI machines. That's especially important for paediatric patients, where time inside an MRI must be restricted. The speed-up also allows for lower costs per patient.

The benefits are only now becoming widespread, but it was DMS-funded basic research that led to the new MRI technologies. Compressed sensing highlights the benefits of interdisciplinary research, as researchers from three different mathematical fields – geometric analysis, statistics and computational math – and from astronomy came together to work on this problem. It has been one of the great successes in the mathematical community, with a societal impact that is only just beginning.

Driving US mathematics research

DMS is the largest supporter of mathematical sciences research in the United States and accounts for more than 60% of federally funded basic mathematics research, including studies in algebra, topology and geometric analysis, number theory, applied mathematics, analysis, combinatorics, probability and statistics, computational mathematics and mathematical biology. We also support conferences and workshops and a portfolio of national mathematical sciences research institutes.



NSF-Simons centers to search for the Rules of Life

Image: © Northwestern University

DMS' six Mathematical Sciences Research Institutes run programmes for the research community and have a long history of bringing mathematicians together from around the world to share their work, which often leads to new collaborations.

Some of the activities supported by the institutes include programmes to discuss challenges in the development of materials for quantum computing, machine learning applications for computer vision and data-driven methods for precision medicine to guide treatment decisions – all of which have deep mathematical questions at their heart.

Bridging disciplines

Another DMS guiding principle is collaboration with other science disciplines to develop new mathematics. For example, biology is now more quantitative than ever before because of new technologies like high-throughput, next-generation sequencers and high-resolution imaging and microscopy techniques. Such technologies have led to an abundance of new data for biologists to analyse, data that may answer fundamental biological questions, as well as raise new ones.

Building from that need is one of the most exciting activities emerging from DMS this year: a new partnership with the Simons Foundation – a private foundation that supports discovery-driven scientific research in mathematics and the basic sciences – to create four new Centers for Mathematics of Complex Biological Systems.

This $40 million programme is funded equally by NSF and the Simons Foundation and involves DMS and two other divisions in NSF's Biological Sciences Directorate: Integrative Organismal Systems and Molecular and Cellular Biosciences.

The centres will apply mathematical approaches in the hopes of developing predictive frameworks for understanding the pathways from DNA within cells to organisms interacting in nature. Such findings have potential for both pure scientific discovery and for a wide range of applications, from agriculture to health. One of the defining characteristics of the centers will be the close and sustained collaborations between biologists and mathematical scientists leveraging their complementary expertise and diverse perspectives.

DMS programmes span a wide range of energy and security applications, as well. Some mathematicians and statisticians are working on developing mathematical models for modelling efficient and reliable electrical power grid systems, while others work on mathematical algorithms for detecting threats such as outbreaks of epidemics like severe acute respiratory syndrome

Continued on page 39 →

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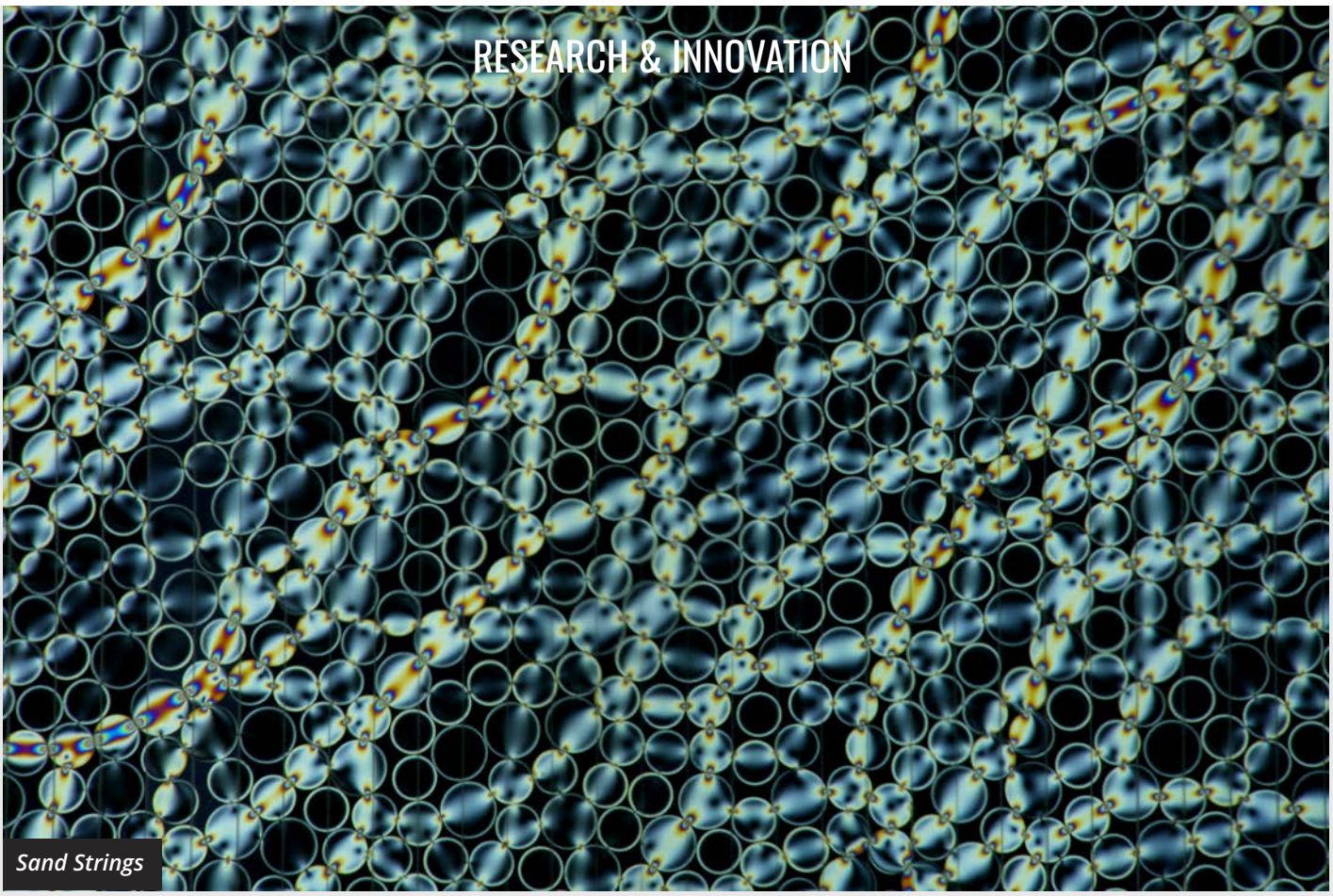

Sand Strings

← ***Continued from page 37***

Image: © Jie Ren, Joshua Dijksman, Robert P. Behringer; Center for Nonlinear and Complex Systems, Duke University

(SARS). Yet others look for hidden patterns in large graphs (like the World Wide Web) that could indicate emerging threats. Mathematicians are even studying ways to help manage and mitigate the aftermath of natural disasters such as hurricanes.

The future of mathematics

In addition to basic research, DMS also places a strong emphasis on training the next generation of mathematicians and statisticians. Through research fellowships, we provide an opportunity for mathematical sciences doctoral students to participate in internships at national laboratories, in industry and at other approved facilities.

Our Mathematical Sciences Graduate Internship fellowship program is aimed at students who are interested in understanding the application of advanced mathematical and statistical techniques to real-world problems, regardless of whether the student plans to pursue an academic or non-academic career.

In 2017, we placed 40 graduate students from 38 universities in 10 national labs. All of the students were able to apply the theoretical coursework they had learned in school to real-world problems like improving computational meshes for simulations, deblurring images and machine learning.

Through the many such programmes and initiatives funded by DMS, new and exciting mathematics research is providing insights into some of the hardest challenges society is facing today, from understanding complex biology to deciphering the fundamental properties necessary to build quantum computers – and understanding their security implications.

While one cannot know where the next breakthrough in science or technology will emerge, mathematics will have been used to better understand or even predict it. Mathematics is essential to society and NSF's Division of Mathematical Sciences is positioned to support the needed mathematics that will help realise that new and better future. ■

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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

Most 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 more-than-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.

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Physics: Optical microscopy in 3D

Dr Chunqiang Li, PhD from the Physics Department at University of Texas at El Paso explains the fascinating area of physics, optical microscopy in 3D

"Seeing is believing." Of course, we must validate what we see as a full picture. Living in a 3D world, dynamic information obtained from 3D space will provide much more enriched information than that from individual 2D snapshots. Two-photon excitation has the advantages of reduced photobleaching, photodamage and background signal suppression compared with one-photon excitation and has been widely used in biomedical research, particularly for *in vivo* imaging. Laser scanning two-photon fluorescence microscopes are the workhorse. These commercially available microscopes typically can acquire two dimensional (2D) images in the range of one to one hundred images/second by raster scanning the laser beam in a sequential manner. Typically, the laser beam scanning is the bottleneck of acquitting high-speed imaging.

In the last decade, several groups have demonstrated temporal focusing as a way of implementing two-photon microscopy for wide-field 2D imaging, without scanning the laser beam. In a temporal focusing two-photon microscope, the focal region is a light sheet with a diameter around a few hundred micrometres, depending on the focal length of lenses and femtosecond laser pulses. which only reach its shortest temporal profile at focal region. Therefore, when using a CCD camera as a 2D detector, this temporal focusing two-photon microscope can obtain wide-field 2D images without scanning laser beams. Based on the success of this technique, several groups have adopted temporal focusing to image cellular dynamics in thick tissues. Since it does not require scanning the laser beam, it could reach 1000 frames/second 2D imaging speed with an amplified femtosecond laser system as the light source.

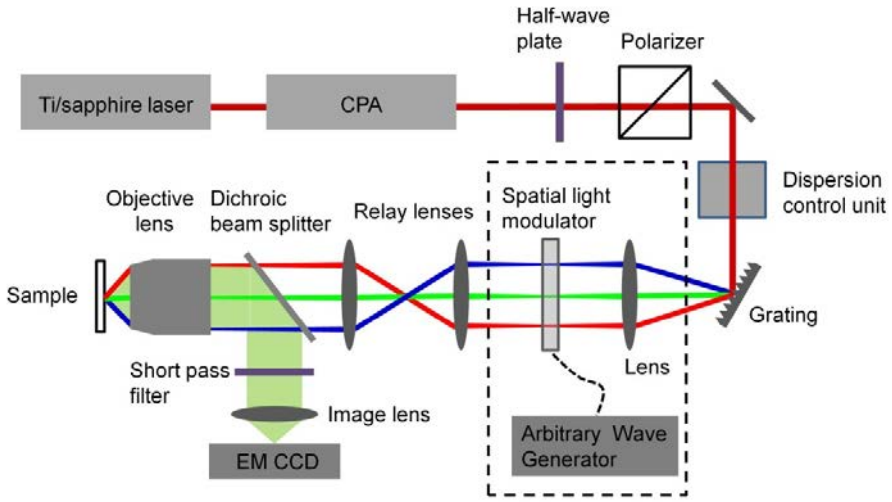

Fig. 1 Temporal focusing two-photon microscope with a pulse shaper setup.

In many applications, especially in live animal imaging, it is necessary to acquire information in all three dimensions. To achieve 3D volumetric imaging, most modalities still need to mechanically move the sample stage or the objective lens to acquire depth information (z-scanning). In the temporal focusing two-photon microscope, it has been demonstrated that changing the group velocity dispersion (GVD) of the femtosecond laser pulses could lead to the displacement of the plane of the temporal focus, along the optical axis of the objective lens, yielding z-scanning as a function of GVD. Femtosecond laser pulse shaping is a technique that spreads femtosecond laser pulse spectrum in space, then modulates each wavelength component with a spatial light modulator (SLM) to arbitrarily shape an ultrafast pulse. Hence, pulse shaping could electrically control the GVD of the femtosecond laser pulse without any mechanical motion, which could further control the z-scanning in the temporal focusing two-photon microscope. Therefore, the goal of our project is to integrate pulse shaping into temporal focusing two-photon microscopy to achieve 3D volumetric imaging without mechanical scanning.

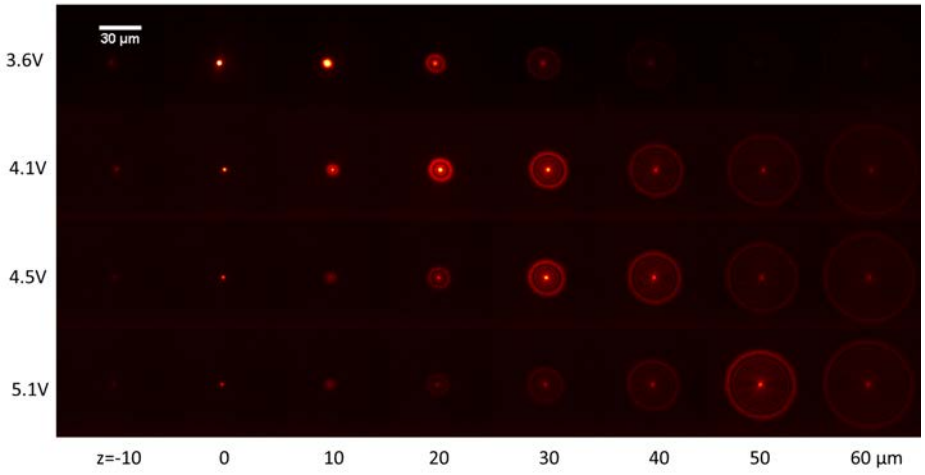

Fig. 2 Temporal focal plane shift by varying GVD. Series of fluorescent images of microspheres at different z positions (z= -10 to 80 µm) after the temporal focal plane is shifted at z=0, 20, 30, and 40 µm planes with varying GVD.

Figure 1 illustrates a schematic setup of the temporal focusing two-photon microscope. To achieve higher imaging speeds, a high peak power laser is needed. Therefore, a chirped-pulse amplifier (CPA) is added after the Ti:Sapphire laser to achieve high peak power (>1 uJ/pulse) at a repetition rate of more than 1 kHz. The incident angle of the grating is adjusted to ensure the central frequency follows the optical axis and propagates through the $4f$ setup, which comprises the collimating lens, relay lenses and the objective lens. Since the spectrum of femtosecond laser pulses has been spread out spatially by the grating, the next step is to add a pulse shaper (dash box in Figure 1) to use acoustic waves to control the dispersion of the femtosecond laser pulses in the spectral domain to achieve scan-less 3D volumetric imaging. The spatial light modulator (an acousto-opto modulator, AOM) is located at the $1f$ location to the left of the first collimating lens. The AOM is driven by a radio frequency arbitrary wave generator to create the desired radio frequency wave that controls the GVD of the femtosecond laser pulse.

Our microscope demonstrated the capability of shifting the temporal focal plane via pulse shaping. We applied different voltages on the arbitrary function generator and the z position of the sample was scanned by moving the 3D sample stage with x and y positions fixed and finally, a fluorescence image was acquired at each z position. This varying voltage function induced GVD on the laser spectrum and changed the temporal focal plane, as shown in Figure 2. This shifting of the temporal focal plane by applied GVD depends on several parameters, such as laser spectral width and the numerical aperture of the objective lens. The temporal focal plane was shifted to z= 60 µm plane by applying a voltage of 10.2 V. This separation of the temporal focal plane from the geometric focal plane has a negative effect on the image quality. When the temporal focal plane is slightly shifted away from a geometric focal plane in the range of ±10 µm, the single fluorophore image becomes blurry. When this shift is larger, the single fluorophore image has the characteristics of concentric rings with peak intensity in the outermost ring and the central lobe becomes blurred as shown in the second to fourth row in Fig. 2.

Overall, we integrated ultrafast laser pulse shaping with the temporal focusing two-photon microscopy and achieved a high-speed 3D imaging method. This 3D imaging system requires neither laser beam steering nor sample mechanical scanning. The depth scanning is achieved by controlling the femtosecond laser spectrum. The dependence of scanning depth on the applied electronic signals which can be tuned at a millisecond timescale. Its high-speed 3D imaging capability was demonstrated by imaging fluorescence microspheres in a volume of 100×100×80 μm^3.

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Image: © Mikephotos | Dreamstime.com

Microbes and the rigour of space flight

William B. Miller, Jr., M.D. argues that without the planning to do so, we have launched microbial life from this planet

It was the greatest car ad ever conceived. A red Tesla Roadster was launched into space with a jaunty spaceman mannequin at the wheel. As it streaks around our solar system at speeds of seven miles per second, its dashboard screen reads a playful, 'Don't panic'. Initial press coverage was fawning. The biggest question was, "Is this art or advertising?" It was never mentioned that the car and its mannequin are loaded with microbes. There hadn't even been any real attempt to clean it prior to launch. No big deal. It's just floating in space and won't impact a planet for a million years or more.

However, its elliptical orbit around the Sun has it crossing Mars orbit every 18.8 months. It will often get close. No one seems to care that this craft will gradually deteriorate over time from the impact of innumerable micrometeorites during its endless loops throughout the solar system. And no one seems to understand that particles of those micrometeorites will ricochet off the car and mannequin and carry bits and pieces of it wherever they go. And no one has noted that on every minuscule bit, there will a new set of travelling companions. Wherever those particles go, associated microbes will now circulate with those particles, some of which will travel outward for light years.

It is the same for all the NASA spacecraft that have ever been launched. To NASA's credit, they have tried to be careful. NASA has been rightfully concerned about the possibility of sending our planetary life out into space. To that end, they enacted rigorous 'clean' rooms. Prior to launch, vehicles were carefully scrubbed to get rid of any lurking microbes. When our spacecraft was launched, they were thought to be sterile. Unfortunately, what NASA believed to be true, was not. It is now under-

stood that the culture techniques that NASA relied upon to determine sterility were utterly insufficient.

In our contemporary era, there are new tools of genetic assessment that permit our identification of a much wider range of microorganisms than in prior decades. In fact, it is now known that fewer than 10% of all microbes can be cultured in the standard manner that NASA was diligently applying. Therefore, the tests that NASA relied upon to issue their declarations of sterility were unfortunately completely inaccurate. Although the NASA spacecraft were culture negative upon launch, they were abounding with covert microbial life.

Furthermore, we now know that many microbes can withstand every rigour of space flight. In the vacuum of space, with its absolute cold and bursts of destructive radiation, humans would instantly die. Yet, some microbes do not, nor do singular small animals, called Tardigrades. These incredibly resilient microscopic eight-legged creatures can withstand all the extremes of space. We know that this is true since some of them have even survived re-entry back to our planet from other space flights.

It is these exact findings that inform us that single most important event in our entire human history is currently transpiring. This unheralded event is the passage of the Voyager 1 and 2 spacecrafts beyond our solar system and exiting into interstellar space. What makes this passage so momentous is that both crafts carry life.

As originally envisioned, the mission of the Voyager spacecraft was to study the outer planets of our solar system. In this regard, that mission has been highly successful. The Voyager craft left Earth in 1977, arrived at Jupiter in 1979 and then passed by Jupiter, Saturn and Uranus, to arrive at Neptune by 1989. Important physical discoveries were catalogued at each planet, such as the magnetospheres of Uranus and Neptune. By mission design, there was never any possibility of return. Instead, the craft was tasked towards an endless continuation into deep space.

Now, Voyager 1 is over 13 billion miles from Earth, with Voyager 2 close behind. Currently, they are just at the margin of the heliosphere which is the large zone influenced by our Sun. Thereafter, interstellar space looms and the Sun's influence rapidly fades.

Although the milestones of the Voyager craft are being minutely detailed, NASA astronomers remain completely silent about the most portentous aspect of this Voyager mission. That silence is not entirely surprising since, until the Tesla car launch, the Voyager mission represents the most egregious example of unintended consequences in human history.

Though this event receives no attention, it is immensely more significant than any war in human history, or any ideology, or all our art and culture. Without planning to do so, we have launched microbial life from this planet. Now, for endless eons, that tenacious life will be propelled outward into deep space. Everywhere Voyager goes, life will be shed. It is the same, but even more so, for the supremely egotistical Tesla in space. Both are instances of singular technical achievement and delinquent government oversight.

There is a theory of the origin of life that suggests that it began on Earth as an instance of Panspermia. In effect, life on this planet began elsewhere, finding a home here and thriving. Now, without explicit intent, both Voyager spacecrafts and the Tesla advertisement have begun the process of seeding of life throughout the Cosmos. In our uniformed hubris, we have become an unintentional agency of Panspermia. Now, in a direct sense, we have become a Cosmic invasive species.

Let it be our earnest hope that we will be forgiven. ■

Dr Bill Miller had been a physician in academic and private practice for over thirty years. He is the author of The Microcosm Within: Evolution and Extinction in the Hologenome. Dr Miller is an internationally recognised evolutionary biologist and an expert on the emerging science of the microbiome. He is the author/co-author of numerous academic papers on the microbiome and evolution, serves as guest editor of a major academic biology journal and is co-editor of a forthcoming textbook on developmental and evolutionary biology. Connect with him on Twitter, @billmillermd.

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Pesticides: A contributing factor to the increase in asthma?

Pamela J. Lein at the University of California, Davis discusses the evidence suggesting that pesticides are risk factors for asthma

Asthma is a chronic inflammatory lung disease, characterised by episodic and reversible bronchoconstriction (contraction of the smooth muscles that line the airways), excessive secretion of mucus in the airways and airway hyperreactivity (an exaggerated reaction of airway smooth muscle to contractile stimuli). All of these effects interfere with breathing.

Worldwide asthma prevalence and severity has increased markedly over the past two decades, especially in urban settings. Many hypotheses have been proposed to explain the increased asthma in urban residents, including exposure to allergens, air pollution, differences in healthcare and stress. However, an environmental factor associated with agricultural asthma that is beginning to receive increased attention in the context of urban asthma is exposure to organophosphorus pesticides (OPs).

OPs are the most widely used class of pesticides worldwide and are applied extensively in not only agricultural but also in suburban and urban settings to control insects. Although residential uses of OPs are being phased out in the United States and many European countries, OPs are still used heavily in agricultural, industrial and commercial settings and OPs are widely detected in the general human population in all countries in which this has been assessed.

Occupational exposures associated with the production, distribution and application of OPs occur primarily via dermal absorption, with more limited exposure via inhalation. The general population is exposed to OPs via ingestion of food and water contaminated with OPs and by dermal and inhalational exposure to pesticide drift and "overspray". The latter is not an insignificant source of exposure as extensive OP contamination has been documented in the air, homes and urine from pregnant women and children living in communities near agricultural fields sprayed with OPs

OPs inhibit the enzyme acetylcholinesterase, which functions to inactivate the neurotransmitter acetylcholine. Acetylcholinesterase inhibition significantly increases acetylcholine levels at the synaptic junction between nerves that secrete acetylcholine and their target tissues, causing excessive stimulation of target tissues.

Acetylcholinesterase activity is functionally important in not only insects, but also humans. It is well established that OPs cause neurotoxicity in humans by inhibiting this enzyme, a medical condition referred to as the cholinergic crisis. Acute exposures to OPs that inhibit acetylcholinesterase by more than 80-90% of control levels can cause death in humans, typically by inhibiting the respiratory centres in the brain that control breathing. Thus, many regulatory agencies have identified safe levels of OPs as those that do not inhibit acetylcholinesterase.

Case reports published in the 1960's provided the first indication that exposures to OPs at levels that do not cause cholinergic crisis may trigger asthma in adults. Subsequent cross-sectional studies of farmers and their families, farmworkers and commercial pesticide applicators in multiple countries around the world provided further evidence that occupational exposures to OP pesticides are associated with adult-onset asthma.

More recent epidemiologic data suggest that not only occupational exposures, but also exposures to environmentally relevant levels of OPs, such as might be experienced by the general public, are associated with increased risk of asthma and asthmatic symptoms in adults and adolescents. OP-induced asthma may not be limited to these age groups, as indicated by emerging data from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), the longest-running longitudinal birth cohort study of pesticide effects on children's health, which has been studying children in a farmworker community in the Salinas Valley of northern California. Data from the CHAMACOS study suggests that OP exposures during pregnancy and the first year of life, as determined by analysis of urinary OP metabolites in pregnant women and their infants,

Farm worker spraying pesticide treatment on fruit garden

are associated with respiratory symptoms in children at five and seven years of age.

While systematic reviews of the published epidemiologic literature generally support an association between OP pesticide exposure and asthma, it is difficult to establish a cause-effect relationship based on human data. This is due in large part to the fact that it is extremely challenging to accurately quantify OP exposure in humans. Thus, studies in animal models are critical for determining whether OPs are causally linked to asthma. The animal studies published to date support the hypothesis that OPs directly cause airway hyperreactivity, a key symptom of asthma.

Importantly, OP-induced airway hyperreactivity is observed at levels that do not inhibit acetylcholinesterase. Several different OPs, including chlorpyrifos, parathion and diazinon, can induce airway hyperreactivity in guinea pigs following subcutaneous injection, a route of exposure that mimics dermal exposure in humans. In contrast, pyrethroids, a class of pesticides structurally and mechanistically distinct from OPs, do not induce airway hyperreactivity in guinea pigs, suggesting that the airway response to OPs is not a generalised property of all pesticides.

Interestingly, the effect of OPs on airway hyperreactivity was not evident immediately after exposure, but rather were manifest 24 hours later and persisted for at least seven days after a single injection of the OP. Further studies in the guinea pig model suggest that OPs cause airway hyperreactivity by interfering with neural mechanisms that normally function to limit the release of acetylcholine from airway nerves onto airway smooth muscle. This effectively increases the amount of acetylcholine available to cause contraction of the airway smooth muscle.

How OPs cause dysfunction of airway nerves remains an outstanding question, although preliminary data suggest that the mechanism may vary depending on the allergic status of the individual. Answering this question will be critical for identifying susceptible subpopulations and for designing more effective therapeutic interventions for preventing or reversing OP-induced airway hyperreactivity. More immediately, these findings raise significant questions regarding the use of acetylcholinesterase activity as a point of departure for regulatory action. Furthermore, these findings suggest the possibility that the increased prevalence of asthma is related less to the insects that we live with than to the chemicals we use to kill them.

UCDAVIS VETERINARY MEDICINE

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How developmental biology changes our lives

Shyh-Jye Lee (Jeff), Ph. D, President of the Taiwanese Society of Developmental Biology (TSDB) explains the way in which developmental biology impacts upon our lives

Developmental biology (DB) is an expansion of traditional embryology, which studies the development of a single-cell fertilised egg to a multicellular free-living organism. Today, DB research covers beyond embryogenesis to include growth, sexual maturation and ageing.

DB affects our life in many aspects. One of the key issue related to our life and the sustention of species is the control of fertility and infertility. The understanding of oestrous cycle and the development of sexual organs and gametes helps us control conception and increase fertility. Birth control pills and condoms are both effective tools for population control. The development of in vitro fertilisation (IVF, i.e. test-tube baby) technology is another good example to show how DB research can change our lives. The desire of having their own baby was often a dream that never came true for infertile couples.

But since the development of IVF and other assisted reproductive technologies, many couples regain their hope to have biological babies. The success of IVF in mammals, including human, was based on the basic understanding of fertilisation mechanisms of marine invertebrates like sea urchins. From those studies, we appreciate the importance and regulation of ionic flows during fertilisation. By manipulating those factors along with others, scientists gradually broke through the IVF barriers in mice, human and other larger mammals. IVF is thus one of the most fascinating stories of how DB research can improve the wellbeing of human life itself.

How could a single-cell fertilised egg develop into a multicellular functional adult is a key fundamental question asked by developmental biologists. Throughout centuries of research, we understand that cells in early-stage embryos have the full potential to become all types of adult cells that are called “totipotency”. The totipotency is gradually lost in later stage embryos, but they still retain “pluripotency” to become multiple types of cells. Eventually, embryonic cells limit their developmental potential to one specific type of cells. However, we know that even terminal differentiated somatic cells contain the same genome as that of a fertilised egg.

Theoretically, it can be totipotent if properly reprogrammed back to the original state. Although the astounding generation of Dolly Sheep proves the principle by somatic nuclear transplantation experiments, low success rate and unhealthiness of cloned animals imply that reprogramming the differentiated genome to its default state is not reached by using this method.

Many animals, like planarians, salamanders and zebrafish can replace missing body parts. In contrast, mammals only have a limited regenerative ability in tissues and organ-like skin epithelial layers, hair and liver. This may lead to severe health problems like fibrosis, accumulation of extracellular matrix proteins like collagens in heart and other organs. Heart injuries often lead to scars and subsequent fibrosis. Fibrosis results in the stiffness of heart, impaired function and eventually heart failure.

The studies of fibrosis prevention and resolution have attracted the attention of medical professionals, as well as DB researchers. DB researchers often use animal models capable of regeneration to understand how the regeneration is induced and accomplished. They are now more eager to apply the gained knowledge to screen drugs or devise tools or strategies to repair injure tissues or organs in mammals and human that have been established in a new discipline called “regenerative medicine”.

During development, a group of cells called stem cells not only can become other types of cells, but they can renew themselves to keep their stemness. The most competent stem cells are embryonic stem cells (ESCs). ESCs are cells from the inner cell mass of a blastocyst. They contain pluripotency that allows them to be induced into many other types of cells in vivo or in vitro and is potentially a great cell source to be cultured to tissues, or even organs to be used in regenerative medicine.

> "Developmental biology (DB) is an expansion of traditional embryology, which studies the development of a single-cell fertilised egg to a multicellular free-living organism. Nowadays, the DB research covers beyond embryogenesis to include growth, sexual maturation and ageing."

However, it is unavoidable to destroy a blastocyst while collecting ESCs. It becomes a major hurdle that prevents the practical use of ESCs due to ethical and religious reasons. Terminal differentiated somatic cells still retain the same genome as that of fertilised eggs. Triumphantly, we now can reprogram somatic cells like fibroblast cells to become stem cells called inducible pluripotent stem cells (IPSCs). Using IPSCs different types of cells, including blood, neuronal cells, muscle cells, germ cells and others have been created in vitro. The next challenge will be how to consistently produce those cells to be reliably used in regenerative medicine.

IPSCs may also push the development of medicine to the next level. Traditionally, the development of drugs relies heavily on the use of immotile cell lines and animal models, mainly mice. However, only less than 1% of drugs tested in clinical trials are approved. The failure of drug testing can be for a variety of reasons. The suitability of screening model is certainly one of the issues. Although mice resemble human in many ways, they are not human. Even in humans, there are variations between different people.

In addition, drugs entered the market are suitable for most people that may not fit you well. Therefore, the idea of "precision medicine" emerges. The IPSCs may fit in the precision medicine nicely. We can use patient-derived IPSCs for drug testing before administrating to patients. We can also use human-derived IPSCs for drug screening as well. However, we still have a long way to go and proper animal models are still needed.

Shyh-Jye Lee (Jeff), Ph.D.
President

One of the most exciting discoveries in biology lately is the invention of CRISPR/Cas9 technology, which allows much more convenient targeted genome editing in cells and organism levels. DB researchers quickly apply this technology to edit genomes of different model systems, as well as for IPSCs. It is then of great potential to correct human genetic diseases with known mutation(s) using CRISPR/Cas9 if it is proven to be safe and effective in the future.

Overall, although most DB research still focuses on the basic regulations of developmental processes, developmental biologists are prompt to apply their findings for practical use in both medicine and agriculture. So far, many great discoveries have been made that have affected our lives, but I can only name a few here. To go further, we will need more efforts from DB researchers, along with continuing support from governments, the private sector and the public. ■

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Rediscovering observations of the environmental factors affecting tissue regeneration in aquatic species

Graciela A. Unguez, PhD, Professor of Biology and student Bahiyyih Mitchell at New Mexico State University explore the environmental factors affecting tissue regeneration in aquatic species

What controls the regeneration of entire body parts and organs in some animals, even multiple times in adulthood? This "million-dollar" question has fuelled the curiosity of many scientists for centuries. Today, the number of both terrestrial and aquatic species tested for their response to injury continuously grow, expanding the comparative analysis of regeneration capacities throughout the animal kingdom.

At the same time, the availability of molecular approaches and tools to manipulate genomic sequences has driven the focus of scientific studies towards elucidating the genetic basis of regeneration processes. This has led to a growing identification of distinct molecular switches and signaling pathways that activate or inhibit stem cell progenitors and other cellular mechanisms of tissue regeneration[1-2].

However, and perhaps unintentionally, the emphasis on establishing model systems amenable to genetic manipulation under controlled lab conditions has led many of us to overlook and/or underestimate the environmental effects on regeneration.

A case in point is the effect of artificial light exposure on tail regeneration of the gymnotiform electric fish *Sternopygus macrurus*. *S. macrurus* is a highly regenerative species and our lab has exploited this property to characterise the differentiation of myogenic cells in response to repeated tail amputations, the effect of neural input on the differentiation of myogenically-derived cell types and the activation of myogenic stem cells to restore original skeletal muscle and muscle-derived electrogenic tissue lost[3-6].

Surprisingly, we recently performed an experiment in which 12 adult fish had their tails amputated, but none of the fish regenerated a blastema as expected even two weeks after amputation. These fish had been kept in a room adjacent to the main aquaria room. Upon return to their original tanks in the main aquaria, these fish began regenerating their tails. This observation led us to hypothesize that decreases in light exposure negatively affected tail regeneration in *S. macrurus*. *S. macrurus* fish (n=5) were then placed in either constant darkness conditions or on a control 12hr-on/12hr-off light cycle condition (Figure 1) and regeneration blastema length measured seven and 14 days post-amputation.

In general, regeneration blastemas from fish kept in restricted light or "dark" conditions appeared smaller than those in control lighting conditions at seven and fourteen days after tail amputation (Figure 2). Quantitation of cell proliferation in regeneration blastemas under control and dark conditions using the 5-ethynyl-2'-deoxyuridine (EdU) labelling assay

Figure 1: Experimental lab setup to modify external lighting conditions.

Top Row: Fish in the Control group were housed in individual tanks and had no changes in ambient light exposure.

Bottom Row: Fish in the Restricted Lighting or "dark" group were housed in individual tanks and their exposure to light was greatly reduced by covering their tanks with thick black plastic bags.

showed mean lower numbers of EdU-positive cells in blastemas from fish kept in dark, compared to that of fish in control lighting conditions.

These observations led us to our rediscovery of a study published in 1977[7] on stunted forelimbs of newts *Triturus* (Notophthalamus) *viridescens* when these were kept in constant darkness following limb amputation. Specifically, animals exposed to continuous light reached the regeneration stage four to five days before those who were kept in total darkness. Moreover, the difference in regeneration rate was first evident in the moderate early stage; it then increased during subsequent stages and the difference persisted during the observation period – observations similar to those in our study of *S. macrurus*.

"Today, the number of both terrestrial and aquatic species tested for their response to injury continuously grow, expanding the comparative analysis of regeneration capacities throughout the animal kingdom."

In 1983, a study by Young et al[8] also reported that restricted lighting conditions could retard regeneration in the adult salamander, Ambystoma. These two studies are not cited in the numerous papers dissecting the genetic and molecular factors of regeneration processes under controlled lab conditions. Whether or not changes in environmental lighting act through any of the currently known pathways or regulatory protein factors that activate or inhibit regeneration is currently unknown. Certainly, of more importance is whether or not the molecular switches and signalling pathways of current interest retain their predicted function in the mechanisms of tissue regeneration in less controlled environmental conditions.

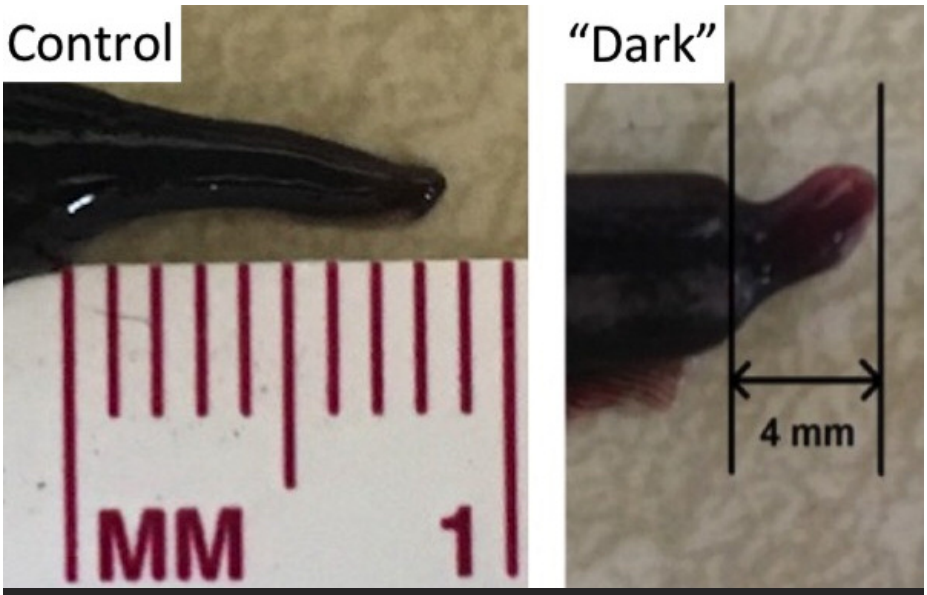

Figure 2: Light restriction leads to smaller regeneration blastemas. Images of partial S. macrurus tails 2 weeks after tail amputation under control and restricted light (i.e., "dark") conditions.

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Promoting polar science in the United States

The work of the Office of Polar Programs (OPP), part of the National Science Foundation (NSF), is examined here by Open Access Government

Within the National Science Foundation (NSF), the Office of Polar Programs (OPP) exists to promote innovative and creative scientific research that concerns the polar regions. They achieve this by catalysing fundamental understanding and discovery of polar systems and their global interactions to educate the United States and to advance the welfare of everybody.

Science, Technology, Engineering and Mathematics (STEM) engagement and workforce development (education & people) are very much a part of OPP's remit, as they aim to undertake their duties in a collaborative and sustainable manner. OPP works with a wide array of partners, including native Arctic communities and Alaskan residents from the polar regions, as well as local, state, federal and international educational and research agencies and institutions.

Ice stream draining Greenland Ice Sheet

One of the many examples of research highlighted on OPP's website is all about a study which shows that a ribbon of ice more than 600 km long that drains around 12% of the gigantic Greenland Ice Sheet which has been smaller than it is today, a new study explains. We find out that the loss of ice from the Northeast Greenland Ice Stream (NEGIS) took place during the warm Holocene period, and during a time preceding the last glacial maximum that is thought to be very cold one, the researchers argue.

"There are some parts of the ice sheet that are relatively stable and others that show evidence of very rapid retreating – a pattern we're seeing today as well as thousands of years ago," says Anders Carlson, from Oregon State University, who is a co-author of the study. "Some of it relates to bed topography – when the bed is below sea level, it stabilises that part of the ice sheet. In low spots, it is unstable", he adds.[1]

International Thwaites Glacier collaboration

In other recent news, we learn that the collapse of the Thwaites Glacier in West Antarctica could affect global sea levels significantly. In April, the National Science Foundation (NSF) and the United Kingdom's Natural Environment Research Council (NERC) announces that teams of scientists in various U.S. institutions will deploy to Antarctica to collect the data required to find out if the glacier could begin to collapse during the next few decades or centuries.

This is part of a new $25 million research collaboration, which will continue until 2021 and we discover that The Thwaites Glacier already drains an area that is similar to the size of Britain or the state of Florida, which accounts for around 4% of global sea level rise.

"Satellites show the Thwaites region is changing rapidly," says William Easterling, NSF assistant director for Geosciences. "To answer the key questions of how much and how quickly sea level will change requires scientists on the ground with sophisticated equipment collecting the data we need to measure rates of ice-volume or ice-mass change. The challenges of conducting fieldwork of this scope and scale in such remote locations are enormous. The only practical way for nations to do this is to work collaboratively, each bringing scientific and logistical resources to enable complex and comprehensive field studies", he adds.

The Office of Polar Programs manages the U.S. Antarctic Program, which will support the collaboration's researchers and provide U.S. logistics for the project's vital work. "The fate of the Thwaites Glacier is one the big unknowns in Antarctic science," says Duncan Wingham, NERC's chief executive. "We currently do not know enough about the likelihood, timing and magnitude of the collapse of West Antarctic glaciers such as Thwaites to be able to plan accordingly. NERC and NSF, working

together, are uniquely placed to attempt to reduce the scientific uncertainty about these unknowns, providing answers to one of the most important questions facing us about global sea level rise", he adds.

> "Within the National Science Foundation (NSF), the Office of Polar Programs (OPP) exists to promote innovative and creative scientific research that concerns the polar regions. They achieve this by catalysing fundamental understanding and discovery of polar systems and their global interactions to educate the United States and to advance the welfare of everybody."

This is the largest joint project undertaken by the two nations in Antarctica in more than 70 years and includes about 100 scientists from research institutes in both countries alongside those other nations, including Germany, Sweden, South Korea, New Zealand and Finland. Kelly Falkner, director of NSF's Office of Polar Programs, underlines that the U.S. Antarctic program has: "decades of experience in supporting large-scale international research initiatives – from building the world's largest neutrino detector at the South Pole to supporting ice-core and sediment drilling projects that provide glimpses into the thawing and freezing of Antarctica over timescales of millions of years."[2]

In closing, it's worth just saying that these two examples illustrate the Office of Polar Programs clear aim to promote, "creative and innovative scientific research...in and about the polar regions, catalysing fundamental discovery and understanding of polar systems and their global interactions to...advance the welfare of all people."[3] ■

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The Antarctic notothenioid fishes: An especially interesting and unique marine species flock

Arthur L. DeVries, from the University of Illinois provides a comprehensive insight into a unique marine species flock, the Antarctic notothenioid fishes

At one time the Antarctic Ocean was home to a temperate fish fauna which included sharks, rays and bony fishes (teleosts). About 20 million years ago the Antarctic waters began to cool and all the temperate fishes died out, except for a bottom-dwelling fish that probably looked like a northern hemisphere sculpin. This hypothetical ancestor gave rise to a group of closely related fishes that survived the cooling waters, which today are known as the notothenioid fishes: (a sub order Notothenioidei nested within the modern bony fishes (Perciforms). Some of the shared features of this group are the lack of a swim bladder making them negatively buoyant in seawater, paired pelvic and pectoral fins positioned one above the other and just distal of the opercula and mostly benthic species.

This suborder includes eight families most of which are found in the Southern Ocean south of the Antarctic convergence. Members of five of the eight families are primarily confined to the narrow shelf region of the Antarctic continent. The families include the Nototheniidae, Channichthyidae, Bathydraconidae, Artedidraconidae and Harpagiferidae. They make up about 90% of the fish biomass of the shelf and the populations of some of the species are huge. The other three families (fig 1) are confined to the waters of the sub-Antarctic islands and the Patagonian region of South America.

When the waters surrounding the Antarctic continent began freezing – a novel trait evolved in some of the progeny of the notothenioid ancestor – which permitted them to avoid freezing; this trait was a blood-born glycoprotein which had antifreeze properties. This antifreeze glycoprotein (AFGPs) lowered its blood freezing point a few tenths of a degree below the freezing point of seawater (-1.9°C). The antifreeze trait allowed them to survive and diversify into many species which filled the ecological niches vacated by the extinction of the temperate fish fauna. Presently, there are a variety of body morphs. Some of the nototheniids and harpagiferids resemble north temperate bottom dwelling thorny sculpins (Cottids).

Other species of the nototheniid family are like smelt and salmonids in body form with a fusiform shape. The nototheniid, Trematomus borchgrevinki inhabits the waters at the underside of the fast ice and finds refuge in the platelet layer and has a body form similar to a codfish. The two nototheniid fishes, Pleuragramma antarctica (Antarctic smelt) and giant Antarctic toothfish, Dissostichus mawsoni inhabit the water column and are neutrally buoyant even though they lack a swim bladder. They have achieved neutral buoyancy by reducing mineralisation of their skeletons and scales and accumulating lipids which are less dense than seawater. The smelt accumulates sacs of clear lipid under its skin and between its dorsal vertebral spines. Neutral buoyancy adaptations allow these two species to cruise through the water column expending energy only for directional swimming rather than swimming to counteract sinking.

Channichthyids, often called crocodile fishes because of their large mouths as adults are sit and wait predators and can gulp and swallow a fish half their size. The most amazing trait found in this family is the lack of red blood cells and hence hemoglobin the oxygen transport pigment. Oxygen taken up at the gills is transported only as dissolved oxygen in their hemoglobinless blood.

However, they have evolved adaptations to partly overcome the lack of hemoglobin such as larger gills for a larger gas exchange surface to absorb oxygen, a larger blood volume with a larger heart and the absence of scales which allows some gas exchange through the thin skin. Despite these adaptations, they do not tolerate stress like their red-blooded relatives

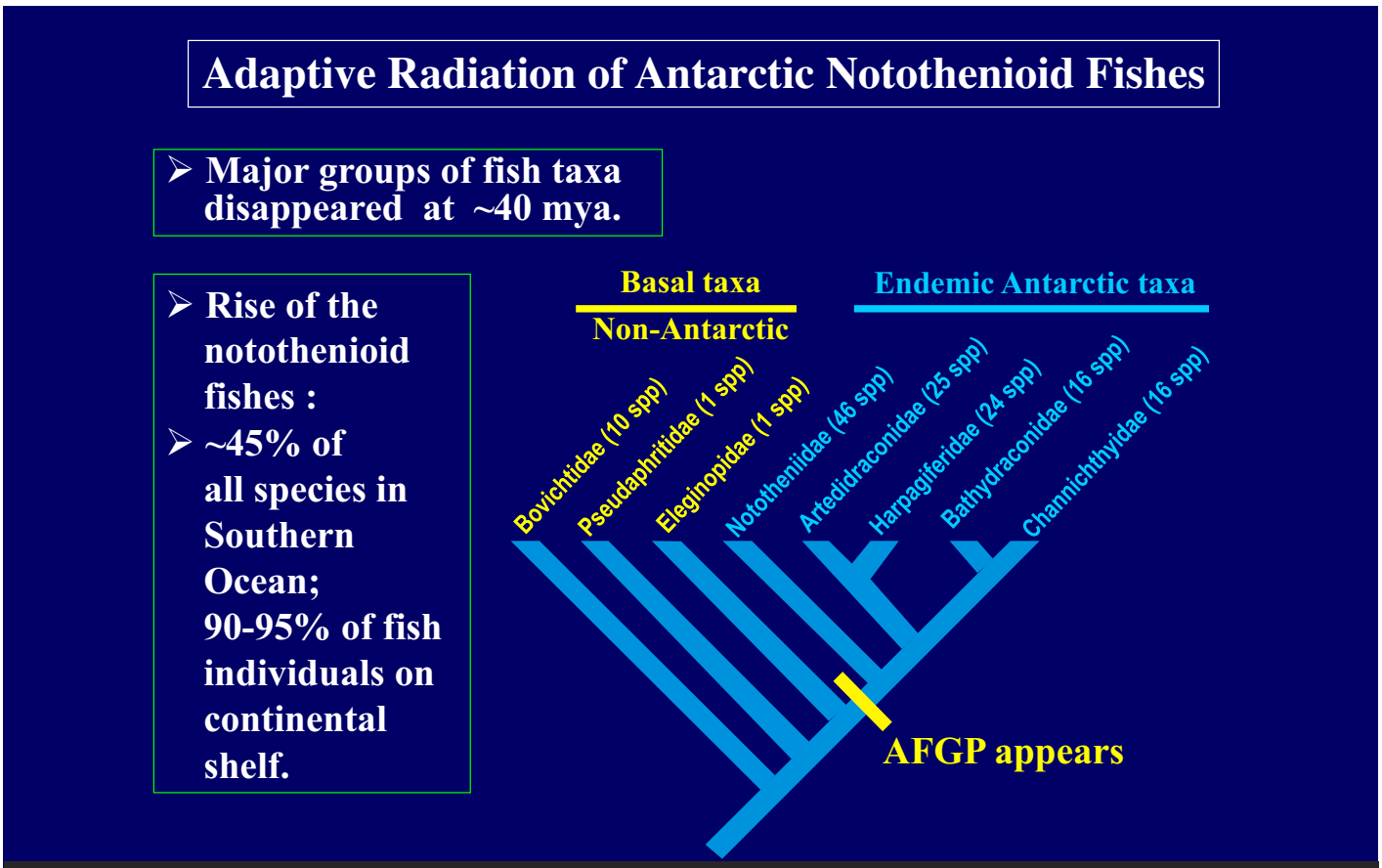

Figure 1. Cladogram of Antarctic fishes of the Suborder Notothenioidei and characteristics of the group

and are therefore at a physiological disadvantage relative to the other notothenioids.

However, they have been able to survive for millions of years because the cold Antarctic Ocean contains more oxygen than warm temperate waters because oxygen solubility is greater in cold water than warm water. The presence of one species of the channichthyid species in 12°C waters of Tierra del Fuego exemplifies the creativity of evolution as this one species can tolerate temperatures well above those ice fish species endemic to the Antarctic Ocean which fail to survive at temperatures higher than +6°C. Although this South American fish appears to exist near it physiological limit, it does attest to its evolutionary success despite having to compete with many coexisting red blooded species, such as salmonids and other non-Antarctic fish species.

The notothenioid group is an excellent example of a marine species flock. That is, a closely related clade of species that arose from a common ancestor and underwent an adaptive radiation that gave rise to a variety of species with unique morphological and physiological characteristics that allowed them to successfully invade and fill most of the underutilised ecological niches that were vacated by the extinct temperate fauna. Because they are closely related the similarities and differences in some of their biochemical, physiological and morphological traits can be more easily compared without having to deal with a phylogenetic signal that would be present if they originated from unrelated ancestors.

Thus, a clearer picture can be gleaned from comparative studies of their morphological, biochemical, physiological adaptations and the underlying genomic changes that gave rise to them. This marine species flock is like the African Rift cichlids which also arose from a common ancestor and evolved into hundreds of species which exhibit morphological, behavioural and reproductive differences and utilise different ecological niches in the fresh water lakes.

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Ocean sciences: Advancing the frontiers of knowledge

The activities of the Division of Ocean Sciences (OCE), a section of the National Science Foundation (NSF), in advancing the frontiers of knowledge around ocean sciences, are reviewed here by Open Access Government

The Division of Ocean Sciences (OCE) is a section of the National Science Foundation (NSF) in the U.S. that strongly supports research, infrastructure and education to further understanding of the global oceans and ocean basins, including their interactions with the integrated Earth system and human beings.

OCE's activities provide essential knowledge for addressing many of the U.S.'s most pressing challenges in the area of earth processes. OCE advocates collaboration in the field and encourages the development of a diverse scientific and educational community, at home and abroad.

Working in partnership with the U.S. ocean sciences academic community, OCE directs funding towards advancing the frontiers of knowledge, enhancing the public's understanding of ocean sciences and developing the next generation of researchers.

While OCE represents this community in the Federal context, they coordinate with international partners in areas such as funding for research and managing infrastructure. OCE also takes part in the development of policy by means of a number of forums and programmes in the U.S. and further afield.

NSF experiments on giant kelp

In recent news from OCE, we discover that a giant kelp can grow two feet a day and reach nearly 150 feet in length – in one growing season. Researchers affiliated with the NSF) Santa Barbara Coastal (SBC) Long-Term Ecological Research (LTER) site aimed to find out how giant kelp can maintain their impressive growth in seasons when nitrate all but vanishes.

Details of their findings on one of the fastest-growing organisms on Earth appeared in June 2018 in the journal, Limnology and Oceanography Letters. "This report provides an explanation for how giant kelp in Southern California is able to persist and grow when nitrate concentrations in coastal waters are extremely low," says David Garrison, a program director in NSF's LTER program, which funded the study.

"It turned out that kelp consistently showed no preference, and used urea at equal rates as ammonium," lead author Jason Smith of the University of California, Santa Barbara (UCSB) explains. "Our results suggest that there's enough urea available to sustain kelp growth when levels of ammonium and nitrate are low."

Having said that, calculating a rate of use for the

various compounds provided just some of the answer, we are told.

"We performed a set of controlled experiments on kelp tissue to prove that the urea molecule itself enters the tissue," Smith adds. "We're the first to document for any seaweed that the whole urea molecule is consumed, which greatly expands the known physiology of giant kelp and the kinds of nitrogen forms the plant can use."[1]

The impact of hurricanes on coastal ecosystems

In other news, we learn that scientists have set out to chronicle how two decades of hurricanes have affected North Carolina's Neuse River, the second-largest estuary in the U.S. The NSF supports this fascinating area of research through its Biological Oceanography and Chemical Oceanography programs, which included a rapid response grant following 2016's Hurricane Matthew.

> "OCE's activities provide essential knowledge for addressing many of the U.S.'s most pressing challenges in the area of earth processes. OCE advocates collaboration in the field and encourages the development of a diverse scientific and educational community, at home and abroad."

"One manifestation of climate change may be a higher frequency of storms," says David Garrison, a program director in NSF's Division of Ocean Sciences. "This study provides valuable insights into how coastal estuaries will be affected."

Hans Paerl, a scientist at the University of North Carolina at Chapel Hill adds: "Understanding how an increase in extreme events such as hurricanes affects coastal ecosystems is critical to preparing for a stormier future."

Understanding how coastal ecosystems respond to hurricanes and other major storms, including nor'easters and severe thunderstorms, says Paerl, "is important at a time when such extreme weather events are becoming more frequent and intense."

This perspective examines the effects of hurricanes on estuaries, also indicates that the increased CO in coastal waters could impact upon the climate. "The impacts of these infrequent but significant pulses of nutrients into sensitive coastal ecosystems have been mostly unknown," Paerl underlines.[2]

Dispersants to clean up oil spills

Finally, other news worth exploring concerns the NSF's research with the Woods Hole Oceanographic Institution (WHOI), which discovered that sunlight chemically alters crude oil floating on the surface of the sea within a matter of days or hours.

"It's been thought that sunlight has a negligible impact on the effectiveness of dispersants," explains Collin Ward, a scientist at WHOI and lead author of the study. "Our findings show that sunlight is a primary factor that controls how well dispersants perform. And because photochemical changes happen fast, they limit the window of opportunity to apply dispersants effectively."

Henrietta Edmonds, a program director in NSF's Division of Ocean Sciences, which funded the research adds, "This study shows how important it is to do basic research on the chemical reactions that take place in the environment. The results will help us learn how to effectively respond to oil spills."[3]

Final remarks

The above examples of research into the ocean sciences reveal exactly how OCE directs funding into areas that advance "the frontiers of knowledge", develop "the next generation of researchers" and enhance "the public's understanding of ocean sciences."[4] It also fits in with the wider aim of the NSF to "support basic research and people to create knowledge that transforms the future."[5] ■

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Oceans heated by volcanic ridges and seamounts

Dr Karen Bemis from Department of Marine and Coastal Sciences, Rutgers, The State University of New Jersey gives a fascinating explanation of how oceans are heated by volcanic ridges and seamounts

Have you ever wondered what controls the temperature and the chemistry of the deep ocean? If you are interested in climate change, you should. Many factors, including dense surface waters that sink to the depths, can affect the deep ocean temperature and chemistry. One of the most surprising and spectacular controls on deep ocean temperature and chemistry are the volcanic hot springs that line the mid-oceanic ridges and cap seamounts providing chemosynthetic energy to support fantastic ecosystems. These hot springs transfer sufficient heat and chemicals into the ocean to affect the deep ocean circulation patterns, the ocean chemistry (for example, the dissolved Fe content), and the biomass productivity of the ocean. [1]

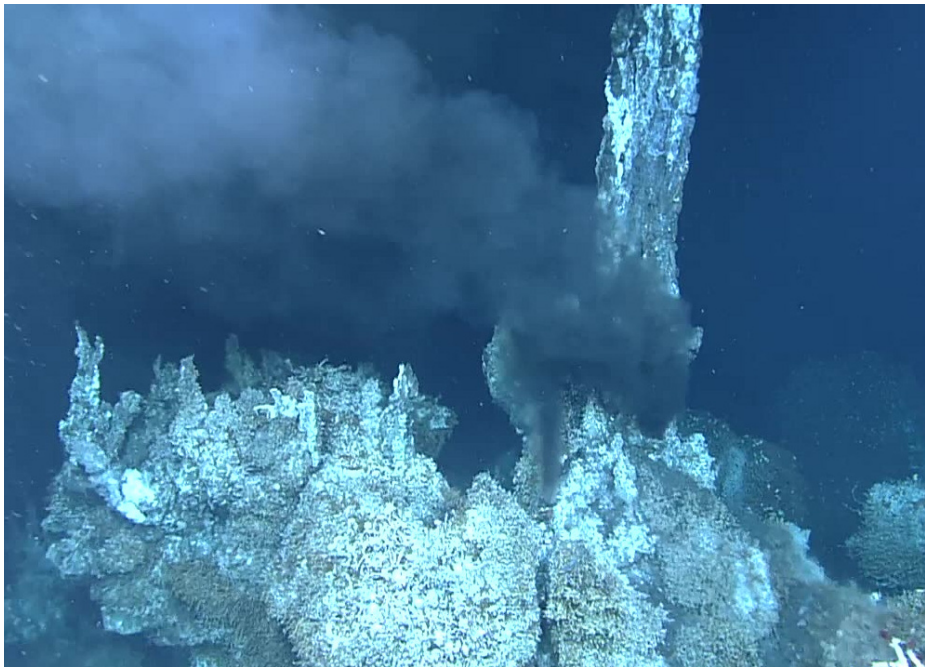

Figure 1. Black smoker on top of Grotto vent in the Main Endeavour Field on the Juan de Fuca Ridge. Video frame taken on July 9, 2011, at 04:41 GMT courtesy of Ocean Network Canada

In volcanic systems under the ocean, seawater infiltrates deeply into the fractured crust warming up due to heat from magma and reacting with the crustal rocks. This altered hot seawater rises back to the seafloor forming hot springs. Some of the hot water forms and exits from sulfide chimneys, creating rising plumes. Other hot water mixes with cold seawater below the seafloor and exists through cracks in the seafloor and porous sulfide deposits forming lower temperature distributed deposits and supporting extensive communities of microbes and animals.

Measuring the heat flux transferred by such fluids is critical to both understanding how seafloor hydrothermal venting works and to quantifying the amount of magmatic heat transferred into the ocean over time. [2] The Cabled Observatory Vent Imaging Sonar, known as COVIS, detects and measures such fluxes and their spatial distribution using a multi-beam sonar from a stationary platform to measure backscatter and phase variations within a 3D volume. [3]

COVIS emits sound which is scattered by particles and rapid turbulent changes in temperature; COVIS records the amount and locations of back-scattered sound. Because COVIS is a multi-beam instrument, each ping of sound covers a fan-shaped area; mechanical rotation is used to control the orientation of the fan. This results in information on the amount and phase of backscattered sound from every point within a 50m x 50m x 50m volume, creating an image of plumes rising from hot springs within that region of seafloor. Detailed waveform information is combined with the observed plume geometry to infer vertical variations in rising speed and the overall heat transferred. COVIS also operates in an alternate mode which produces a map of hot spring incidence on the seafloor over a 50m x 50m area.

In 2010, a joint team of scientists and engineers from Rutgers, The State University of New Jersey, and the University of Washington worked with

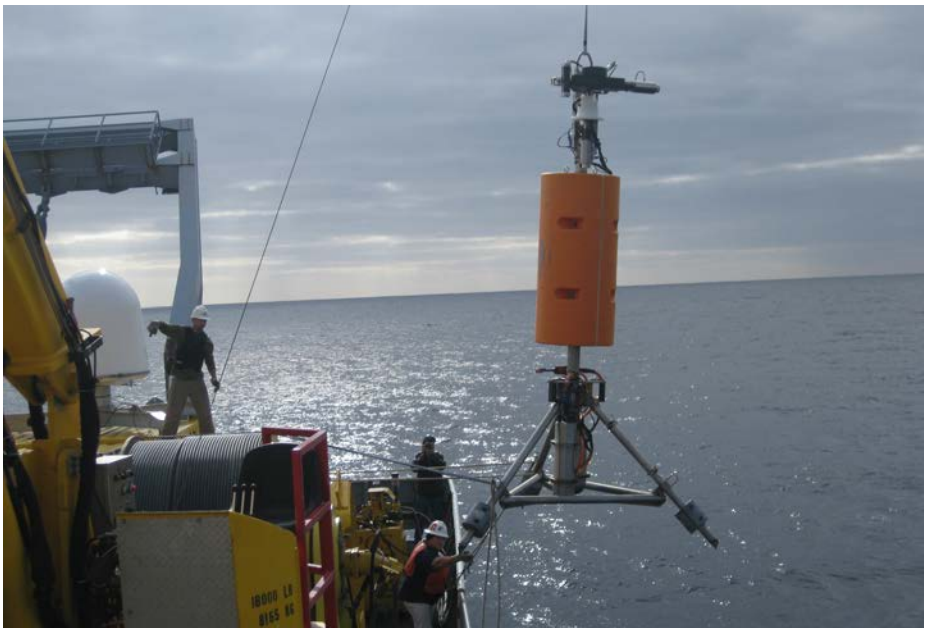

Figure 2. COVIS was lowered into the ocean in September 2010 over the Juan de Fuca Ridge from the R/V Thompson. Photo taken by Peter Rona who headed the project until his death in 2014

Ocean Networks Canada to attach COVIS to their underwater cabled observatory which extend to sites on the northern part of the Juan de Fuca Ridge, more than 100 km off the coast of British Columbia. [4] From 2010 to 2015, COVIS monitored the heat transferred by a small hydrothermal vent called Grotto Vent. During this period, the average heat transfer rate of 20 MW changed little reflecting the very low rates of even tiny earthquakes. [5] Researchers suspect that heat transfer rates would be higher during times of greater earthquake or volcanic activity.

After extensive refurbishing, COVIS is soon to be installed in a new location for monitoring heat from seafloor hot springs: COVIS will be connected to the US National Science Foundation's Cabled Array node in the ASHES vent field in the caldera of Axial Volcano, which erupted in 1998, 2011 and 2015. [6] The COVIS scientists and engineers are hoping to observe changes in heat and the distribution of hot springs during a volcanic eruption.

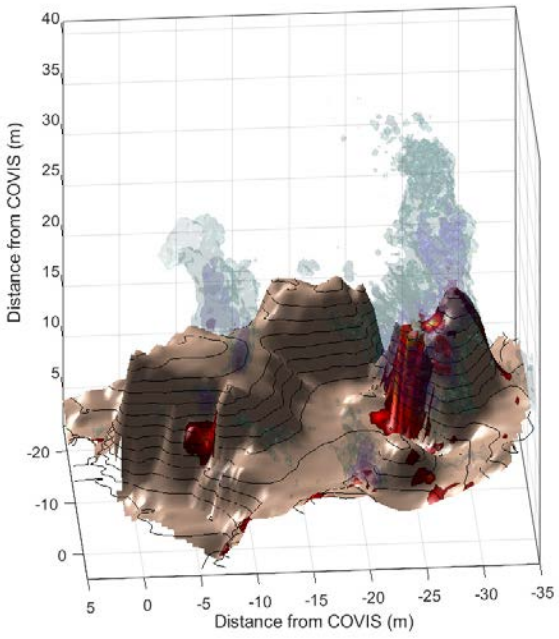

Figure 3. Example image from COVIS data at noon on Oct. 22, 2012. Blue-green colours highlight the plumes rising above the seafloor (light brown) while yellow-red-blacks highlight areas of intense diffuse output. Black lines are lines of constant seafloor depth. All distances (and heights) are relative to COVIS's location. COVIS data downloaded from Ocean Networks Canada; bathymetry from Dave Clague at MBARI

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Recognising the important role of biodiversity

Pamela S. Soltis, Director, University of Florida Biodiversity Institute, reveals the key work being done in the U.S. to respond to the 'biodiversity crisis'

Biodiversity refers to the extraordinary variety of life on Earth. While widely accepted that natural biological diversity is fundamental to a healthy, sustainable planet and that its loss has negative impact on human well-being (for example, see Science magazine, July 2014), the connections between biodiversity, ecosystem function and services that contribute to human well-being – from the flow of fresh water to pollination of crops – are less well understood. Ecological economists note the effect of invasive species (>$120 billion annually in the U.S. alone) and have begun to quantify the economic benefit of ecosystem services, but less is known about the impact of lost ecosystem services on other aspects of both environmental and human well-being.

Global responses to societal problems arising from both loss and alterations of biodiversity suffer from insufficient information and inadequate policies for sustainable use of natural resources, in part, due to the slow rate at which biodiversity data are gathered and the difficulty in accessing the information once it is available. Consequently, much of the diversity of our planet is likely to disappear before it can be discovered and understood. This "biodiversity crisis" – that is, the loss of biodiversity and its attendant consequences – creates both the necessity and the opportunity for a new type of response.

Why biodiversity matters

Recognising the important role of biodiversity in the biological and sociological health of the planet, the U.N. declared 2010 the "Year of Biodiversity" and 2011-2020 the "Decade on Biodiversity" to focus attention on the accelerating loss of biodiversity in the face of human population growth, landscape modification and climate change. In 2011, the U.S. President's Council of Advisors on Science and Technology called for improved accounting of ecosystem services and greater protection of environmental capital, citing the need for further biodiversity science and application of informatics to enhance our understanding of ecosystem services and develop an appropriate policy to protect them.

More recently, the International Platform on Biodiversity and Ecosystem Services (IPBES), with 118 member nations and modelled after the Intergovernmental Panel on Climate Change (IPCC), has begun assessing the scientific and social knowledge of Earth's biological diversity and how environmental change will impact ecosystems and human societies. Like IPCC, the IPBES does not conduct primary research but assesses knowledge and attempts to influence policies aimed at protecting ecosystems and pursuing sustainable economic growth.

The recent establishment in the U.S. of NEON (the National Ecological Observatory Network) is beginning to provide extensive environmental data

and baseline ecological monitoring at select sites across the country, with fully operating data streams from nearly all sites now in place. Current and future assessment targets include the impact of declines in pollinator populations on food production, invasive species and habitat degradation, all topics that will threaten food security during the coming century and are relevant to agencies such as the U.S. Department of Agriculture, which governs not only food production, but also forestry in the U.S. Despite an increased awareness, more integrated, accessible science and technology platforms are needed to leverage novel planetary data, models and tools to create and link knowledge to policy.

The University of Florida (UF) Biodiversity Institute

The University of Florida (UF) Biodiversity Institute was launched in 2016 to bring together scientists, social scientists and policy experts to address critical societal issues of the 21st century related to biodiversity: invasive species, emerging pathogens, climate change and food security, to name a few. This interdisciplinary 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, develop relevant conservation, educational and outreach programmes and shape policy to protect and enhance environmental capital.

The Mission of the UF Biodiversity Institute is to conduct high-quality research and develop programmes to advance three primary goals: (1) Initiate and lead large-scale, collaborative biological surveys to document and monitor biodiversity on a global scale; (2) Conduct collaborative and interdisciplinary research on biodiversity, with an emphasis on the use of big data; and (3) Translate biodiversity science to solve major societal problems.

> "The UF Biodiversity Institute has already established strong links to data science, informatics, computer science and engineering, as well as to specialists in environmental law, agricultural economics, climate science, land use and human population growth."

The UF Biodiversity Institute is exploring the world's past and present biological diversity at scales 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 has already established strong links to data science, informatics, computer science and engineering, as well as to specialists in environmental law, agricultural economics, climate science, land use and human population growth. The 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. iDigBio currently serves 110 million specimen records, representing approximately 300 million of the estimated 1-2 billion specimens in U.S. collections. This growing resource is driving innovations in management, analysis and interpretation of biodiversity data, both in the U.S. and globally, with a promise to address problems ranging from food security to invasive species to the response of species to climate change.

In a recent series of articles on the UF Biodiversity Institute, we have addressed the resources of iDigBio, the global need for innovative biodiversity training programmes for students and practitioners to take advantage of ongoing developments in data availability and use, as well as the economic value of ecosystem services.

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First EU TF Magnet undergoes cold testing

Fusion energy: Making history

Laban Coblentz, Head of Communication at ITER explains his thoughts on how history is being made when it comes to the exciting world of fusion energy

Last November, the ITER fusion project – 35 countries collaboratively building the most world's most complex machine – reached the 50% mark in "total construction work scope through First Plasma." Nearly 800 publications and media outlets in more than 40 countries hailed this milestone. Scientists, government ministers and industry CEOs congratulated each other on the joint progress to date.

Which feature captures the significance of this accomplishment? Is it ITER's ground-breaking science and engineering? The multinational project management required? The potential impact of fusion energy on society? Perhaps it is a combination of the three?

Part one: The science and engineering

The physics of magnetic confinement fusion is well understood. A few grammes of hydrogen in two forms – deuterium and tritium – are injected into a large, doughnut-shaped vacuum chamber. The hydrogen gas is superheated to form an ionized plasma, its atoms separated into positively charged nuclei and negatively charged electrons. At temperatures approaching 150 million °C, the charged particles are moving fast enough that when they collide, they overcome their natural repulsion and fuse. Adhering to $E=mc^2$, a miniscule portion of mass is converted to a massive release of energy.

ITER's engineering has also been largely validated in past tokamak reactors. Multiple sets of superconducting electromagnets – cylindrical, round, D-shaped and more – create an invisible magnetic cage that confines the charged particles of the plasma away from the

metal chamber walls. Only the neutrons, which have no charge, escape the plasma to convert their immense kinetic energy into heat. These behaviours have been demonstrated in smaller machines, as have most of the cryogenics, vacuum systems, robotics and power electronics in the ITER design.

What sets ITER apart is the combination of scale and precision required. Each of ITER's main magnets weighs several hundred tonnes; some have dimensions as large as 25 metres; yet the intense magnetic fields they generate must be cross-woven so intricately that charged hydrogen nuclei – sized at roughly 10^{-15} metres – cannot escape. Components so large they must be fabricated in shipyards will be positioned with the delicacy of a watchmaker.

> "The physics of magnetic confinement fusion is well understood. A few grammes of hydrogen in two forms – deuterium and tritium – are injected into a large, doughnut-shaped vacuum chamber. The hydrogen gas is superheated to form an ionized plasma, its atoms separated into positively charged nuclei and negatively charged electrons."

These extremes are driving a host of innovations and firsts, from fabrication techniques to new materials, instrumentation and tools. They are required by ITER's mission: to demonstrate the feasibility of fusion energy on a commercial scale, by creating for the first time on Earth the conditions necessary for a "burning plasma," in which the plasma heating is largely self-generated: in brief, to create a star on earth.

Part two: Multinational project management

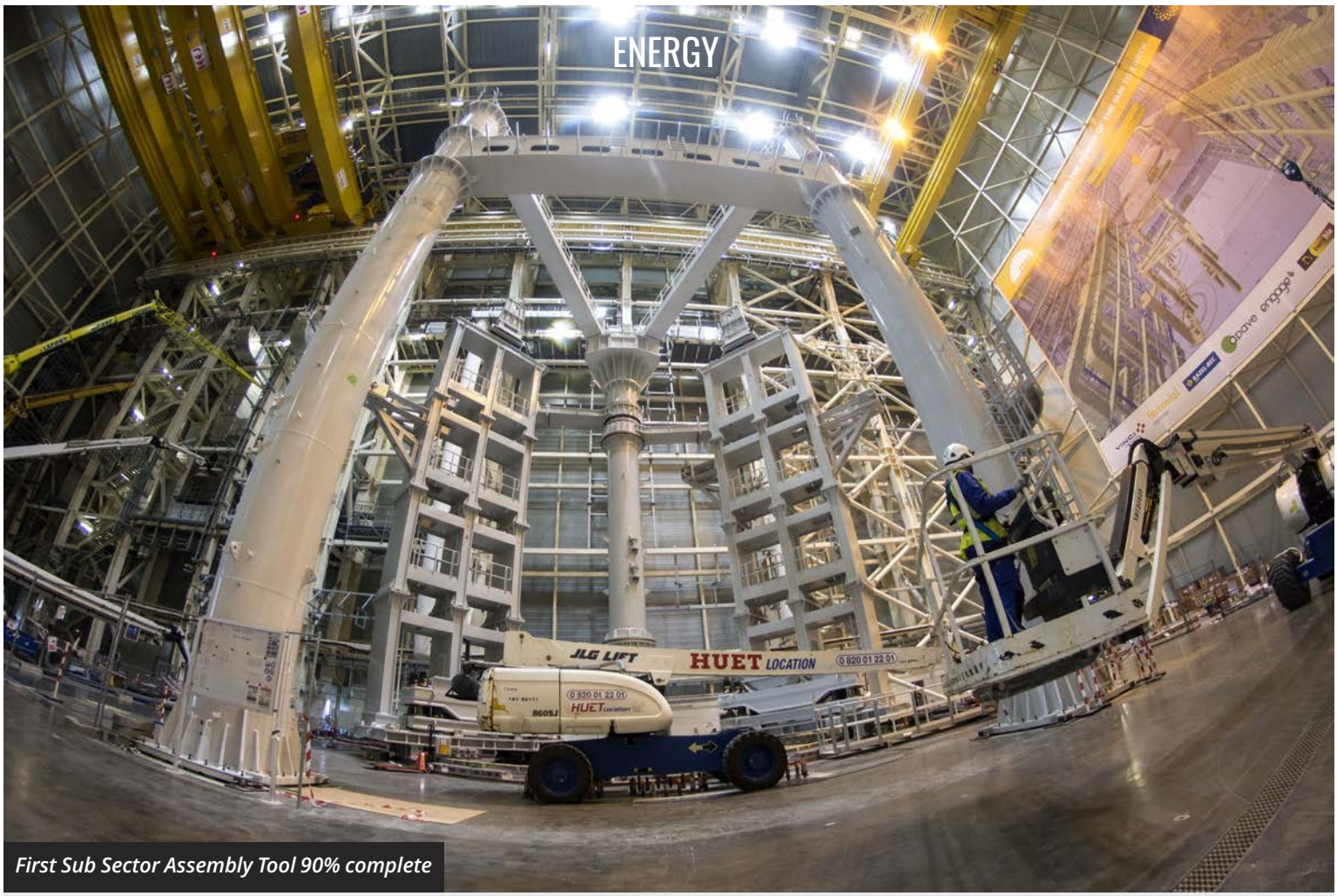
As if the complexity of a full-scale tokamak were not demanding enough, the ITER Agreement stipulates that each member will contribute most of its financial support "in-kind," in the form of hardware. In other words, the million-plus ITER components being manufactured across the globe, in Japanese factories, American laboratories, Indian foundries, Korean industrial plants, Chinese workshops, Russian shipyards, European innovation centres – must be fitted together into a single, functional device: a sort of reverse Tower of

Japanese TF Coil Case

Babel that begins with no one speaking the same language, connecting through the common vocabulary of mathematics, physics and three-dimensional CAD drawings.

Yet this is not lunacy. As the ITER Director-General, Bernard Bigot, said recently: "No country or organisation could do this alone. By choosing to build this machine in an integrated way, we have made our success interdependent. Our project is built on this condition: if our partnerships perform well, each partner contributes its expertise, we all learn from each other, the interfaces are well-managed, the project succeeds, and everyone wins." Multinational project management at ITER – systems engineering, risk management, configuration control – is a herculean effort; but in this crucible, new models for cross-border collaboration are being forged.

Consider one example: In December 2017, Japan celebrated the completion of ITER's first toroidal magnet case: at first glance, merely an oddly shaped, giant piece of steel. But the devil is in the details: the 16-meter case, fabricated in sections by Mitsubishi and Hyundai, successfully achieved tolerances of less than 1 millimetre. In January it was shipped to Italy, where a 310-tonne magnet, containing more than 5 kilometres of niobium-tin superconductor manufactured in China, Europe, Russia and the United States, will fit snugly into



First Sub Sector Assembly Tool 90% complete

the case. When finished, the component will be received at the ITER worksite in southern France, where an 800-tonne, Korean-made assembly tool – standing 10 stories tall, arms outstretched like a mechanical angel's wings – will cradle it gently, together with a European-made sector of vacuum vessel and a Korean-made ultra-thin silver-plated thermal shield; and will slowly, ponderously merge the pieces together to form a single, unified tokamak section.

To quote Bigot again: "The future of fusion – like the future of science – is partnership." Almost from its inception, magnetic confinement fusion has been uniquely collaborative. In 1968, when Russian scientists announced that their T-3 Tokamak had achieved plasma temperatures of 10 million degrees, their next action defied precedent: they invited a team from the United Kingdom, their Cold War enemies, to work with them at the Kurchatov Institute to verify and build together on this breakthrough. From that point forward, fusion has been a globally collaborative R&D effort.

This is the genius of ITER: the study of a controlled burning plasma is the convergent next step in the fusion roadmap of every country involved. Gargantuan, audacious, hellishly complex, yet elegant in the simplicity of its civilisation-changing goal: ITER seeks to enable the human animal to harness the power of the heavens. Safe, environmentally friendly and with abundant supplies of fuel available to every country, fusion energy aims to transform the socio-political landscape.

The stakes are high for humankind. ■

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Physics: Plasma-Jet-Driven Magneto-Inertial Fusion (PJMIF)

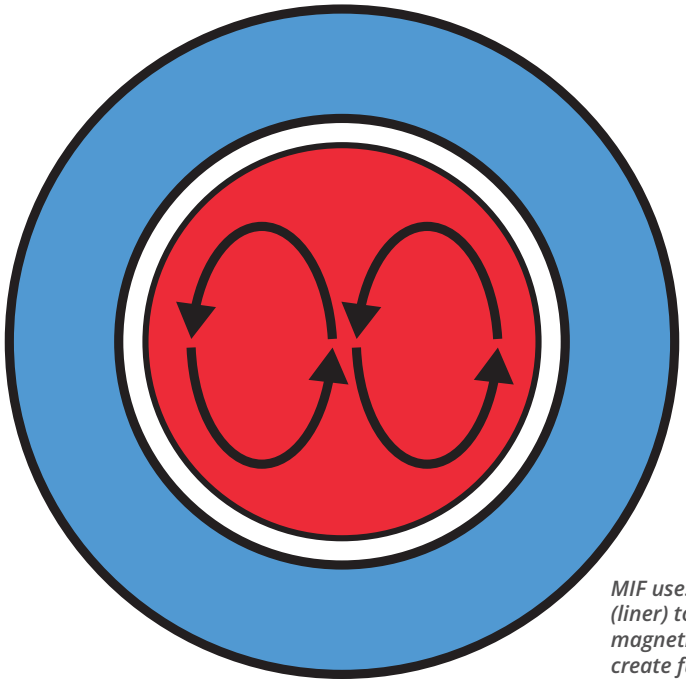
Professor Y. C. Francis Thio and Dr. F. Douglas Witherspoon of HyperJet Fusion Corporation, USA share their expert views on physics, with a focus on Plasma-Jet-Driven Magneto-Inertial Fusion (PJMIF)

In the previous article in this series[1], we reported on the plasma physics reasoning showing there is a sweet spot in the fusion parameter space with a density of the burning plasma intermediate between the two extremes typified by the two conventional approaches to fusion, namely magnetic confinement fusion (MCF) and inertial confinement fusion (ICF).

A new class of modern fusion approaches, magneto-inertial fusion (MIF), designed to exploit this intermediate density regime has emerged over the last two decades, thanks to the stewardship provided by NASA, DOE Fusion Energy Sciences (FES), DOE National Nuclear Security Administration (NNSA) and the Advanced Research Project Agency for Energy (ARPA-E).

The parameter space of MIF is very broad. MIF covers a density range for the burning plasma from 10^{24} deuterium-tritium ions per m^3 to 10^{29} per m^3. In terms of the implosion velocity, it ranges from 1 km/s to more than 100 km/s. The liner may be solid, liquid or gaseous. The many combinations of the key parameters for the target and the liners give rise to a rich and potentially large portfolio for MIF, presenting ample opportunities for innovations in the field.

At HyperJet Fusion Corporation, our goal is to develop economical fusion power, through a systematic exploitation of the broad principles of MIF, without regards to the particular choice of liners and targets. Our pursuit at present focuses on the use of hypersonic plasma jets as the main driver due to its several attractive attributes that may enable rapid progress in our quest. The fusion approach is called Plasma-Jet-Driven Magneto-Inertial-Fusion (PJMIF)[2,3]. Los Alamos National Laboratory is our partner in this development, together with several universities and institutions.



MIF uses a material shell (liner) to compress a magnetised plasma target to create fusion reactions.

In PJMIF, a magnetised target plasma is first formed at the centre of an otherwise vacuum spherical vessel. A spherical array of hypersonic plasma jets, up to perhaps 600 in total, with velocities up to about 100 km/s are launched from the periphery of the vessel, which has a radius of about 3 m. The plasma jets merge at a radius of about 1.5 m to form a plasma liner that continues to converge towards the centre and compresses the preformed magnetised target plasma down to a diameter of approximately 1 cm when fusion burn occurs in the target. The fusion burn lasts for about 0.3 μs resulting in a micro-explosion and a burst of energy. Because the efficiency of the plasma guns may be as high as 50% or more, the fusion gain needed for a practical fusion power plant may be as low as 20 or less. A thick liquid wall (FLiBe for example, approximately 1 m thick)

contained between two concentric spherical walls is used as a blanket to absorb the fusion neutrons, transforming their kinetic energy into heat and to breed tritium by an exothermic nuclear transmutation to feed the fusion reactor. The liquid wall also serves as a coolant in a heat exchanger to extract the heat from the fusion reactor to generate electricity. Each pulse of the fusion burn produces about 500 MJ of energy. If the pulse is repeated at 1 Hz, approximately 500 MW of average thermal power is produced. Because the cost of recycling the plasma guns and the first wall is relatively low, the PJMIF reactor vision allows for the guns and the first wall to be replaced and recycled after approximately every 20 million shots (~7 months)[4].

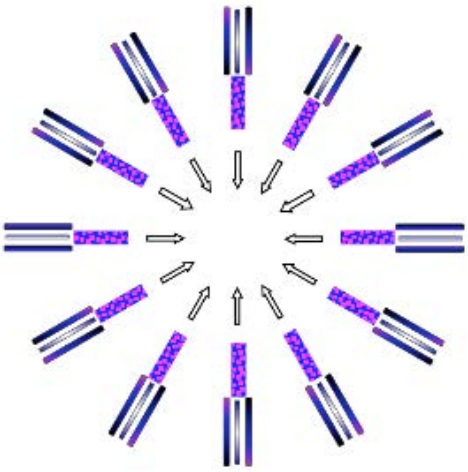
Why are plasma liners and PJMIF among other choices of liners (solid, liquid) and drivers (z-pinches, lases) for MIF?

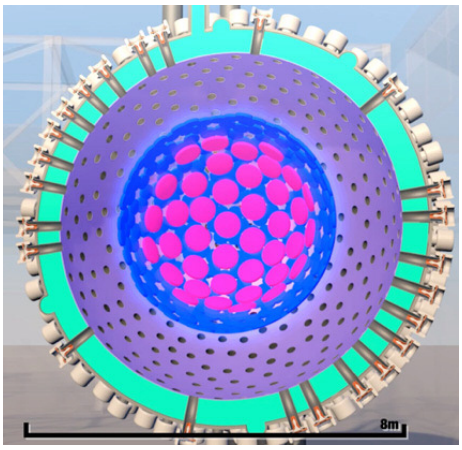
Solid-liner MIF typically employs a hollow cylindrical aluminium shell with a diameter of ~10 cm, thickness of ~1 mm and ~30 cm long. The advantages of the solid liner are that the technology of imploding a solid liner is relatively matured, the liner is extremely compact and has a high Mach number and the implosion can be made to follow a low adiabat, leading to high hydrodynamic efficiency. With a modest a radial convergence, the implosion is also hydrodynamically stable.

However, the solid liner is imploded at a relatively low velocity of about 5 km/s to 10 km/s. The implosion time is thus about 5 to 10 μs, with a plasma density of about $10^{24\text{-}26}$ per m^3. For the heating of the target plasma to be adiabatic, the timescale for the loss of heat from the target plasma (its thermal timescale) should be greater than 50 to 100 μs, which is a challengingly long thermal timescale for the density and size of the magnetised plasma targets currently known. Initial target plasma diameter much larger than 10 cm may be required to match the thermal timescale to the implosion velocity, increasing the overall cost of the reactor. Furthermore, the implosion produces debris, leading to low shot rate and high cost per shot during R&D.

Diagnostic access to the target plasma is also challenging, due to the opacity of the liner to most diagnostics. These factors tend to limit the rate of progress in R&D. Hardware destruction makes implementing solid-liner driven MIF as an economical, repetitively pulsed, commercial fusion reactor a real challenge.

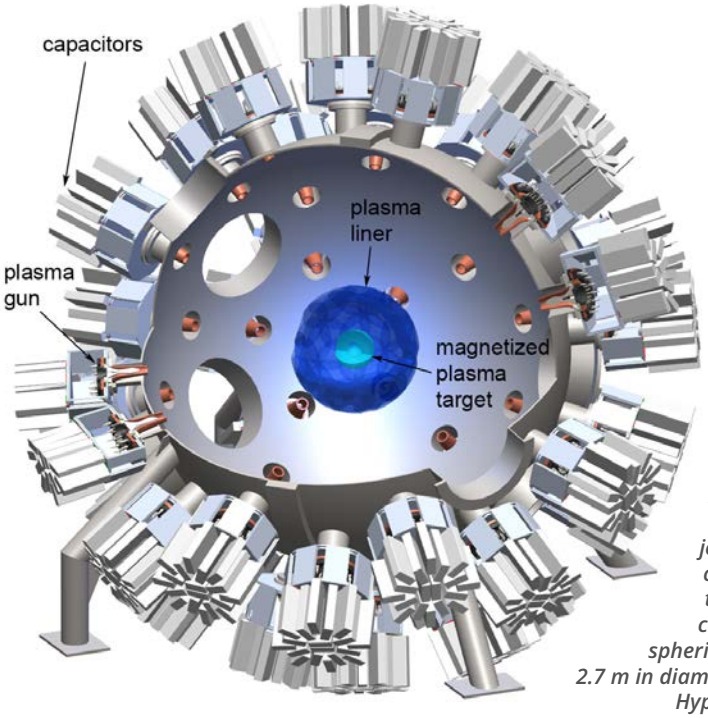
Liquid-liner driven MIF uses a liquid metal vortex to compress a magnetised target plasma. The liquid liner is imploded by pistons driven by very low-cost compressed gas in a favourably distributed configuration. The liner is non-destructive and is capable of high shot rate and doubles as a protective blanket against the fusion neutrons and a tritium breeding blanket, as well as a primary-loop coolant in a heat exchanger for the extraction of the fusion energy for electricity generation. Rotation of the liquid liner in a vortex further stabilises the implosion against hydrodynamic instability. The liquid liner is also massive and is capable of providing long plasma containment time during fusion burn. However, the implosion velocity is limited to about 2 km/s or less, even slower than in the case of the solid liner, thus requiring





an even larger initial magnetised plasma target, resulting in a larger cost for the reactor. The liquid liner directly faces the fusing plasma, creating the potential for severe disruption and a mix of the liquid vortex with the imploding plasma and as such, both may be highly detrimental to the fusion burn. Similar to the solid liner, diagnostic access to the target plasma during R&D is also challenging due to the opacity of the liner to most diagnostics. The lower density of the target plasma necessitated by its larger size may lead to plasma instabilities that cause a turbulent and anomalously high rate of thermal losses, further exacerbating the adverse consequences of the low implosion velocity.

The PLX facility at Los Alamos National Laboratory for investigating the basic physics of jet merging to form a plasma liner.



The immediate near-term objective of our research: to form a spherically imploding plasma liner (by merging 60 plasma jets) that will be used to compress a magnetized target plasma to fusion conditions. The cutaway spherical vacuum chamber is 2.7 m in diameter. Figure courtesy of HyperV Technologies Corp.

In PJMIF, implosion can be accomplished with suitably high velocity from 50 km/s to over 100 km/s with the implosion energy and momentum generated in a distributed manner. The high implosion velocity overcomes target heat loss with relatively small targets. It allows high-density targets thus avoiding plasma instabilities that may lead to anomalously high thermal losses. The plasma guns are relatively inexpensive. Like the liquid liner, it produces no hardware debris, thus enabling high repetition rate and low cost per shot for commercial fusion power plant, as well as high shot rate during R&D to provide high data rate for rapid resolution of scientific and technological issues. The spatial and temporal scales of the implosion and the open geometry allow convenient access for diagnostics. Because of these attributes, rapid progress at relatively low costs in R&D is possible. Its main disadvantage is that being the newest fusion approach, it is at a very early stage of development. Technically, the main challenges are the development of the appropriate plasma accelerators (guns) to deliver plasma jets with the required density, velocity, Mach number and precision in mass, velocity and launch synchronisation, to form a plasma liner with suitable uniformity to limit the amplitude of hydrodynamic instabilities and developing the magnetised target plasma with the required high density.

An attractive feature of the PJMIF concept is that its component technologies have near-term commercial spin-offs including the making of metallic powders for additive manufacturing, thermal spray and medical isotopes, as well as the processing of nuclear wastes.

In the next article, we will report on the state of the development of the PJMIF approach.

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The research priorities for the cereals and oilseeds sector

Tim Isaac, Head of Arable at the Agriculture and Horticulture Development Board shares his thoughts on research into the cereals & oilseeds sector

When it comes to the cereals and oilseeds sector, there are a variety of programmes and tools AHDB has put together to enable the delivery of key objectives.

AHDB has three core research areas in cereals and oilseeds comprising:

1. Understanding the genetic potential of new cereal and oilseeds varieties, the recommended lists;

2. Understanding soil health and plant nutrition and;

3. Crop protection, to evaluate new methods of monitoring, prevention and control of crop pests and diseases.

These three areas provide outcomes in their own right, but together they provide a valuable resource for integrated crop management based on robust independent information. AHDB, through its links to the research community, growers and end users, can provide an important linkage to ensure innovative research ideas can be tried and tested for the benefit of the whole industry.

Confidence in the independent evaluation of new varieties is a good example, leading to faster uptake of new varieties with good quality benefits to the end user and better agronomic and disease resistance to the farmer.

As part of AHDB's soils research, AHDB and the British Beet Research Organisation (BBRO) announced an ambitious new research partnership to develop practical soil biology management guidance, worth £1 million. The five-year partnership looks to improve on-farm understanding of soil health by benchmarking current academic and industry knowledge, developing and validating indicators of soil biology and soil health in research trials and integrating a far-reaching knowledge exchange programme throughout the five-year programme. The £1 million project is part of the AHDB GREATsoils programme, complementing a £1.5 million initiative looking at soil structure.

In addition to longer-term research, AHDB has to be able to respond and move quickly in an ever-changing environment. Issues can suddenly occur which require a rapid response to provide new information to inform the industry across the supply chain. This may include a new disease outbreak, loss of important products, or changes in quality requirements by end users, usually as a consequence of changes in legislation.

Understanding plant pests, weed and disease epidemics, including challenges associated with new threats, resistance and a reduction in agrochemicals to manage them is a situation which requires a systems approach. Research tends to focus on individual components, which is important to understand, but the practical cost-effective solutions require a whole farm approach based on crop rotations over several years.

AHDB, with its expertise both in applied research and an understanding of growers' businesses, is in a good position to help farmers deal with future challenges.

Its Farm Excellence Platform inspires the industry to improve performance and succeed through farmer-to-farmer knowledge exchange. For the arable sector, this includes Strategic Farms, Monitor Farms, Arable Business Groups and technical events across the UK.

Monitor Farms bring together groups of like-minded farmers who wish to improve their businesses by sharing performance information and best practice around

a nationwide network of host farms. AHDB organises and facilitates the meetings for farmers, who own and operate the scheme – by farmers, for farmers. Monitor Farms also incorporate the use of AHDB's benchmarking tool, Farmbench, throughout their three-year term to track and improve performance.

A key connection between research and knowledge exchange is where knowledge gaps are identified in on-farm activity and fed back to the research community for further analysis and guidance. For example, the significant rise in interest in no-till establishment systems led to a three-month review published in April 2018 – AHDB was also able to conclude that there is insufficient evidence to change autumn nitrogen guidance for no-tilled cereal and cover crops.

Other knowledge gaps can be addressed on a farm. Some Monitor Farmers are investigating how different spring barley varieties perform under different conditions. Different varieties from across northern Europe are being grown on farms across the UK alongside more conventional options. The aims are twofold – firstly to look at the resilience of different varieties in different conditions and secondly to challenge growers to get the most out of their crops.

These are just a few examples of the huge range of work that AHDB is doing to inspire British farmers to be more competitive and resilient in light of the changes that lay ahead. They clearly demonstrate that the key to achieving this is by accelerating innovation and productivity growth through coordinated R&D and knowledge exchange.

The Agriculture and Horticulture Development Board (AHDB) is a statutory levy board, funded by farmers, growers and others in the supply chain and managed as an independent organisation (independent of both commercial industry and of government). AHDB's purpose is to inspire our farmers, growers and the industry to succeed in a rapidly changing world. Our vision is for a world-class food and farming industry inspired by and competing with the best.

This is summarised in AHDB's four core priorities:

- Inspiring British farming and growing to be more competitive and resilient;
- Accelerating innovation and productivity growth through coordinated R&D and knowledge exchange;
- Helping the industry understand and deliver what consumers will trust and buy and;
- Delivering thought leadership and horizon scanning. ■

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Water, temperature and crop productivity research

Prof Robert Aiken, research crop scientist at Northwest Research—Extension Center tells us about his fascinating research into water and temperature, including the extent to which they limit crop productivity

Planting an agricultural crop requires a degree of optimism. In the semi-arid region of Kansas, which I study, water and temperature frequently limit crop productivity. These components of weather, along with sunshine and relative humidity, comprise the weather-related risks which limit the productivity of the crop just planted. As an agricultural scientist, I query the climate scientists: Are there periodic behaviours in weather patterns? Are there long-distance signals indicating wetting and drying trends? Is long-term weather forecasting feasible? If so, accurate forecasts can inform the optimism required to plant that crop, infusing an additional hope that the bet has been hedged.

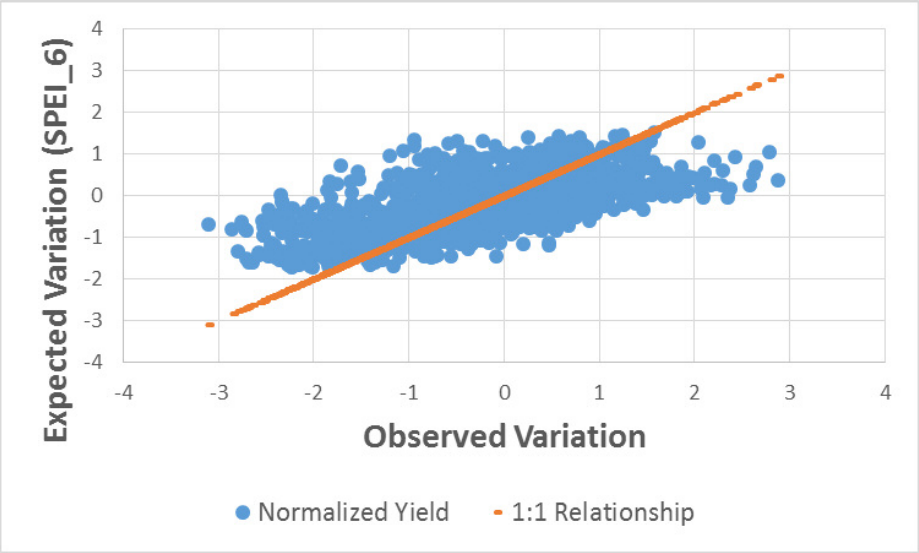

Figure 1: The in-sample predictive ability for wheat yield variation of multiple regression based on the NINO_3 surface temperatures of the Equatorial Pacific is compared against observed yield variation for wheat yield in Kansas counties W of the 99th Meridian. Observed variation represents variation after removal of a linear historic trend (1970 – 2007 period) as normalised by dividing by the standard deviation of the time series for each county.

> "There is an opportunity to develop climate-informed decision-support for cropping systems in the U.S. central High Plains."

Seeking information about weather forecasting skill, I learned about 'teleconnections' at recent American Meteorological Association meetings. The El Nino-Southern Oscillation (ENSO) phenomena serves as an example. Warming and cooling trends in the surface waters of the equatorial Pacific Ocean impact fisheries and rainfall in coastal Peru. Indeed, ENSO trends impact the productivity of winter wheat growing in the Texas High Plains. Louis Baumhardt, a USDA-ARS soil scientist and his colleagues found a degree of association between ENSO patterns and winter wheat yields in the Texas Panhandle[1]. Does this ENSO signal convey information about wheat productivity further north, in the central U.S. High Plains?

We know that winter wheat is vulnerable to drought conditions; wheat can also respond positively to wet conditions, though subject to disease impacts[2]. The Standardized Precipitation-Evapotranspiration Indicator (SPEI) provides a metric for wetting and drying conditions, generally varying between values of -4 and 4 to indicate drying (negative) and wetting (positive) conditions. We compared wheat yields, reported for counties[3] in Kansas (1970 through 2007) against monthly SPEI values, after removing linear historic trends attributed to improved genetics and production technologies.

A moderate relationship (R^2 = 0.41)[4] emerged for wheat yields reported for counties in W Kansas, indicating positive effects of weather conditions in February, March and April. A weaker relationship (R^2 = 0.25) resulted for counties in sub-humid E Kansas,

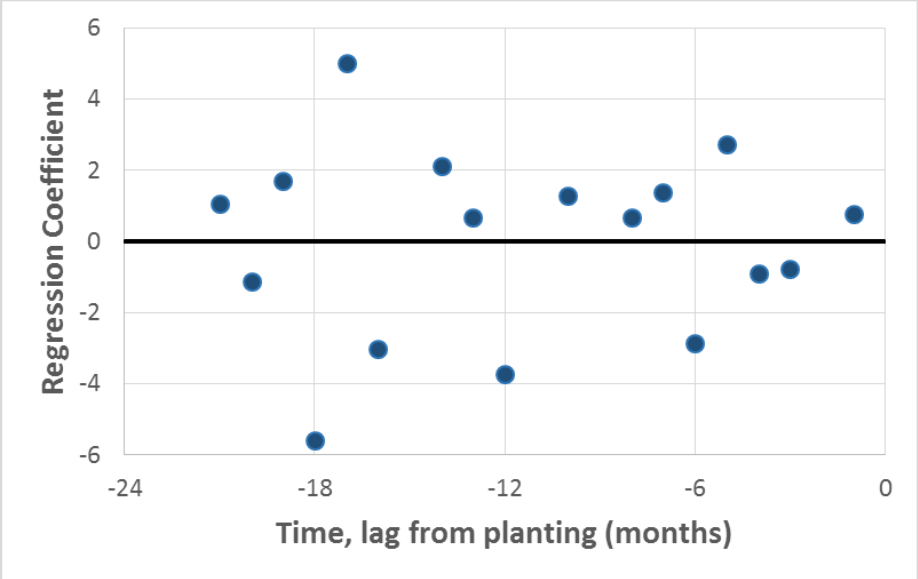

Figure 2: Regression coefficients of the NINO_3 multiple regression model is shown in relation to corresponding time lag (months prior to a September planting period for winter wheat in Kansas). Positive coefficient values for a given time lag indicate a positive association with expected wheat yields for that lag interval; negative coefficient values indicate a negative association.

indicating both positive (October, February, April) and negative (August, December, May, June) relationships with the SPEI metric. This regression analysis quantified the relationship of winter wheat productivity to weather variation during the growing season. However, the utility of forecasting skill depends on the information available prior to planting decisions.

> "Are there periodic behaviours in weather patterns? Are there long-distance signals indicating wetting and drying trends? Is long-term weather forecasting feasible? If so, accurate forecasts can inform the optimism required to plant that crop, infusing an additional hope that the bet has been hedged."

Thus, we evaluated a hypothesized ENSO signal: is winter wheat grain productivity in W Kansas related to equatorial Pacific Ocean surface temperatures in preceding years? We tested the null form of this hypothesis using multiple regression for W Kansas county yield reports and monthly ENSO data for the 24-month period prior to wheat planting (September, a year prior to harvest). We found a positive result. A moderately strong relationship (R^2 = 0.53) resulted from regression analysis (Figure 1). Interestingly, the strongest influences were ENSO values 18- and 16-months prior to the wheat planting period (Figure 2). This indicates that complex patterns in equatorial Pacific Ocean temperatures can convey information which is pertinent to subsequent winter wheat yields in W Kansas. There is an opportunity to develop climate-informed decision-support for cropping systems in the U.S. central High Plains.

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3 National Agricultural Statistics Service

4 'R' squared (R2) indicates the fraction of observed variation which can be accounted for by a regression relationship.

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Genomics of thermotolerance – helping beef cattle adapt to the climate change

Developing genomic tools for increased thermotolerance in beef cattle is imperative, says University of Florida's Associate Professor Raluca Mateescu

Climate change and beef cattle

Heat stress is the principal factor limiting production of animal protein and negatively affecting the health and welfare of cattle in subtropical and tropical regions. Detrimental effects on livestock productivity associated with heat stress are expected to intensify and expand into currently temperate zones upon the realisation of predicted climate change (Figure 1). The Intergovernmental Panel on Climate Change (IPCC), which includes more than 1,300 scientists from the United States and other countries, forecasts a temperature rise of 2.5 to 10 degrees Fahrenheit over the next century. Most animal-producing areas in the US are predicted to experience extreme summer conditions and by 2100, average temperatures in the US are projected to increase 2° to 6°C, depending on the emissions scenario and climate model applied. The number of days with maximum temperatures above 32°C (90°F) is expected to increase. The SE and SW areas of the US currently average 60 such days per year but is projected to experience at least 150 such days a year by the end of the century.

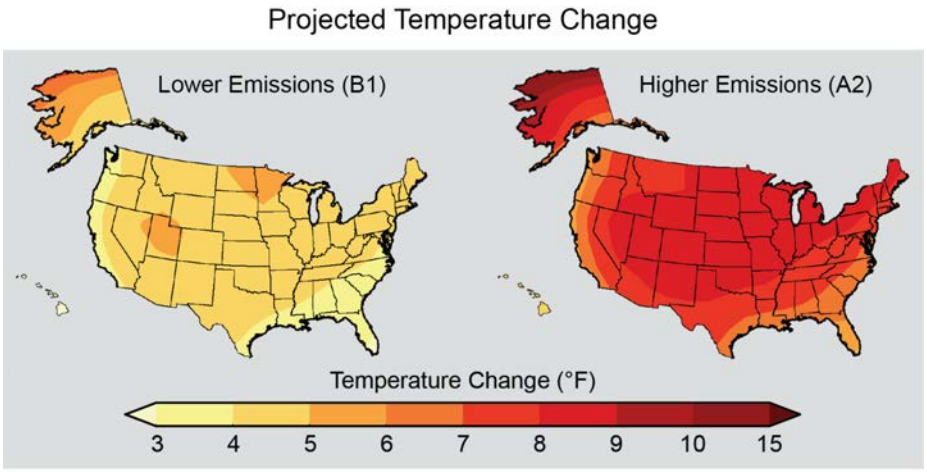

Figure 1: Projected Temperature Change. Warming is projected for all parts of the nation during this century. In the next few decades, this warming will be roughly 2°F to 4°F in most areas. By the end of the century, U.S. warming is projected to correspond closely to the level of global emissions: roughly 3°F to 5°F under lower emissions scenarios (B1) involving substantial reductions in emissions, and 5°F to 10°F for higher emissions scenarios (A2) that assume continued increases in emissions. (Figure source: NOAA NCDC / CICS-NC)

Importance of genomics for improved thermotolerance

Development of effective strategies to improve the ability to cope with heat stress is imperative to enhance the productivity of the US livestock industry and secure global food supplies. Although swine, poultry and dairy cattle are more severely affected by heat stress than beef cattle, their confinement and intensive production systems make climate control via housing design and management interventions feasible. Beef cattle, particularly those in the cow-calf segment, are typically reared in extensive systems with limited opportunities for controlling environmental stress (Figure 2). Genetic improvement is one of few feasible strategies for ensuring adequate and sustainable production of beef protein in an increasingly hot world. Substantial differences in thermal tolerance exist among breeds and among animals within breeds indicative of opportunities for selective improvement. For example, Bos indicus cattle exhibit increased resistance to many environmental stressors relative to Bos taurus, but tend to have slower growth, lower fertility and meat quality as they have not been as intensively selected for these traits as specialised Bos taurus breeds. Use of genomic tools to produce an animal with superior ability for both thermal adaptation and food production represents an energy-efficient sustainable approach to meet the challenge of global climate change.

What is thermoregulation?

Thermoregulation is a process in which environmental information provokes an appropriate response (e.g., vasoconstriction, panting), to maintain body temperature within the narrow range necessary for optimal cellular and molecular function. This is accomplished by jointly regulating heat production and heat loss. Beef cattle regulate internal heat production (by

Figure 2: Bos Indicus cattle are naturally adapted to survive in tropical and subtropical environments

modulating basal metabolic rate through thyroid hormone actions and changing feed intake, growth, lactation, and physical activity) and heat exchange with the environment (by increasing blood flow to the skin, and increasing evaporative heat loss through sweating, panting and behavioural wetting of the skin). Hyperthermia results when these adjustments are not able to mitigate the environmental heat stress and body temperature increases. Improvements in production, such as increased growth rate, lead to increased metabolic heat production and exacerbate the problem of thermoregulation. Thus, for example, there is a negative genetic correlation between milk yield and ability to regulate body temperature during heat stress in dairy cattle. Unless accompanied by changes that increase heat loss capacity, improvements in production make animals more susceptible to hyperthermia during heat stress.

Genomics for climate smart beef

The strategy we are undertaking is to reveal the genetic architecture of traits defining thermal tolerance using Bos indicus influenced cattle, in particular, Brangus (Brahman x Angus). In comparison to straight Bos taurus populations, we expect that the major genetic variants controlling thermal tolerance will be segregating in these indicine-influenced populations due to the length of time since divergence of the two subspecies, natural adaptation to different environments, and exposure to an artificial selection of different intensities and with different objectives. Our goal is to discover genetic variants responsible for thermal tolerance and use this knowledge to develop genomic tools to improve thermal tolerance in cattle populations at risk of exposure to heat stress.

Our research will use a system biology approach by integrating genomics and phenomics with additional -omics data to understand the genetic architecture of thermal tolerance. Frequent body temperature measurements, skin temperature, and perspiration rate in free ranging cattle will be recorded during heat stress on 2,000 Brangus heifers genotyped with the 250K functional SNP chip. Phenomics for thermal tolerance and genomic data will be integrated to identify chromosomal regions associated with regulation of body temperature. We will use this information to develop tools to be used in selection and management programs designed to mitigate the effect of heat stress in indicine-influenced beef cattle populations that predominate in hot and humid regions of the US and globally.

In depth knowledge of the genomic variants with major effect on thermal regulation and the maturation of technologies for gene, editing means that thermotolerance genes can be rapidly introduced into thermally-sensitive breeds such as Angus, Simmental, and Holstein to allow producers to exploit genetic lines of cattle selected for high productivity with minimal disruption by heat stress. Development of 'the cow of the future' with high productivity and resistant to heat stress will be realised through the use of genomic selection within indicine-influenced breeds and through the application of gene editing technologies that allow genetic variants conferring thermal tolerance to be rapidly incorporated into non-adapted breeds.

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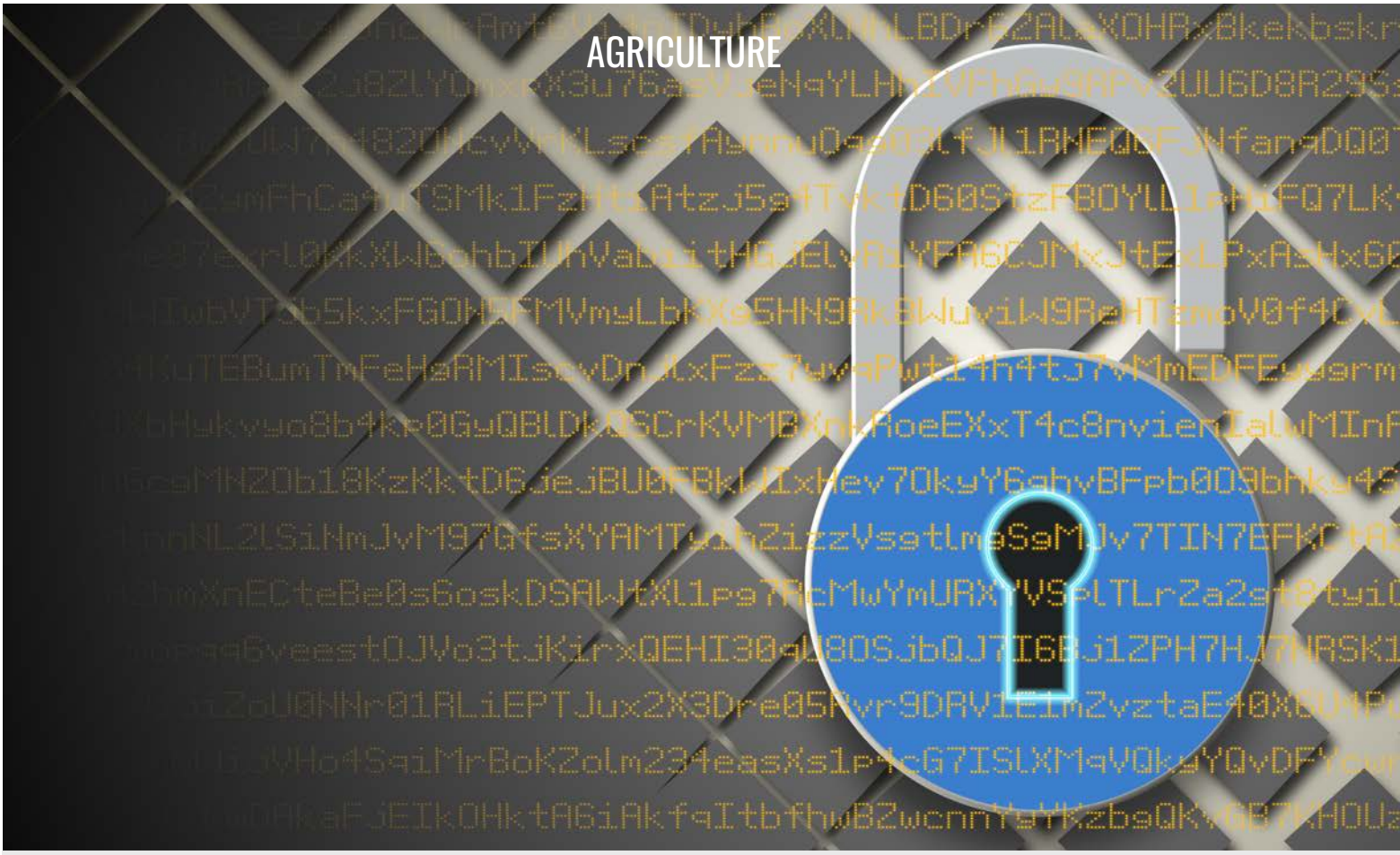


Advancing open access and open data in higher education

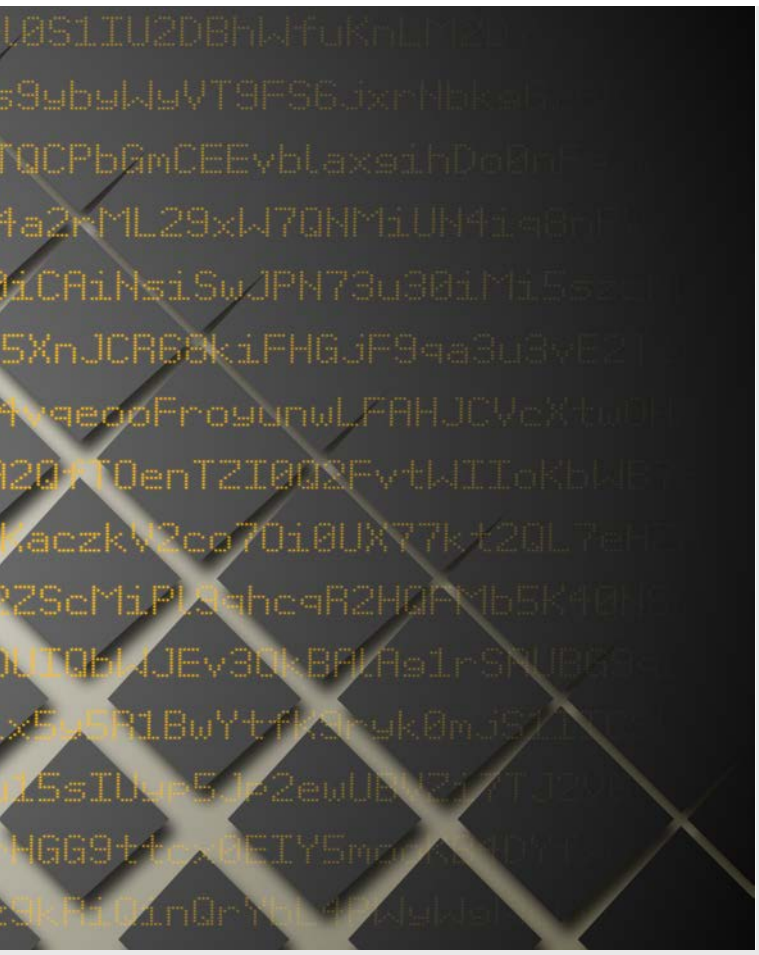
Jaime Adams and Anne Mims Adrian, PhD shares their views on advancing open access and open data in higher education

Every year, the U.S. Government provides billions of dollars to U.S. universities to conduct scientific research. In 2013, the U.S. Government began the process to increase public access to the results of research funded by the federal government, to ensure these results were made available to the American taxpayer. Opening research results may lead to many advancements, including accelerating scientific discovery, stimulating innovation, reducing duplication of effort and enhancing economic growth and job creation.

As the U.S. Government continues to fine-tune open access requirements, many universities are finding themselves at a crossroads. U.S. universities often receive funding from various sources including the U.S. Government. Many funders are instituting open data requirements, which often vary creating a very challenging situation. To explore the issue further, a consortium of universities from around the world known as Presidents United to Solve Hunger – or PUSH – conducted a study assessing open access and open data policies and practices.

> "Opportunities for new knowledge, more informed decisions, predictions and innovations are created when data collected throughout the research process are shared. Open data policies that balance the requirements from funders and researchers on standards and practices are needed for successful and effective data exchange and use."

Open data practices are currently driven by funders' requirements, yet very few universities have policies and procedures to address these requirements. Scientific



disciplines like biomedicine, veterinary medicine and pharmacy have established standards and repositories open to the research community but lack the infrastructure to freely share research data with the public.

In a recent PUSH study, no PUSH member universities have open data policies and only 15% have open access policies. Many participants believe that clarity must be given to data ownership before developing open data policies. This report, released in June 2018, also provided several recommendations to advance open data implementation to include greater alignment between funders' expectations and universities' capabilities, by including costs of sharing and maintaining data sets in project budgets and delineating standards and protocols.

In a separate Global Open Data for Agriculture and Nutrition (GODAN) study, researchers found that funders recognise that cost and lack of infrastructure and standards are preventing data to be shared in ways that are free, accessible, interoperable and re-useable.

In both studies, it is evident that there is a growing need for standards, common language (ontologies) and protocols to make data discoverable and useable. In November 2017, the Association of American Universities (AAU) and Association of Public and Land-grant

Universities (APLU) released the Public Access Working Group Report committing to a set of shared principles and minimal levels of standardisation across institutions and agencies to ensure access to publicly funded research.

> "Open data practices are currently driven by funders' requirements, yet very few universities have policies and procedures to address these requirements. Scientific disciplines like biomedicine, veterinary medicine and pharmacy have established standards and repositories open to the research community but lack the infrastructure to freely share research data with the public."

Opportunities for new knowledge, more informed decisions, predictions and innovations are created when data collected throughout the research process are shared. Open data policies that balance the requirements from funders and researchers on standards and practices are needed for successful and effective data exchange and use. ■

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Woody breast: A hard problem for the poultry industry

Dr Macdonald Wick, Associate Professor at The Ohio State University's Department of Animal Sciences explains why Woody Breast is a hard problem for the poultry industry

Several decades of selective breeding have changed the genetics of chickens, with breeders selecting for faster growth, ever-increasing body weights, but more specifically, increased breast muscle *(P. major)* meat to carcass ratios (breast muscle yield). This has resulted in the generation of 'broiler' chickens – genetically designed for meat production. Optimisation in genetics and nutrition have contributed to affordable and plentiful poultry. In 2016, over 15 million metric tonnes of broiler meat were consumed in the US and nearly 90 million tonnes worldwide. However, this success has not been without costs – both for the birds themselves and consumers.

In addition to systemic challenges, these genetic and rearing strategies, have contributed to correlated increases in developmental breast muscle abnormalities (myopathies). These myopathies result in decreased consumer acceptability. The two most important myopathies currently challenging the poultry industry are white striping and wooden breast. Studies have reported a strong correlation between white striping and wooden breast. It has been argued that accelerated growth, breast muscle yield, with the accompanying impaired vascularity are predisposing factors to all three anomalies. Macro- and microscopic characterisations of white striping and wooden breast have striking similarities, including mild to severe edema hemorrhagic/inflammatory lesions and loss of vasculature (pale/yellow colour). Microscopic similarities include polyphasic degeneration, perivascular necrosis and infiltration of connective and fat tissue.

Muscle development – or 'myogenesis' – is a complex yet tightly regulated temporal and spatially specific process in poultry that begins with the embryo while still in the egg. Precursors to muscle cells, known as myoblasts, migrate and fuse together to form fibres known as myotubes, which subsequently differentiate into mature muscle fibres. The molecular/cellular mechanisms induced by the genetic selection for the increased growth ratio of a single muscle, the P. major, remains unresolved but it is likely that it lies at the root of the myopathies.

Wooden breast was first described in live broilers as extremely stiff breast muscles that could be detected by palpation. The phenotypic hardness of wooden breast is associated with varying degrees of firmness, pale colour, surface haemorrhaging and white striping. The hemorrhagic lesions and diffuse, hardened areas, when examined histologically, exhibit polyphasic degeneration, perivascular necrosis, interstitial inflammation, perivenular infiltration of T lymphocytes with the infiltration of connective tissue and fat. Hypoxic conditions limit the regenerative capacity of muscle fibres by favouring the replacement of degenerated muscle fibres with lipid and fibrotic tissue. Various potential contributing factors to wooden breast have been identified, such as localised muscular

hypoxia, oxidative stress within the affected muscle and increased levels of intracellular calcium.

Not surprisingly, these anomalies can have a significant impact on consumer acceptability, most notably through visual, white striping and textural, wooden breast, changes. With white striping, the surface of the breast muscle exhibits white strips of fat tissue. In the case of wooden breast, there is an increase in compression force and shear force using Allo-Kramer, Warner-Bratzler shear force analyses. As such, these affected breast muscles are often downgraded or even condemned. The potential economic loss due to downgrading was previously offset by the continued gains in growth and breast muscle yields and management practices which minimised the predisposition for the myopathies. Unfortunately, since the initial description of these anomalies, the industry has experienced a rapid increase in the percentage of affected broilers within a given flock, as high as 90%.

There is ample data to support an association between white striping and wooden breast, with nearly all reported cases of a wooden breast having some degree of white striping. In addition, the onset and severity of each anomaly is influenced by: Genotype (high > standard breast yield), gender (males > females), growth rate (fast > slow), diet (high > low energy), P. major breast muscle weight (heavy > light) and slaughter weight (heavy > light). Again, the cause and effect relationships underlying this association have not been reported.

Many studies are underway, using combinations of transcriptomic, proteomic and statistical modelling to elucidate the molecular mechanisms underlying poultry muscle growth and development to elucidate the molecular/cellular mechanisms of white striping and wooden breast. These studies are focused on various influences – both genetic and environmental – that affect poultry muscle development, as well as the post-slaughter conditions that directly affect meat quality with particular emphasis on meat processing characteristics.

> "In 2016, over 15 million metric tonnes of broiler meat were consumed in the US and nearly 90 million tonnes worldwide. However, this success has not been without costs – both for the birds themselves and consumers."

New information is emerging, using combined morphological and quantitative transcriptomic strategies in which the P. major of broiler chickens were evaluated for the changes in muscle-specific transcription factors and the morphology of the breast muscle every other day post hatch until market weight to elucidate the myogenic signals and proteins associated with the progression of white stripping and woody breast. The data supports the notion that white striping is a harbinger of wooden breast and that nutrition can play a role in reducing the onset of wooden breast. That is, reducing growth rates can delay the onset of myopathies.

In conclusion, the demand for inexpensive, affordable poultry meat has pushed chickens and turkeys to their physiological limits – impacting the welfare and muscular health of the birds, as well as the quality of their meat. Studies are underway in an attempt to unravel the biological mechanisms behind muscle problems in poultry. These studies will eventually lead to the establishment of biomarkers for future breeding strategies that balance welfare with the economic value of meat products.

For example, recent reports describe the macroscopic changes associated with WB ontogeny in the development of a ranking system and the contribution of growth parameters in the determination of rank wooden breast severity. Results suggest that physical measurements inherent to selection for high-yielding broiler genotypes are contributing to the occurrence and severity of both white striping and wooden breast. These studies are leading to a ranking system to describe the ontogeny of wooden breast and a model relating the rank probabilities to the severity of the myopathy, based on physical measurements during the post-hatch growth period with the potential development of an economic model to simultaneously optimise bird's welfare and the economic return of poultry operations.

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What next for children and young people with speech, language and communication needs?

Mary Hartshorne, I CAN's Head of Evidence shares her thoughts on the report Bercow: Ten Years On and the next steps for children and young people with speech, language and communication needs

Many reports are criticised as spending too much time admiring a problem and not enough time doing something about it. In March 2018, I CAN, the children's communication charity and the Royal College of Speech and Language Therapists (RCSLT) launched the Bercow: Ten Years On report, an independent review of provision for children and young people with speech, language and communication needs (SLCN) in England. The report found a fractured system failing thousands of children and young people by not identifying their needs early enough or providing adequate levels of support.

It's not a new problem. So, if we've all been guilty of 'admiring the problem' before, now is really the time for action.

Action is needed because the findings of this report matter. They matter for the two or three children in every classroom who have developmental language disorder (DLD): a condition where children have problems understanding and/or using spoken language, but where there is no obvious reason for these difficulties – no hearing problem or physical disability that explains them. Around half of these children go unnoticed in primary schools and because good language skills underpin the ability to learn to read, to learn and to develop socially and emotionally, this can have a drastic impact. We have the evidence for this: just 15% of pupils DLD achieved the expected standard in reading, writing and mathematics at the end of primary school compared with 61% of all pupils, likewise only 20% of pupils with DLD gained grade 4/C or above in English and maths at GCSE, compared with 63.9% of all pupils. There is also a much higher risk of mental health issues in children and young people with DLD, increased risk of behaviour difficulties and language difficulties are highly prevalent in the youth offending population. But this does not have to be the case, with the right support; children with DLD can do well academically, socially and emotionally.

Mary Hartshorne, Head of Evidence

In taking action, thousands of children and young people with DLD will get this support. To, ensure that the report will not just stay on the shelf, quickly becoming out-of-date as governments come and go; there is both a 'top-down' and 'bottom-up' approach to change.

From the top, strategic recommendations demand change from national and local leadership. The report asks for systemic change, which considers the impor-

How people can act locally, to support the strategic recommendations	
Top-down	**Bottom-up**
Strategic recommendations	www.bercow10yearson.com/supportingchange
Ofsted should ensure that training for inspectors should ensure a focus on SLCN, including specific advice on how schools assess and monitor progress in the spoken language.	Use our information sheet and PowerPoint presentation for primary or secondary schools to share information about progress in spoken language and the impact of SLCN support with Ofsted inspectors.
NHS England and the Department for Education should fund a programme of training for local commissioners on commissioning for SLCN.	Use our prevalence information to share information with people responsible for commissioning SLCN support. Talk about local prevalence or about the numbers of children with SLCN in your school or college.
Local area SEND reviews should consider the evidence from this review for effective joint commissioning of support for SLCN.	Look out for your LA SEND inspection here and take up the invitation to meet with inspectors when they inspect your local SEND services. Use our information sheet for advice about questions you can ask and ideas for useful information to share.

tance of speech, language and communication in children and young people's development and asks for SLCN to be embedded within government policies. So, for example, where the government is taking steps to change mental health provision, this should recognise the link with SLCN; current plans for reforming early career support for newly qualified teachers should include training in SLCN; commissioners of SLCN services need to understand about effective ways of supporting children and young people with SLCN.

The bottom-up approach draws from the evidence presented to the review. As well as challenges and issues, the review also found many examples of innovative, effective practice. Based on these, a series of calls to action encourages everyone to take bold first steps to make change happen: school staff, early years practitioners, speech and language therapists, parents and young people themselves. Accompanying the report is a website www.bercow10yearson.com/supporting-change, which is full of practical resources: information sheets, top tips, email templates, presentations and guidance to support people in doing this.

As far as possible, the calls to action support recommendations both top-down and bottom-up – here are just a few examples of how this works:

I CAN and RCSLT have committed to reporting on progress one year on; in the meantime, there are things that you can do. You can sign a petition asking for the government to respond to the review at https://petition.parliament.uk/petitions/215643.

Visit www.bercow10yearson.com/supportingchange and find out how you can act and watch out for the progress report in 2019. ■

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Language development: Learning from what children say

Mabel L. Rice, Distinguished Professor of Advanced Studies at the University of Kansas argues that children's utterances provide valuable clues about how their language develops and hallmark areas of grammar weaknesses in those with Specific Language Impairment (SLI)

When we want to learn a certain language, we have many kinds of reference materials to consult, benchmarked to the adult language system. In contrast, children's grammar has not yet been fully documented. An important source of information in this area of study is what children say. Early studies were done by parent scientists, keeping diaries of what their child said. In 1973, Roger Brown realised the value of new technologies for recording speech with portable devices for the purpose of studying children's early language in detail; he reported the outcomes in a benchmark book[1] and established new scientific methods for recording child utterances.

Language appears late in children with Specific Language Impairment (SLI), although other developmental benchmarks follow age expectations. The causes of delayed language acquisition are unknown. The details in what children say provide valuable clues about weaknesses in their linguistic system. Informative dimensions are what they talk about (i.e., content) and the sentence structures they use (i.e., linguistic form).

For example, during the preschool years, children learn the names of colours. This can take longer than expected for children with SLI. Consider a six-year-old boy, Stevie, whose language is immature for his age. He does not know the names of colours, which is a limitation in a classroom with colour-coded spaces and signs. For example, an adult tries to teach him the names of the colours "red," "blue," "green" and "yellow," using simple blocks and toy objects and repeatedly asking "what colour is this?" This approach is pursued for several months, with no apparent success. One day, Stevie asks the adult, with genuine bewilderment, "Why you call that red?"

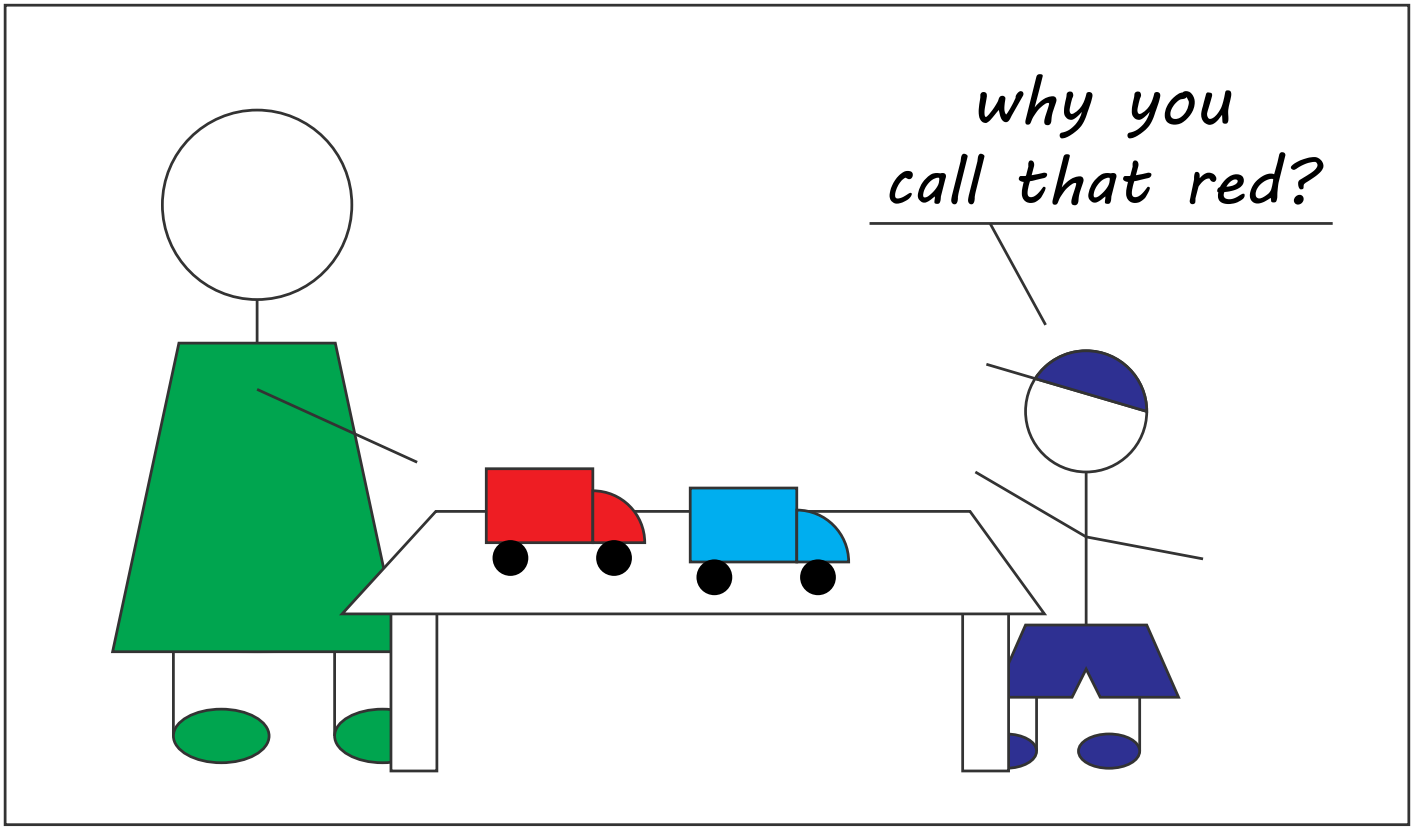
What clues are provided by his question? On the content level, Stevie is perplexed about using a word to refer to the hue of an object, or that this is a meaningful way to differentiate objects (although he certainly knows about broken objects, dirty objects and his versus my objects). Stevie subsequently works this out on his own, without continued prompting and with pride in his accomplishment.

However, his more significant problem with language is less apparent and is at the level of sentence structure. His sentence: "Why ___ you call that red?", is missing the required auxiliary *DO* (the italicised capitalisation conveys the citation form that would include the words "do", "does," and "did"). This is often thought of as a "little word" that can be omitted without hampering communication.

Although most speakers of English use the rules that apply to the use of auxiliary DO, they rarely know the structure of the underlying rules and are highly unlikely to explain the rules to their children, in contrast to the ways parents often focus on the names of colours. Instead, parents may sense that a six-year-old's grammar is "immature" if such forms are omitted, although they are unaware of exactly what is missing.

"Language appears late in children with Specific Language Impairment (SLI), although other developmental benchmarks follow age expectations. The causes of delayed language acquisition are unknown."

Advances in linguistic theory in the early 1990s identified systematic ways in which young children learn the property of grammar known as "finiteness marking"[2]. In English, a set of forms mark finiteness: Auxiliary DO in questions (but main verb DO is different grammatically), copula and auxiliary BE, past tense -ed, or a default to the citation form of the verb for irregular past tense ("run" instead of "ran") and third person singular -s, as in "walks"[3]. In the case of children with SLI, a stage of omission of these forms is likely to



persist into adolescence, long after unaffected children have mastered it[4]. This part of the grammar has served as a reliable clinical marker of children with SLI[5] with high heritability[6,7].

Stevie's question reveals the need for understanding two distinct dimensions required for language acquisition: 1. Children's conceptual development as a basis for language concepts expressed in words and 2. The ways in which grammar works with linguistic constructs such as tense marking, subject/verb agreement and word order requirements, such as the insertion of auxiliary DO in Wh- questions.

Although the meaning part may be more intuitively obvious and more likely to be overtly taught, for most children no explicit teaching is needed for learning grammar. Yet, for children with SLI, the requirement to mark finiteness is not readily learned and instead continues to be treated as optional, even though it is a required element of a well-formed sentence. Perhaps Stevie's question reminds us that the most obvious "error" is not necessarily the only error or the most important one to note. Our sense of what to notice is affected by our knowledge of where to look, even for something as commonplace as children's language.

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The current status of blockchain technologies

Marta Pierkarska, Director of Developer Ecosystem at Hyperledger reveals her thoughts on the current status of blockchain technologies

We are midway through 2018 and it seems everyone has bought into blockchain. But have they really?

When we go to staple industry conferences, it definitely feels like there is not a single person in the world that has not heard about blockchain. At Hyperledger, we are proud and grateful to get public and social media attention. We have almost 45,000 Twitter followers and a webinar series where our community can learn, on a monthly basis, about blockchain and our frameworks.

> "Governments, while struggling to regulate cryptocurrencies and ICOs, are absolutely bought into the blockchain space. Today, there are 203 different initiatives around the world implementing solutions in different governments."

Thankfully, though, we also get invited to speak at conferences that are not industry specific. That's where we learn that not everyone is crazy about blockchain. Many have often never even heard about it! From big to small, there is a whole world outside of our echo chamber. They ask: "what is blockchain?" and "how is it different from a database?", "can I have a blockchain where I don't share any information with anyone?" and, of course, "what is the killer app for blockchain?"

It is good to step out of the comfort zone. It challenges us to look from the outside and ask: "what is the adoption of blockchain in enterprises today?"

Hyperledger has now reached almost 250 members, showing how much interest there is in enterprise blockchain applications. If you belong to the Innovators on the Rogers' Diffusion Curve, then 2018 is a year of deployment. We see enterprises going live with their platforms in the supply chain, financial technologies, healthcare and the government. In fact, the need for a collaboration platform was so high that we have launched Public Sector and Healthcare Working Groups.

The working groups reflect a significant shift in thinking from those getting deeper into the deployment process. While developing Proofs of Concept, enterprises believed that one can simply do it alone. That there can be one blockchain per company and the technologist can develop ways for the ledgers to talk to each other. However, blockchain is a Peer-to-Peer network. To scale and make use of its full benefits peers, or nodes should come from different parties. This means evolving from "blockchain is a decentralised database system" to "blockchain is a distributed record of data" mindset. The shift has led to the creation of a number of consortia in various domains since the beginning of 2018. Some examples: we.trade, developed by nine different banks; TReDS, a similar platform in India; the Intelligent Healthcare Network for claims management in healthcare and Realtor® Association Blockchain, which created regional repositories of activity of their 1,200 members. This aim for collaboration and modularity shows a new level of maturity in the space.

Not everyone is crazy about blockchain though. Many are still looking to understand the return on investment in the blockchain space. Or are still looking at how to choose the right technologies – ones that will scale with time – and for the right use cases. Is it better to use a sniper approach and target a small number of big projects or a machine gun one: blockchain everything and see what sticks? Which of the solutions implemented today will stand the test of users and time? Frustration when experimenting with blockchain is unavoidable. Departments spent money on horizon 2 projects, but only a few of them can move to horizon 1. Even then it requires more financial engagement.

Blockchain will not solve all our problems and will not be valuable in all industries. All sectors are facing challenges around security, as well as the usability of the newly developed DLT-based projects. While blockchain is being used for security updates in The Internet of Things (IoT) or a better voting mechanism, it also brings new attack vectors. Questions arise about how we evaluate smart contracts, how we ensure the consensus cannot be broken, what information should be stored on a blockchain and how. On the usability front, there is a need for better user interfaces and the integration tools to encourage a wider adoption.

The maturing market is starting to ask the right questions and new industries are adopting the technology. Governments, while struggling to regulate cryptocurrencies and ICOs, are absolutely bought into the blockchain space. Today, there are 203 different initiatives around the world implementing solutions in different governments. In art and music for IP protection and proof of provenance, in shipping and logistics for a bill of lading or in education for certification storage, there is growing interest and increasing adoption. Still, there remains a huge demand for education. Not only on what blockchain is, but also how to share data through a blockchain, while preserving the most important IP in enterprises and PI in the case of individuals. As with any new technology, the demand is there but supply remains scarce. But we are getting there. ■

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Educational philosophy and theory: Priorities and new directions for research

The editorial team of Philosophical Inquiry in Education, Bruce Maxwell, Lauren Bialystok, Kevin McDonough and David Waddington, outline their views on promising new directions for research in educational philosophy and theory

Like philosophy itself, the field of educational philosophy is notoriously difficult to define even, if not especially, for the very people working in it. Other areas of educational research are more straightforwardly delineated in terms of a characteristic object of inquiry. Researchers in mathematics education, for example, investigate matters relating to how that subject is taught and learned in schools and researchers in teacher education study the acquisition of professional competencies among new and experienced teachers.

What unifies scholarship in educational philosophy and theory is something more abstract: a commitment to a particular mode of inquiry. Philosophers of education tend to explore fundamental questions that touch on meaning, value and purpose in education and pursue the answers to such questions using the tools of critical inquiry and argumentation.

During the early years of its history as a distinct area of scholarship, expounding and developing what great thinkers of the past had to say about education was the bread and butter of educational philosophy. This orientation was largely driven by the demands of teacher education programmes, which generally considered that exposure to the "classics" was an essential part of the professional socialisation of future teachers. As teacher education has evolved in recent decades, the philosophy of education has changed with it. "Modern" educational philosophy has coalesced into four discernible thematic areas which, taken together, embrace the research activities of the vast majority of scholars who identify as philosophers of education.

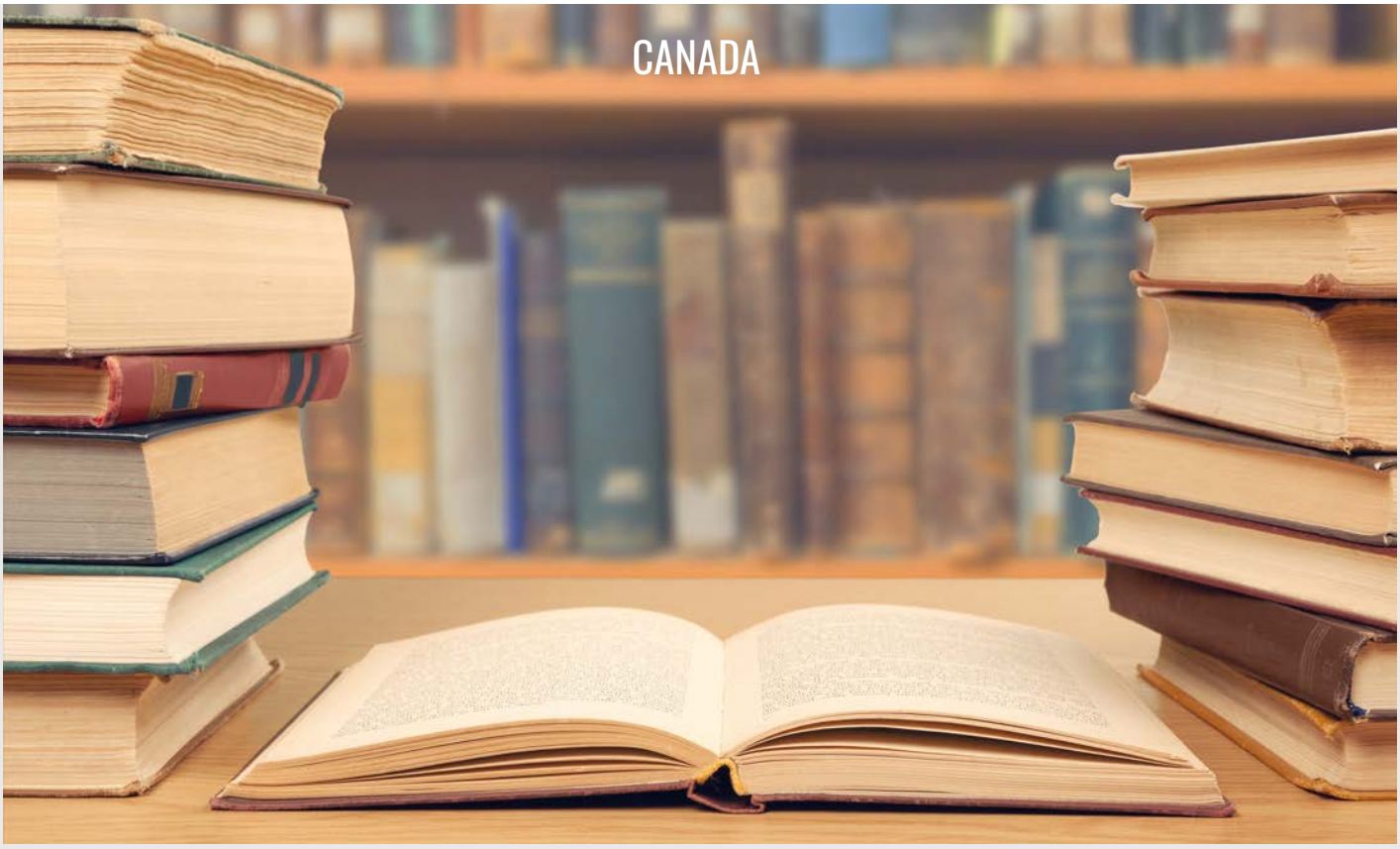
Roughly in the order that they emerged historically from the 1960s on, these areas are:

Analysis of the language of education. What began as a project to clarify fundamental questions about education (e.g., what is an educated person?) by clarifying the meaning of words, the quest for coherence in the language of education is now more likely to consist in subjecting to critical scrutiny terms that have gained currency in educational discourse (e.g., constructivism, brain-based education).

Critical pedagogy. Drawing on intellectual currents in the social sciences and humanities such as critical race theory, Marxism and postmodernism, this approach to educational philosophy applies a critical lens to educational questions to unmask forms of identity-based discrimination and other social injustices perpetrated by educational institutions.

Politics and ethics of education. Primarily concerned with how educational philosophy can contribute to public debates around policy and ethics, thinkers associated with this approach gravitate towards two broad issues: the proper aims of citizenship education in liberal democratic societies (autonomy? patriotism? civic engagement?) or the ethical analysis of policy options and other ethically laden questions facing teachers, educational leaders and parents. Such questions include school choice, banning religious clothing in schools and "zero tolerance" disciplinary policies.

History of educational thought. The philosophers of education who continue in this tradition are inclined to reinvent the history of educational ideas as a dialogue between education's past and present, either by seeking to uncover insights from the work of philosophers of the past that can shed new light on contemporary educational questions or by turning to such writings to



retrieve valuable ways of thinking about education that have been lost or forgotten.

Prognosticating about the future of any field of scholarly inquiry inevitably involves making uncertain distinctions between passing trends and stable tendencies. The philosophy of education, like other areas of the humanities, is highly subject to both occasional enthusiasms for particular authors and peaks of interest in issues determined by the ambient political climate. As editors of Philosophical Inquiry in Education, a philosophy of education journal with a deliberately open and inclusive editorial policy, we are regularly exposed to new work emanating from all four of the thematic areas described above. From this vantage point, we see two recent shifts in scholarly activity that already show signs of shaping the contours of research in educational philosophy and theory.

The first of these is assigning greater importance to public engagement. Bringing to bear a philosophical perspective on current educational issues has always been a concern in work on educational policy and ethics. However, recent years have seen philosophers of education being more pragmatic in the choice of questions to address and finding ways to write about ethical and policy issues that can make educational philosophy accessible to decision makers and educators. Two notable recent examples are Amy Shuffelton and Bryan Warnick's work on gun violence in schools and Doris Santoro's work on teacher burnout.

Paralleling a similar development in mainstream philosophy, a second promising direction for research in the philosophy of education involves a new appreciation of how the philosophical perspective can be enriched through greater integration with empirical work. In the past, philosophers of education were largely expected to engage primarily with the work of other philosophers and to eschew empirical inquiry.

Today, we find philosophers of education increasingly attentive to how appropriately designed empirical studies can complement the traditional activities of conceptual analysis and social critique. The finest recent example of this approach may be Paula McAvoy and Diana Hess's investigations into teaching about controversial issues in schools, which has won accolades for breathing new life into old debates about teacher neutrality. ■

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Featured ebook

Respectful Relations: Enacting Reconciliation in Canadian Universities

What role are Canadian universities taking in reconciliation? The mission of a university is to provide education within an environment that fosters curiosity, creativity, and research. Universities provide students with opportunities to engage in critical thinking, explore new ways of analyzing information, and make room for new intellectual growth as students question all that they have been taught and all that they know. It would seem that universities would offer an ideal place to begin work on reconciliation and yet universities continue to face tensions and challenges when attempting to address the Truth and Reconciliation Commission (TRC's) calls to action.

To read the digital ebook

www.brocku.ca

Reconciliation in a higher education context: Tensions and challenges

Dawn Zinga, Associate Professor and Chair at the Department of Child and Youth Studies at Brock University explores reconciliation in a higher education context, by detailing the tensions and challenges in this area

In August 2017, I wrote about how Canadian institutes of higher education were taking up the Truth and Reconciliation Commission's calls to action. Almost a year later, higher education contexts continue to face tensions and challenges in addressing those calls to action. There has been much talk of how to address the calls and some policy changes, but it is clear that there are a lot of tensions and challenges around the implementation of any changes. Lakehead University offers an example of how those tensions and challenges can be expressed. The university's response to Recommendation 28 was to ensure that all law students were provided with opportunities to better understand Indigenous peoples and the law by weaving Indigenous content throughout the law curriculum. However, in practice, there appear to be challenges with the implementation of significant changes. Angelique EagleWoman was hired by Lakehead University as the first female Indigenous law school dean in 2016 but resigned citing systemic discrimination and racism in 2018. This unfortunate situation underscores the difference between a surface response to the calls to action and meaningful action.

> "The conundrum facing higher education is how to proceed to address the calls when institutions are having difficulty being able to recognise how the very structures of the institutions are getting in the way."

Universities and colleges are struggling to address the calls to action and to understand what reconciliation means. Indigenous scholars Marie

Battiste, Jan Hare, Jackie Ottman and Dwayne Donald spoke eloquently at the 2018 Congress of the Humanities and Social Sciences about reconciliation within a higher education context. Each of them remained committed to the conviction expressed by the Commission that education will be pivotal in putting Canada on the road to reconciliation. Battiste spoke about the importance of decolonising and how everyone has been "marinated in Eurocentrism" and that the tenets of Eurocentrism that are characterised by superiority, hegemony and a monopoly over all other knowledge systems, stand in the way of reconciliation. Battiste speaks about cognitive imperialism and how every Canadian student has been a victim and beneficiary of the same education system that has exposed them in Eurocentrism and cognitive imperialism. These act as some of the greatest barriers to reconciliation and the serve to blind people to the colonialism embedded throughout education at all levels.

Dwayne Donald agrees that it is difficult to accomplish much when the very institution that claims to want to take steps towards reconciliation gets in the way when tensions arise. He argues that part of the problem is the tendency within higher education contexts to take shortcuts by attempting to make changes without examining the embedded colonialism. When change is implemented in those contexts, tensions quickly rise and the response to those tensions is to reassert "colonial terrain".

Jackie Ottman also spoke to the hidden curriculum and unconscious codes that are triggered by attempts to meaningfully address the TRC. She stated that while the Royal Commission on Aboriginal Peoples issued its report in October 1996 and offered over 400 recommendations, the TRC's 94 calls to action has engendered a more lasting response. However, she warns that the weight of addressing those calls to action within higher education contexts could not be left to Indigenous students and scholars to do all the heavy lifting, but that non-indigenous students and scholars needed to walk alongside and share the weight and the work. Jan Hare agreed with her colleagues and calls for a continued commitment to reconciliation that is grounded in an understanding of everyone's roles and responsibilities.

> "Universities and colleges are struggling to address the calls to action and to understand what reconciliation means."

The conundrum facing higher education is how to proceed to address the calls when institutions are having difficulty being able to recognise how the very structures of the institutions are getting in the way. Most institutions are implementing policies and directives, but not doing the hard work of exploring what it will mean to actually implement those policies and directives. The end result is window dressing without any meaningful change or a resurgence of colonialism and a return to the status quo that hides behind claims of cultural inclusion or returns to pathologising Indigenous students and scholars.

Reconciliation requires an examination and understanding of what has happened and how current structures, systems and attitudes/biases that are conscious or unconscious continue to uphold colonialism and Eurocentrism. University mission statements can include commitments to Indigenisation but without a meaningful examination of what that term means and an appreciation that decolonisation is the first step and that such commitments will fail to produce any significant change, other than putting a new face on a continued inability to engage in reconciliation.

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The role of research in Canada for the future of ageing

Dr Yves Joanette, Scientific Director at the CIHR Institute of Aging explores how Canada's researchers are meeting the needs of an ageing population, now and in the future

The world's population is ageing. The World Health Organization projects that the number of people of over 60 will double by 2050. Dr Margaret Chan, former Director General of WHO noted it is not enough that people are living longer lives, we need to ensure these extra years are healthy, meaningful and dignified.

As Scientific Director of CIHR's Institute of Aging, I couldn't agree more. We want to make sure that these extra years are functionally healthy, that older people continue to lead meaningful lives and that they are treated with the utmost dignity and respect.

In Canada, we reached a major demographic inversion in 2016. For the first time, the number of Canadians aged 65 and older surpassed the number of Canadians aged 14 and under. That trend is expected to continue with one in four Canadians expected to be aged 65 or over by 2036, thus bringing Canada among the super-aged countries.

The fastest growing segment of our senior population is the 'oldest old' – or people 85 years old and more, with centenarians being the most rapidly growing group.

This increased lifespan results from the excellent quality of life in Canada. It also results from access to high-quality healthcare and the success of our public health programmes. To adjust to this demographic change, it also means that we need to change our social programmes and attitudes towards older people.

In Canada, we have long anticipated this demographic change and from a research perspective, we have worked to establish the infrastructure needed to carry out collaborative research among researchers and institutions within Canada and internationally.

Our first step was to establish an Institute of Aging as part of the Canadian Institutes of Health Research in 2000. I've had the privilege of serving as Scientific Director of the CIHR Institute of Aging since 2011 and our mission is to support research, to promote functionally healthy ageing and to address causes, prevention, screening, diagnosis, treatment, support systems and palliation for those complex health challenges that can be present in older individuals.

"This increased lifespan results from the excellent quality of life in Canada. It also results from access to high-quality healthcare and the success of our public health programmes. To adjust to this demographic change, it also means that we need to change our social programmes and attitudes towards older people."

To provide critical data on the determinants of functionally healthy ageing, we fund the Canadian Longitudinal Study on Aging (CLSA). This cross-Canada research platform involves more than 50,000 Canadians, aged 45 to 85, who will be followed for 20 years. CLSA will provide data and biological samples for Canadian researchers to help identify the determinants of a functionally healthy ageing, from the most basic biological to the most social aspects, including work and retirement trajectories.

The CLSA team recently released a first baseline report. It represents the most comprehensive picture of the health of Canadians over age 45 ever produced. On the bright side, almost 90% of participants rated their health as good to excellent. At the same time, the report revealed potential challenges. Only 25% of participants reach recommended amounts of physical activity. 38% of participants reported having to provide care to

others. And among retired participants, 25% reported health reasons as a factor in their decision to retire.

> "In Canada, we reached a major demographic inversion in 2016. For the first time, the number of Canadians aged 65 and older surpassed the number of Canadians aged 14 and under. That trend is expected to continue with one in four Canadians expected to be aged 65 or over by 2036, thus bringing Canada among the super-aged countries."

Finally, loneliness and social isolation, particularly among women, was identified as a concern. If we want to break down barriers that prevent older adults from continuing to work or otherwise lead fulfilling lives, we will also have to embrace new technologies in ways that will support the mobility and independence of older people.

As we look forward to the future, the Institute of Aging is committed to creating a world that supports health and wellness throughout the trajectory of ageing.

Overall, we want to celebrate and help older adults to participate fully in their communities and to contribute their skills and wisdom to their families, friends and fellow citizens. ■

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Physical activity and ageing: Recommendations that will translate into greater practice

Isabelle J. Dionne, Professor at Université deSherbrooke provides a compelling analysis of physical activity (PA) and ageing, focussing on how to develop recommendations that will translate into greater practice

Physical activity (PA) is a key behaviour in the determination of health and quality of life. Despite massive public health strategies and clear recommendations, physical inactivity remains elevated in developed countries. Increasing the levels of physical activity depends upon innovative and effective avenues of PA promotion.

Physical activity and ageing

The overall objective of the Canada Research Chair is to improve older adults' quality of life and health by determining the best exercise modalities, accompanied or not by nutritional interventions, to prevent or delay T2D or disability (loss of physical function). Indeed, the ageing of the population and the greater prevalence of obesity at all ages leads to major health issues, among which Type 2 diabetes (T2D) and physical disability have important clinical implications. Both conditions could be prevented by the development of specific exercise recommendations.

While the Canadian Society for Exercise Physiology guidelines promotes a minimum of physical activity participation to improve health in the general population: they do not target precise medical conditions or affected populations who may benefit from more specific recommendations. Learning from exercise physiology and performance studies, we know that depending on the exercise type (aerobics, resistance), modalities (number of repetitions or duration of bouts) and intensity (percentage of maximum capacity – heart rate, maximum oxygen consumption, percentage of maximum strength), we can generate specific metabolic and functional adaptations. Hence, specific exercise recommendations could be developed to minimise the risk of developing diseases such as T2D or disability in older individuals who have been identified to be at risk.

Within the past 10 years, the Faculty of Physical Activity Sciences, together with the Research Centre on Aging, has developed a strong expertise in conducting large exercise trials with tight control of the intervention and a wide array of clinical areas, which is instrumental in developing exercise recommendations. Research in this area is especially timely since the high prevalence of physical inactivity and disuse in older adults has led to numerous health problems. In parallel, a surge of research on adherence to physical exercise in all populations focusses on making older adults, among others, to adopt an active lifestyle. It thus appears timely to intensify research not only on the importance of doing it but also on what to do based on the specific health needs of an individual.

The specific case of Type 2 diabetes

Type 2 diabetes (T2D) remains a major chronic disease in Canada and clinical practices need to be revisited for both prevention and management. For instance, gains in muscle mass are still promoted to be associated with improvements in insulin sensitivity. Nevertheless, we found that a small in size, but high-quality muscle mass seems beneficial to cardiovascular risk factors, such as blood lipids and glucose metabolism. Surprisingly, we even showed that during exercise, muscle mass loss was beneficial for insulin sensitivity, possibly through improvements in inflammation and quality. My work thus supports to explore creative strategies where weight loss would be accompanied by changes in muscle mass quality, instead of absolute gains and examine how it would impact metabolic impairments, especially those that will have been determined to increase the risk of T2D in older women with a family history of it.

On the other hand, the level of exercise remains low in adults with health risk and in diabetic patients. In our

lab, older women tend to reduce exercise practice, even after having been supervised for several months and having experienced tangible benefits. We thus intend to extend exercise recommendations to the context of practice and recently began studying exercise adherence using more ecological approaches (i.e. living lab). For instance, my team and I have developed an interest in why people struggle with engagement and compliance in exercise programmes, despite wide education strategies. We thus conducted studies pertaining to personal and contextual factors of exercise practice to determine how to increase exercise programmes adherence and compliance over time. We determined that adherence to exercise programmes is greater outdoors than indoors, with equivalent physiological responses. These results are important because we also showed that current exercise participation is the best predictor of health in older adults, independent of past participation or not. These results allow refining recommendations, by adding key pieces of advice related to the context of exercise practice for older adults.

The need for interdisciplinarity research

In this context, the importance of interdisciplinary research has become evident. Numerous contemporary health problems can be blamed on physical inactivity (a level of physical activity of moderate and vigorous intensity that is below recommendations) and sedentarity (many sedentary activities such as TV watching, computer-based activities, reading, etc.). This applies to several populations (children, adults and elderly) in various contexts (leisure, school, working environment, long-term care facilities, etc.).

Altogether, these complex problems call for more comprehensive strategies supported by a large array of perspectives (physiological adaptations, contraindications, motivation, health education, etc.). Interdisciplinary research, in that sense, appears as one highly pertinent avenue. In this line, the Faculty of Physical Activity Sciences has recently launched the first Doctorate Program in Physical Activity Sciences that is interdisciplinary in nature. We are confident that this type of training will support the training of future researchers who are more open to addressing physical inactivity and its health complications through a wider spectrum of approaches and the most appropriate methodology.

The ultimate goal

Our research will inform clinical guidelines through creative exercise recommendations, both from a prescription (type, intensity) and contextual (setting, environment) standpoints. My research will improve exercise efficiency, adherence and maintenance, leading to a decreased overall risk of developing T2D and related disability, thus contributing to improve older women's health.

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Why Canada urgently needs a national strategy to tackle the diabetes epidemic

Kimberley Hanson, Director of Federal Affairs at Diabetes Canada argues that the country urgently needs a national strategy to tackle the diabetes epidemic

In Canada today, one in three Canadians lives with prediabetes or diabetes. In some communities that rate soars above 60%. Canadians under 20 years of age now face a 50% chance of developing the disease in their lifetime. For Indigenous Canadians, that risk is 80%.

If we continue with the status quo, the direct costs to our healthcare system will top $5 billion per year within a decade and the indirect costs will be triple that. And the human suffering involved is incalculable.

But first, a quick refresher on the disease: Diabetes is a metabolic disorder in which the body either cannot produce insulin or cannot properly use the insulin it produces. Insulin is a hormone that the body needs to use blood sugar as an energy source. The two main types of diabetes are Type 1 – an auto-immune condition that often develops in childhood – and Type 2, which occurs when the body doesn't make enough insulin or use properly that which it does make.

In addition, there's a precursor condition known as prediabetes, when blood glucose levels are higher than normal but not yet high enough to be diagnosed with Type 2 diabetes. Nearly 50% of those with prediabetes will go on to develop Type 2 diabetes if nothing is done.

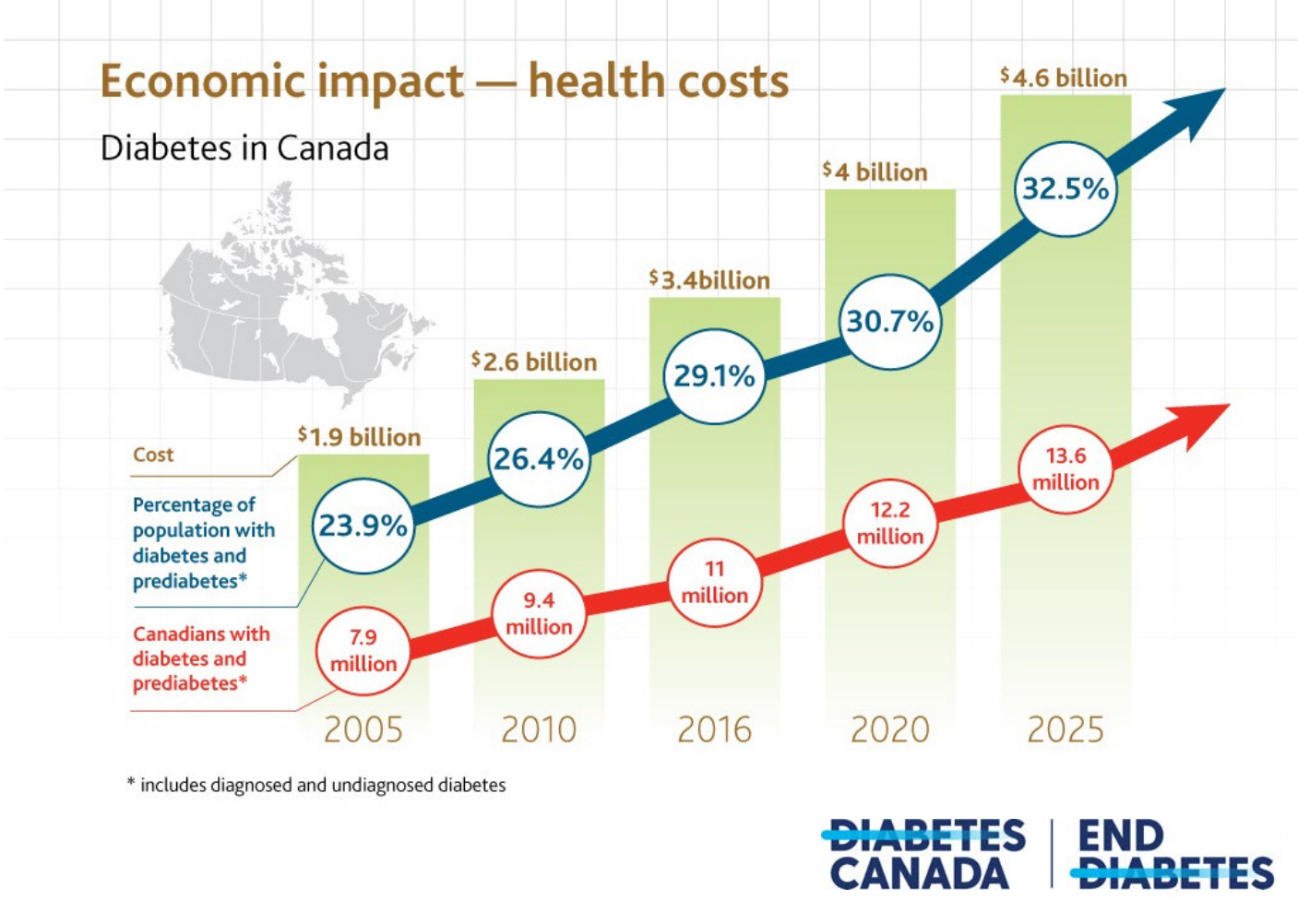
Diabetes can cause serious and life-threatening complications. People with diabetes account for 30% of the strokes, 40% of heart attacks, 50% of kidney failure requiring dialysis and 70% of amputations in Canada each year. The life expectancy of a person with diabetes is shortened by an average of 13 years. In 2012, the disease directly caused 1.5 million deaths worldwide and elevated blood glucose levels linked to diabetes were responsible for an additional 2.2 million deaths that year.

Alarmingly, diabetes is on the rise the world over and Canada is faring worse than many OECD (Organization for Economic Co-operation and Development) countries. Globally, the number of adults living with diabetes has quadrupled since 1980, from just over 100 million to more than 400 million according to the World Health Organization. The International Diabetes Federation lists Canada in the bottom third of OECD countries for diabetes prevalence. Diabetes or prediabetes now affect 11 million of the 33 million Canadians and yet, millions still don't know they have it.

It's time for an urgent change. This is not an epidemic that will be addressed by personal willpower and shame. To blame and stigmatise those living with Type 2 diabetes for their disease is not only unhelpful, it is a vast oversimplification. Type 2 diabetes is caused by a complex array of factors including genetics, lifestyle and environmental factors such as poverty, reduced access to clean drinking water, food insecurity and a disease-promoting food and physical environment. Issues of health inequality are at the core of the diabetes epidemic and addressing this epidemic is wholly reliant on addressing health inequities.

To really turn the tide of the diabetes tsunami, we need a nation-wide approach and in 2018, Diabetes Canada is developing just that. We're building on a successful "90-90-90" model implemented in the global HIV/AIDS community and adapting it to tackle diabetes in Canada.

Implementing such an approach would mean that, in time, 100% of Canadians would live in an environment that does not promote the development of diabetes; 90% of Canadians would know whether they're at risk of, or living with, diabetes; 90% of those with prediabetes or diabetes would be engaged in appropriate



treatment and support to avoid developing diabetes or its complications and, in consequence, 90% of them would be achieving improved health outcomes.

We know from research that when someone with pre-diabetes who makes moderate lifestyle adjustments (losing 5-10% of their body weight, for example), they are 60% less likely to develop the disease. That could mean that if we increase risk awareness and then provide adequate support, we could help 3.5 million Canadians make meaningful changes to avoid or significantly delay developing diabetes.

A coordinated approach to diabetes could translate into preventing diabetes in millions of Canadians who are currently on track to develop it. Millions of Canadians with diabetes who are at risk of developing serious complications like blindness, kidney failure or amputation would see that risk reduced. And significant time and money would be saved or used more efficiently by our health-care system.

Desmond Tutu once said: "There comes a point where we need to stop just pulling people out of the river. We need to go upstream and find out why they're falling in." When it comes to the millions upon millions of Canadians who already have or are well on their way to developing diabetes and its many complications, the time to move upstream and fix the problem is now. With guidance and input from hundreds of experts, in 2018 Diabetes Canada plans to chart a path to doing just that. ■

DIABETES CANADA | END DIABETES

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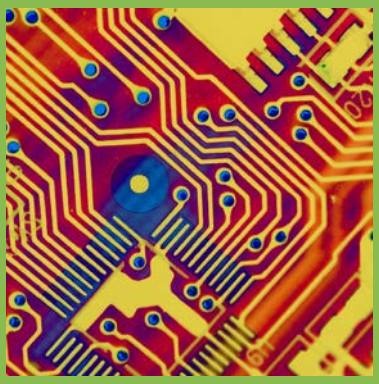





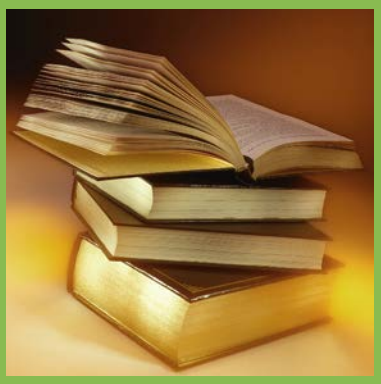

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Department of Child & Youth Studies

Child and Youth Studies (CHYS) is one of the most popular programs at Brock. Students learn from a broad-based approach that considers the individual child or youth within the context of the family, school, peer group and community. With interdisciplinary roots in psychology, education, sociology, cultural studies and criminology, the degree gives academic background to pursue a wide variety of careers or to pursue further studies in a Master's program and the new transdisciplinary PhD program.

CHYS will be hosting a multidisciplinary conference on conceptualizing children and youth October 11-13, 2017.

Watch the CHYS website for more details:

https://brocku.ca/social-sciences/departments-and-centres/child-and-youth-studies

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