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NORTH AMERICA ANALYSIS

THE PROMISE OF BIOMEDICAL SCIENCE AND THE POWER OF DATA

MICHAEL F. HUERTA FROM THE NATIONAL LIBRARY OF MEDICINE AT THE U.S.'S NATIONAL INSTITUTES OF HEALTH EXPLORES HOW DISCOVERY AND HEALTH BENEFIT FROM THE INTERSECTION OF DATA SCIENCE AND OPEN SCIENCE

IN THIS ISSUE

Dr Richard Hodes, Director of the National Institute on Aging, explores the importance of working together to treat and prevent Alzheimer's disease and related dementias

Brian Berridge, Associate Director of the National Toxicology Program (NTP), details how NTP studies the health impacts of chemicals and other factors in this fascinating interview

Dr Yves Joanette, Scientific Director at the CIHR Institute of Aging argues for a balanced approach when it comes to their collaboration-based approach to face the challenge of dementia

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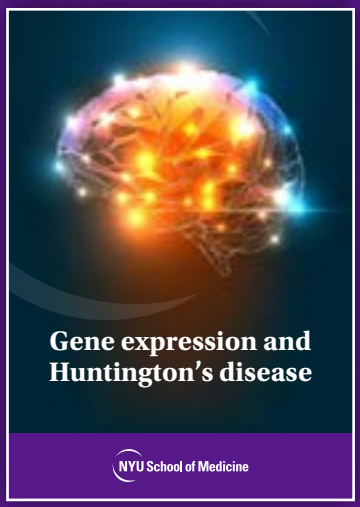
Gene expression and Huntington's disease

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

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



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INTRODUCTION

Welcome to this packed October 2018 edition of North America Analysis.

Heading up this publication, we are honoured to include a piece from Michael F. Huerta from the National Library of Medicine at the U.S.'s National Institutes of Health. In his article, he explores how discovery and health benefit from the intersection of data science and open science.

On the subject of ageing, we include an insightful article from Dr Richard Hodes, Director of the National Institute on Aging within the U.S. National Institutes of Health, who explains the importance of working together to treat and prevent Alzheimer's disease and related dementias.

I enjoyed a fascinating interview with Brian Berridge, Associate Director of the National Toxicology Program (NTP) in the U.S., who details how NTP studies the health impacts of chemicals and other factors. I hope you enjoy reading about the excellent work that NTP does; it was certainly fascinating to find out what they do.

Prior to Hurricane Florence in America, we were fortunate to speak with Dr Michael Brennan, Branch Chief at the Hurricane Specialist Unit within the National Hurricane Center (NHC). In this interview, we learn about NHC's vital work in issuing the best watches, warnings, forecasts and analyses of hazardous tropical weather including, of course, hurricanes.

Looking at the exciting world of blockchain, I am delighted to include a perspective on this from Chris Burruss, the President of the Blockchain in Transport Alliance (BiTA). In his article, he explains that today, moving goods from origin to destination is complex, but this can potentially be solved with blockchain technology. I encourage you to read his article to find out more about how blockchain can benefit the supply chain.

Turning to Canada, I am thrilled to include a return appearance from Dr Yves Joanette, Scientific Director at the CIHR Institute of Aging who argues for a balanced approach when it comes to their collaboration-based approach to face the challenge of dementia.

I hope that you find this publication insightful. Please do get in touch with me if you have any ideas for compelling content for the future, or perhaps you'd just like to provide your remarks on this edition. ■

Jonathan Miles
Editor

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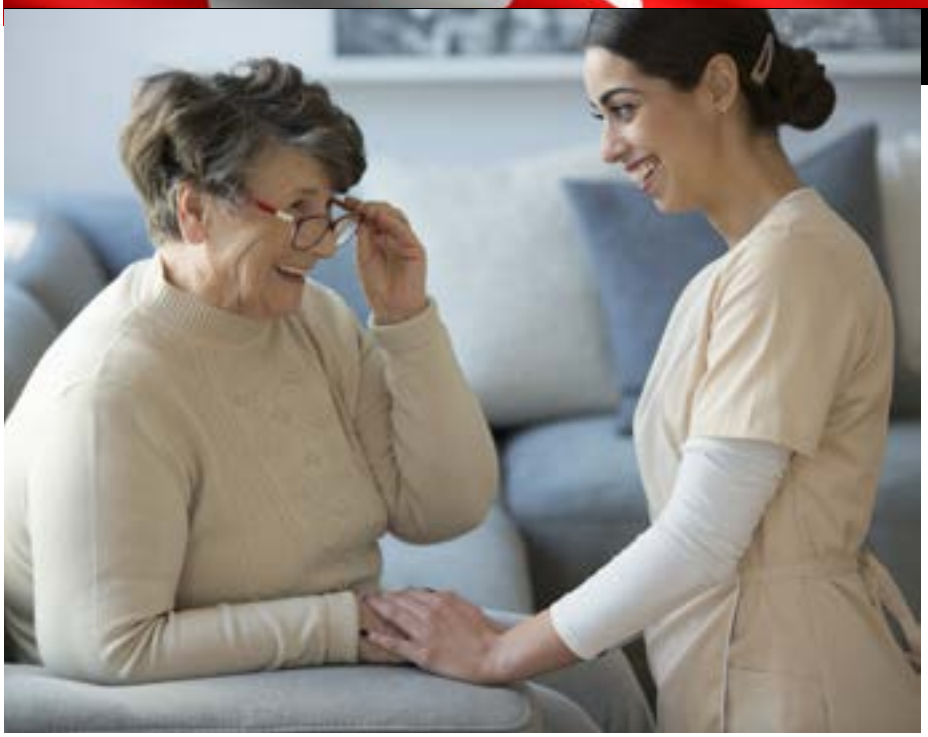

CANADA

Discovery and health at the intersection of data science and open science

Michael F. Huerta from the National Library of Medicine at the U.S.'s National Institutes of Health explores how discovery and health benefit from the intersection of data science and open science

The promise of biomedical science to save and improve lives has never been realised so quickly and spectacularly as it is today. And yet, the nearly universal digitisation of research and healthcare is starting to unlock the power of data and more open paradigms, making possible faster progress and changes in the very nature of discovery. The National Library of Medicine (NLM) lives at the intersection of these forces and is poised to catalyse this transformation.

NLM is an institute of the National Institutes of Health (NIH) with a research and training focus on biomedical information science, informatics and data science. NLM is at the forefront of innovation in computational biology, computing in context, extracting insight from electronic health records and using artificial intelligence (AI) and data science approaches to answer key biomedical questions. This scientific leadership is reflected in NLM's support of extramural research across the country, as well as a robust intramural research programme and internal information engineering efforts aimed at innovating and improving its products and processes.

NLM is also the world's largest biomedical library, creating and hosting major resources, tools and services for biomedical literature, data, standards and more. Every day, NLM sends over 1,000 terabytes of data to nearly five million users and receives over 100 terabytes from more than 3000 users. As a library, NLM has fostered and advanced open science and scholarship by making digital research objects – whether a digital literature citation, dataset, or data standard definition – findable, accessible, interoperable and reusable (i.e., FAIR), as well as attributable and sustainable. Resources like GenBank, PubMed, Medline Plus, PubChem, PubMed Central and ClinicalTrials.gov make data and information findable and accessible and their implementation makes data and information reusable, attributable and sustainable.

NLM facilitates interoperability of digital data by promoting, developing and hosting a range of standards products, such as terminologies like UMLS and LOINC, as well as standards platforms such as the NIH Clinical Data Elements (CDE) Repository and the Value Set Authority Center. NLM also shares its standards expertise, acting as the coordinating body of the Department of Health and Human Services for clinical terminology and of NIH through its leadership of the NIH Clinical CDE Task Force.

The recently released NLM Strategic Plan envisions NLM building on its experience to become a platform for biomedical discovery and data-powered health by achieving three goals.

The first is to provide tools for data-driven research, which includes enhancing innovation by expanding NLM's biomedical informatics and data science research activities. NLM will also work to connect resources, tools and services as the basis of a sustainable, open and trusted digital ecosystem for biomedical and health information, scholarship and science. Emphasis will be placed on ensuring digital research objects such as scientific papers, datasets, models, analytic pipelines and others, are FAIR and appropriately associated with each other – minding appropriate considerations for privacy and confidentiality.

In pursuit of the second goal, to reach more people in more ways, NLM will optimise users' experience with – and use of – its resources, tools and services, to better serve its many different users. The final goal is to expand NLM's training support and activities to: (1) produce experts who will develop next-generation

innovations in biomedical informatics and data science; (2) make sure that biomedical scientists are adept in the use of these advanced approaches; (3) instill an understanding of the opportunities, limits and requirements of data science across the entire biomedical workforce and; (4) assure the public is data-ready to make the best use of health information in the 21st Century.

Maximising the scientific opportunities that sit at the intersection of data science and open science will require addressing some basic issues, but solutions do not seem far off. Non-traditional practices needed for open science, such as sharing data, must be encouraged; this might be addressed by strategically aligning incentives across the biomedical enterprise. And, as digital research objects and their links to each other multiply, at-scale curation solutions will be needed; this might be addressed by using AI to infer the nature of an object based on its location in the network of interconnected objects, with provenance tracked using blockchain.

Finally, the sustainability of an open digital ecosystem is crucial; this will be helped by making sure that decisions about investing in the ecosystem are based on empirical evidence about the value of those investments to the science.

Achieving the goals of the NLM Strategic Plan, especially in the context of the NIH Strategic Plan for Data Science, will usher in a new era of data-driven research and data-powered health – one that is certain to offer more hope to more people more rapidly. ■

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Biology research: The state of health of the gut microbiome

Hannah M. Wexler, Professor at the Greater Los Angeles VA Health Care System and UCLA School of Medicine gives a fascinating glimpse into biology research that focuses on the state of health of the gut microbiome

More than two millennia have passed since Hippocrates declared: "Bad digestion is the root of all evil." In 2018, the importance of the gut flora in human health is at the forefront of scientific and public awareness and the gut microbiome is the new microbial frontier. The state of health of the gut microbiome is associated with GI diseases such as Crohn's disease and irritable bowel disorders. More surprisingly, the state of the gut microbiome is implicated in obesity, diabetes, heart disease, autism and even psychological disorders such as obsessive-compulsive disorder and depression.

Recently, specific bacteria in the gut microbiota were associated with certain food preferences! Now, virtually every health condition seems to be linked in some way to the gut microbiome. The number of journal articles published per year has skyrocketed. A growing public awareness of the importance of a healthy gut microbiome is the foundation for several very profitable industries that we could not have imagined a decade ago!

Bacteroides fragilis (BF), the organism that we have studied for >30 years, is the most important anaerobic gut pathobiont and the most concentrated reservoir of resistance genes in the human gut microbiome[1]. In its normal niche, BF is a commensal and has even been implicated in maintaining immune health by stimulating different arms of the T-cell response. Outside its colonic niche, it is an aggressive pathogen. BF is the most common anaerobic isolate in surgical site infections (SSIs) following colorectal surgery[2], in wound isolates from combat casualties[3], in intraabdominal abscesses and in extra-intestinal infections of intestinal origin. It is the main cause of anaerobic bacteremia and implicated in other serious infections (e.g., brain abscess, soft tissue infections and peritonitis[4].

Our group studies *Bacteroides fragilis* strains that are responsible for serious, multidrug-resistant clinical infections around the world. We are primarily interested in the transition from benign commensal to an aggressive pathogen. Our questions include: Are certain BF more likely to transition from commensal to pathogen and do specific genes facilitate this transition? Are there genes carried by all BF that are regulated differently when BF is in "virulent" mode? What triggers changes that allow BF to persist in the more aerobic environment of abscesses and the even more, aerobic environment of the blood?

Bacteremia is more common for BF than for any other anaerobe[5] (it is the most common anaerobic pathogen identified[6]) and these infections are responsible for a significant burden of disease in general populations. The BF enterotoxin is a known virulence factor[7] but strains enterotoxin-bearing BF do not necessarily cause disease nor do all virulent BF produce enterotoxin.

At this stage, we believe that certain subgroups of BF are more innately virulent than others. We found that BF blood isolates cluster in a highly specific phylogenetic subgroup within the BF species. These strains have never been studied as a distinct group in terms of how they differ from other BF strains. We found that they have unique virulence genes, differentially transcribed genes common to other BF and CRISPR-Cas systems that differ from other BF isolates. CRISPR-Cas systems are considered innate immunity systems in prokaryotes and are important in controlling horizontal gene transfer (HGT), host interactions and can even be involved in cell regulation. Thus, the distinct nature of the BF blood isolates CRISPR-Cas is another indication that BF blood isolates are a group apart.

We also study whether these factors are transferable between strains. Often, a group of genes that contribute to pathogenicity, such as resistance genes and virulence factors, are shared together on large mobile genetic elements. We have identified numerous types of these mobile pathogenicity packages that *Bacteroides fragilis* has acquired, which contribute to its opportunistic pathogenicity[8, 9].

We believe that tolerance and persistence, currently recognised as an alternative mode of evading antimicrobial action[10], are important factors in the tenacity of BF. Persisters constitute a serious clinical problem and are thought to be responsible for the recalcitrance of chronic infections[11]. Data from decades of studying and MIC testing of BF isolates suggests to us that tolerance and/or persistence are important mechanisms that BF uses to survive an antibiotic challenge. Susceptibility studies are not designed to measure tolerance, so this data is almost never published.

In fact, the protocols for susceptibility testing published by the Clinical Laboratory Standards Institute (that, ironically, we helped co-author) specifically instruct the microbiologist reading the test to ignore hazes for MIC determination[12]. On the other hand, we have noted and written about this problem for decades[13]. We noted that MICs of BF are often indistinct; sometimes hazes and sometimes small colonies appear beyond the MIC "endpoint". To estimate just how frequent this phenomenon occurs, we reviewed lab notes from susceptibility studies published over the course of two decades and found that between five and 15% of *B. fragilis* isolates yielded hazes that persisted well beyond the "MIC endpoint" and we think it likely that most of those hazes represent tolerance or persistence behaviour.

We found that the endpoints of growth isolated from these areas often have indistinct endpoints as well[14]. This type of growth is presumed to be an indication of tolerant or persistent cells according to recent studies by Balaban[15]. Almost thirty years ago, we investigated these hazes with two other gram-negative anaerobic bacteria, *Fusobacterium* and *Bilophila wadsworthia* and found that they were cell wall deficient forms that would revert to the normal form after two or three passages on drug-free medium. We believe that these phenomena may be responsible for the chronic nature of BF infections, as well as the clinical non-response in some patients to "appropriate" antibiotic therapy.

We know that antimicrobial therapy brings with it a host of unwelcome side effects, including disruption of the healthy gut microbiome and subsequent opportunistic infections such as Clostridium difficile overgrowth. We believe that the proper approach to treating BF infections would be a narrower one that would target specific virulence factors or antimicrobial evasive mechanisms. Our work is designed to identify precise gene targets that will then inform the emerging targeted therapies so that serious BF infections can be treated while preserving the beneficial gut microbiome.

Bibliography and references

1 A.A. Salyers, A. Gupta, and Y. Wang, Human intestinal bacteria as reservoirs for antibiotic resistance genes. Trends Microbiol 12 (2004) 412-416.

2 J.S. Solomkin, J.E. Mazuski, J.S. Bradley, K.A. Rodvold, E.J. Goldstein, E.J. Baron, P.J. O'Neill, A.W. Chow, E.P. Dellinger, S.R. Eachempati, S. Gorbach, M. Hilfiker, A.K. May, A.B. Nathens, R.G. Sawyer, and J.G. Bartlett, Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg. Infect. (Larchmt.) 11 (2010) 79-109.

3 B.K. White, K. Mende, A.C. Weintrob, M.L. Beckius, W.C. Zera, D. Lu, W. Bradley, D.R. Tribble, E.R. Schnaubelt, and C.K. Murray, Epidemiology and antimicrobial susceptibilities of wound isolates of obligate anaerobes from combat casualties. Diagn. Microbiol. Infect. Dis 84 (2016) 144-150.

4 H.M. Wexler, Bacteroides: the good, the bad, and the nitty-gritty. Clinical Microbiology Reviews 20 (2007) 593-621.

5 K.J. Ryan, Clostridium, Peptostreptococcus, Bacteroides, and Other Anaerobes. in: K.J.R. Ryan, C.G., (Ed.), Sherris Medical Microbiology - An Introduction to Infectious Disease, McGraw Hill, New York, 2004, pp. 309-326.

6 J.T. Ngo, M.D. Parkins, D.B. Gregson, J.D. Pitout, T. Ross, D.L. Church, and K.B. Laupland, Population-based assessment of the incidence, risk factors, and outcomes of anaerobic bloodstream infections. Infection 41 (2013) 41-8.

7 H.M. Wexler, The genus Bacteroides. in: E.Y. Rosenberg, E.F. DeLong, F. Thompson, S. Lory, and E. Stackebrandt, (Eds.), The Prokaryotes: Other major lineages of Bacteria and the Archaea, Springer Verlig, Berlin Heidelberg, 2014, pp. 459-484.

8 F. Husain, Y. Veeranagouda, R. Boente, K. Tang, G. Mulato, and H.M. Wexler, The Ellis Island Effect: A novel mobile element in a multi-drug resistant *Bacteroides fragilis* clinical isolate includes a mosaic of resistance genes from Gram-positive bacteria. Mobile genetic elements 4 (2014) E29801-E29812.

9 F.T. Husain, Kevin; Yaligara, Veeranagouda; Boente, Renata; Blakely, Garry; Patrick, Sheila; Wexler,H.M., Novel large-scale chromosomal transfer in *Bacteroides fragilis* contributes to its pangenome and rapid environmental adaptation. Microbial Genomics In press (2017).

10 A. Brauner, O. Fridman, O. Gefen, and N.Q. Balaban, Distinguishing between resistance, tolerance and persistence to antibiotic treatment. Nat Rev Microbiol 14 (2016) 320-30.

11 J. Michiels, B. den Bergh, N. Verstraeten, and J. Michiels, Molecular mechanisms and clinical implications of bacterial persistence. Drug Resistance Updates 29 (2016) 76-89.

12 CLSI, Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard-Eighth Edition. CLSI document M11-A8 (2012).

13 H.M. Wexler, Susceptibility testing of anaerobic bacteria: myth, magic, or method? Clin. Microbiol. Rev 4 (1991) 470-484.

14 L. Pumbwe, A. Chang, R. Smith, and H. Wexler, BmeRABC5 is a multidrug efflux system that can confer metronidazole resistance in *Bacteroides fragilis*. Microbial drug resistance (Larchmont, N. Y.) 13 (2007) 96-101.

15 I. Levin-Reisman, I. Ronin, O. Gefen, I. Braniss, N. Shoresh, and N.Q. Balaban, Antibiotic tolerance facilitates the evolution of resistance. Science 355 (2017) 826-830.

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Non-radioactive, non-ionising radiation for safe paediatric imaging

E.M. Sevick and J.C. Rasmussen from The University of Texas Health Science Center, The Brown Foundation Institute of Molecular Medicine discuss non-radioactive, non-ionising radiation for safe, paediatric imaging

Medical imaging has transformed the entire spectrum of healthcare, from enabling discoveries in medical science and directing the development of therapeutic interventions, to providing the most optimal and efficient management of diseases in individuals. Yet conventional medical imaging modalities have particular limitations, especially when it comes to the paediatric populations in whom diagnosis and treatment arguably may have the greatest long-term benefit.

Whether it be the ionising radiation of computed tomography (CT) or x-ray imaging; the radioactivity of radionuclide-based imaging agents in nuclear imaging; the long scanning times of magnetic resonance imaging (MRI); or the need to administer substantial amounts of iodinated or gadolinium-based contrast agents whose long-term effects are questionable in adults, much less in infants and children; conventional medical imaging does not advance discoveries in paediatric medicine in the same manner it does in adult medicine.

Under development in our laboratories, near-infrared fluorescence (NIRF) imaging may uniquely meet the requirements for paediatric medical imaging. The technique depends upon administering a trace dose of non-radioactive dye that fluoresces in the near-infrared wavelength range

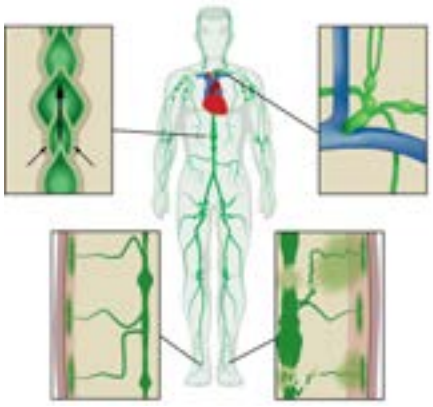

Figure 1: A schematic of the open and unidirectional lymphatic system which begins at the initial lymphatics (lower left panel) that line all organs and carries lymph through lymph nodes and the thoracic duct before emptying into the supraclavicular vein (upper right panel). The system includes series of lymphangions or "lymph hearts" which propel lymph unidirectionally through the lymphatics (upper left panel). The abnormal lymphatic function may be a result of lack of pumping and/or the degradation or malformation of lymphatic vessels (lower right panel). Figure reproduced from O'Donnell, et al., J Vasc Surg Venous Lymphat Disord, 2017.

and illuminating tissue surfaces with dim near-infrared (NIR) light that penetrates several centimetres to excite the dye, causing it to fluoresce. The resulting fluorescence is emitted from the tissues and is captured by an imaging system, consisting of military-grade night vision technology coupled to a digital image capture device.

Because of the superior sensitivity offered by the coupling of these two technologies, trace doses of fluorescent dye can be rapidly imaged with sub-second exposures at tissue depths as great as 3-4 centimetres. This unprecedented performance enables NIRF imaging to be used as a point-of-care diagnostic and removes the need for sedation otherwise needed for paediatric patients. Future developments include extending this depth and generating 3-D imaging, similar to CT or MR angiography.

Owing to its 60 year-record of safe use in humans at much larger doses, we currently employ indocyanine green (ICG) as the NIRF contrast agent, but other far brighter and more useful dyes remain to be translated into humans. ICG strongly associates with plasma proteins, making it an excellent hemovascular contrast agent and in our work, an excellent lymphovascular contrast agent that, when coupled with the NIRF imaging devices, has allowed some of the first glimpses of lymphatic vascular function in disorders of adults and children.

The lymphatic vascular system has largely escaped routine medical imaging and as a result, comparatively little is known about its role in health and disease. The open and unidirectional lymphatic system begins with the initial lymphatics that lie beneath the epidermis and line all organs. Waste products, immune cells and excess fluid (capillary filtrate) that enter the initial lymphatics are actively pumped through series of "lymph hearts" or contractile lymphangions that transit lymph through lymph nodes to the subclavian vein where the fluid

returns to the blood vasculature (Figure 1).

There are few procedures to image the lymphatics: (i) lymphoscintigraphy, in which a radioactive colloid is injected to image lymphatic transport over several minutes to hours using nuclear imaging and (ii) lymphangiography, in which several millilitres of an iodinated or gadolinium-based contrast agent is injected into lymph nodes or into surgically isolated lymphatic vessels for MR or x-ray imaging, provide invasive and cumbersome diagnostic techniques. As a result, there is little understanding of how the lymphatic vasculature mediates immune response and returns fluid and lipids absorbed from the gut back into the hemovascular system.

Today, despite the paucity in procedures to image the lymphatics, it is generally accepted that it plays a critical role in several chronic conditions in adults, including autoimmune diseases, such as rheumatoid arthritis, cancer metastasis, peripheral vascular disease and neurodegenerative diseases. In children, lymphatic dysfunction has been hypothesized to accompany neurological diseases, such as specific forms of Autism, vascular malformations and cardiovascular deformities.

In translational studies funded in part by the National Institutes of Health and conducted under investigational new drug applications from the FDA, we have used the NIRF technology to dynamically image the lymphatics of over 400 subjects, including 30 infants and children. The imaging begins with an intradermal injection of 0.05- 0.1 mL of saline containing microgram amounts of ICG into the region of interest. ICG administration on the top of the foot results in immediate uptake into the main conducting vessels (Figure 2A) that proximally "pumps"

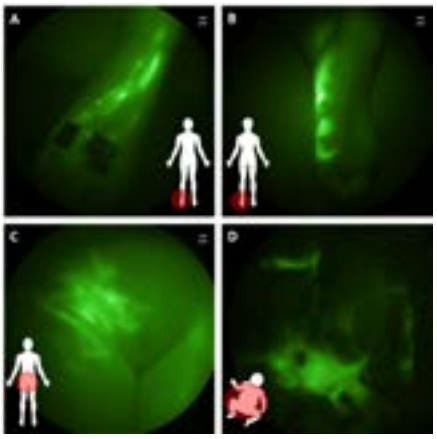

Figure 2: Conducting lymphatics on the top (A) of the right foot and (B) abnormal drainage on the bottom of the left foot of a 17-year girl with congenital lymphedema; Lymphatic congestion in the pelvis of (C) a 16-year girl with congenital lymphedema and (D) a 23-day old male infant with surgery-induced chylothorax.

ICG-laden lymph into the inguinal nodes before entering the central lymph channel that collects mesenteric and peripherally generated lymph for its return to the hemovascular system.

In children and adults with suspected lymphatic dysfunction, we have observed abnormal lymph drainage to the bottom of feet (Figure 2B), as well as pelvic, lymphatic congestion which in adolescents and young adults is associated with lower extremity lymphedema (Figure 2C) and, in some infants, with surgery-induced chylothorax (Figure 2D).

In other studies, concerning infants, we have uncovered impaired lymphatic pumping and imaged retrograde lymphatic drainage into the pleural cavity to ascertain the nature of impaired lymphatic return. These imaging observations, when coupled with genetic and immune profiling, could provide critical clues to develop effective treatments for the paediatric population suffering immune or cardiovascular disorders.

While we have used NIRF to interrogate lymphatic function in children and adults, it also has the unfulfilled potential to interrogate hemovascular function as well as cerebral spinal fluid production and drainage to address some of our most challenging problems in paediatric patients. In addition, the development of molecularly targeted NIRF agents expands the repertoire of imaging diagnostics in the paediatric population to advance therapeutic discoveries.

For more information on NIRF imaging in paediatrics and congenital diseases:

Greives, M.R., Aldrich, M.B., Morrow, J.R., Sevick-Muraca, E.M., and J.C. Rasmussen, "Near-infrared fluorescence imaging of a toddler with congenital lymphedema," Pediatrics, 139(4), 2017 PMID: 28356336.

Rasmussen, J.C., Aldrich, M.B., Guilloid, R., Fife, C.E., O'Donnell, T.F., and E.M. Sevick-Muraca, "NIRF lymphatic imaging in a patient treated for venous occlusion," Journal of Vascular Surgery Cases, 4(1): 9-17, 2016.

Gonzalez-Garay, M.L., Aldrich, M.B., Rasmussen, J.C., Guilliod, R., King, P.D., and E.M. Sevick-Muraca, "A novel mutation in CELSR1 is pathogenic for a new phenotype of hereditary lymphedema," Vascular Cell, 8:1, 2016 PMID: 26855770.

Tan, I.C., Balaguru, D., Rasmussen, J.C., Guilliod, R., Bricker, J.T., Douglas, W.I., and E.M. Sevick-Muraca, "Investigational lymphatic imaging at the bedside in a pediatric postoperative chylothorax patient," Pediatric Cardiology, 2014, PMID: 24972649.

Agollah, G.D., Gonzalez-Garay, M.L., Rasmussen, J.C., Tan, I-C., Aldrich, M.B., Darne, C., Fife, C.E., Guilloid, R., Maus, E.A., King, P.D., and E.M. Sevick-Muraca, "Evidence for SH domain-containing 5'-inosotil phosphatase-2 (SHIP2) contributing to a lymphatic dysfunction," Plos One, 10;9(11):e112548, 2014. PMID: 25383712.

E.M. Sevick-Muraca, "Translation of near-infrared fluorescence imaging technologies: emerging clinical applications," Ann Rev Med, 63: 217-31, 2012, Epub 2011 Oct 27. PMID: 22034868.

Burrows, P.E.*, Gonzalez-Garay, M.L.*, Rasmussen, J.C.*, Aldrich M.E., Guilliod R., Maus, E.A., Fife, C.E., Kwon, S., Lapinski, P.E., King, P.D., and E.M. Sevick-Muraca, "Lymphatic abnormalities are associated with RASA1 mutations in mouse and man," Proc Natl Acad Sci, 110(21): 8621-6, 2013. PMID: 23650393.

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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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Advances in newborn screening for neuromuscular disease

Kristin Stephenson, Sr. VP, Chief Policy & Community Engagement Officer at the Muscular Dystrophy Association details the advances taking place in newborn screening for neuromuscular disease

Spinal muscular atrophy (SMA) is the leading genetic cause of death in infants in the United States (U.S.) and early identification and intervention are key to treating the disorder. The national newborn screening public health program now provides an opportunity to identify babies with this lethal disorder at birth – opening up treatment and care options from day one.

In July, SMA was added to the Recommended Uniform Screening Panel (RUSP) for newborns, which means that now it is officially recommended that every baby born in each state is tested for SMA immediately after birth. This is a landmark decision for the SMA community, recognising both the importance of early diagnosis and intervention in newborns and the new therapeutic options to treat the disease. Because each state ultimately determines which disorders are included on their respective state newborn screening panels, having a disorder added to the nationally recommended list is a critical step toward making sure all babies have the opportunity to be identified. And while states drive their individual testing programmes, there are essential federal supports that help ensure implementation, testing and feasibility are considered.

What is newborn screening?

Babies born in the U.S. are currently screened for more than 30 conditions including two neuromuscular diseases – Pompe and SMA. Early detection of these diseases is vital as it allows for earlier treatment, which can improve health outcomes. Importantly, identifying babies with disorders such as SMA early in life allows for careful monitoring from day one, providing the opportunity to put in place plans and gather insights for long-term care, treatment and follow-up.

In the U.S., more than four million babies are screened annually for serious diseases through the newborn screening program – diseases that would result in significant disability or death if left untreated. Newborn screening, as a public health programme, has proven successful in saving countless lives and has been hailed by the Centers for Disease Control and Prevention (CDC) as one of the top 10 public health successes of the past decade.

Newborn screening and the states

Because newborn screening is a public health programme that falls under the authority of the individual states, the final decision on whether to test for a specific disease is up to each state. Each state must add a disease to its own screening panel. This implementation phase can be complicated and expensive and can take a significant amount of time.

Federal funding is needed to determine which disorders are ready for nationwide screening and to help implement screening in the states. Thus, federal funding for agencies that support newborn screening is essential. Funds from federal agencies such as the Health Resources and Services Administration (HRSA) and CDC provide counselling and other services to newborns and children.

For the 2018 fiscal year, the Newborn Screening Quality Assurance Program at the CDC is funded at $8.4 million and the Heritable Disorders program at HRSA is funded at $13.88 million [(1)]. This funding supports newborn screening initiatives by providing training in new laboratory techniques and educational materials for healthcare professionals, families and patient advocacy and support groups and additional funding will be essential to ensure that the newborn screening program has sufficient resources to fulfil its intent.

Muscular Dystrophy Association (MDA) and newborn screening

MDA is an umbrella organisation committed to transforming the lives of individuals affected by muscular dystrophy, ALS and more than 40 other neuromuscular diseases through innovations in science and innovations in care. To that end, MDA is committed to promoting early screening, diagnosis and treatment. Once babies with these conditions are identified via state newborn screening programs, MDA Care Centers at more than 150 top institutions across the U.S. can play a key role in confirmatory diagnoses, treatment and follow-up. In many cases, the follow-up care may be lifelong and, in some situations, (for example, late-onset Pompe disease) the clinical symptoms may not manifest until later in life.

We are also committed to optimising clinical care and accelerating the development of therapy options while contributing to the understanding of the natural history of neuromuscular disease. When babies are diagnosed early in life, it allows the opportunity to learn more about how the disorder manifests and to insights into how early intervention affects the disease course. To help collect and compile this type of data in a rigorous and uniform manner, MDA has established the provider-entered neuroMuscular ObserVational Research (MOVR) Data Hub, to collect data at MDA Care Centers across the country. MOVR will collect longitudinal insights that are being applied to increase understanding of disorders, including SMA and that support regulatory science and drug development. The same Care Center network and MOVR data hub also support Duchenne muscular dystrophy (DMD) and related neuromuscular diseases, which we anticipate will also be part of the national newborn screening program soon.

As scientific progress continues to accelerate, MDA will remain committed to newborn screening and to advocating for additional neuromuscular diseases to be added to the RUSP. To learn more about MDA advocacy, visit https://www.mda.org/get-involved/advocacy. ■

1 https://www.gpo.gov/fdsys/pkg/CPRT-115HPRT25289/pdf/CPRT-115HPRT25289.pdf

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Keeping watch: The story of a diabetes service dog

Joan Cary from Lions Clubs International explains the organisation's excellent work in providing service dog to assist those with diabetes

Every few months, Minnesota Lion Lu Ommen found himself in the company of an ambulance crew. He had gone into life-threatening diabetic shock, with his blood sugar low enough to cause a dangerous seizure.

But as much as he came to like the 911 responders, Ommen has not seen them for a while. He thanks Gilbert and the Lions Clubs International for that. Gilbert, a 62-pound Black Labrador Retriever became Ommen's 24-7 companion four years ago. Where Ommen goes – the golf course, his Harmony Lions Club meeting where he is now president, the pickle-ball court, to church, or to bed – his diabetes service dog goes too.

When Ommen's blood sugar is too low or too high – under 100 or over 140 – Gilbert alerts him by tapping him with his paw. "The more out of whack it is, the more aggressively he taps," says Ommen. "If I really get out of whack, he might bark."

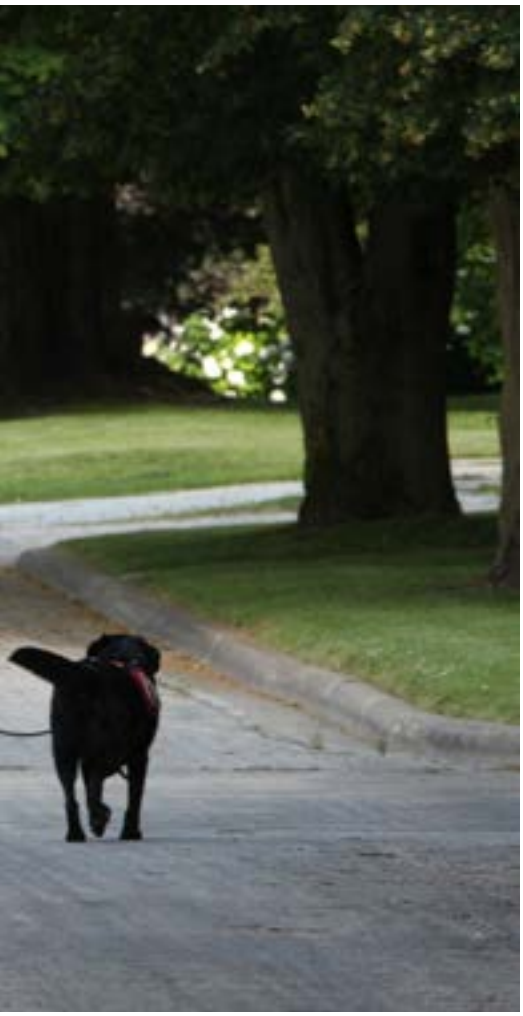
On occasions, Gilbert has also alerted Ommen's companions of blood sugar concerns when he's been around them, catching the signs on their breath and then tapping them with his paw. "What he does, he can do to anybody," says Ommen. "He's a great dog."

Gilbert, six, came to Lu and Sue Ommen from Can Do Canines, a Lions-supported non-profit outside Minneapolis that, since 1989, has provided more than 600 service dogs free of charge to people in Minnesota and nearby Wisconsin. He is trained to monitor his human partner's breath, both night and day.

Lion Alan Peters, the organisation's founder and executive director explains that the change in blood sugar starts in a person's stomach and creates a particular smell on their breath. Although it is impossible for humans to detect, it is clear to the sensitive nose of a trained dog.

Peters is also a diabetic, having discovered it by checking his own blood while volunteering at a Lions' glucose screening event.

Dogs like Gilbert were unheard of



when he began the organisation, but they are now in high demand. Can Do Canines have a waiting list of 184 people and have partnered 42 dogs with diabetics. The other dogs among the 600-plus serve as hearing assistants, mobility dogs, seizure and autism service dogs.

> "When Ommen's blood sugar is too low or too high – under 100 or over 140 – Gilbert alerts him by tapping him with his paw. "The more out of whack it is, the more aggressively he taps," says Ommen. "If I really get out of whack, he might bark."

Often, the people most in need of a service dog are the ones who can't afford them, says Peters. Each service dog costs the organisation about $25,000 from birth to age two, when they are typically introduced to their owner, and that's where the support of Lions in Multiple District 5M has helped.

Minnesota Lions donated more than $182,000 to the organisation during Lion year 2016 to 2017, says Peters.

"They are our biggest single supporter. We see a lot of value in them, and it's not just because of the money. Lions are more likely to know the needs in their community."

With $75,000 in donations from individual clubs and a $75,000 Lions Club International Foundation grant, Can Do Canines was also able to add 10 kennels to their facility.

Gilbert might recall those kennels on a visit, but now he sleeps next to the Ommens' bed, responsibly waking at night to check his partner's breath.

"I keep a pretty close eye on him," says Ommen. If Gilbert could talk, he would say the same.

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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.

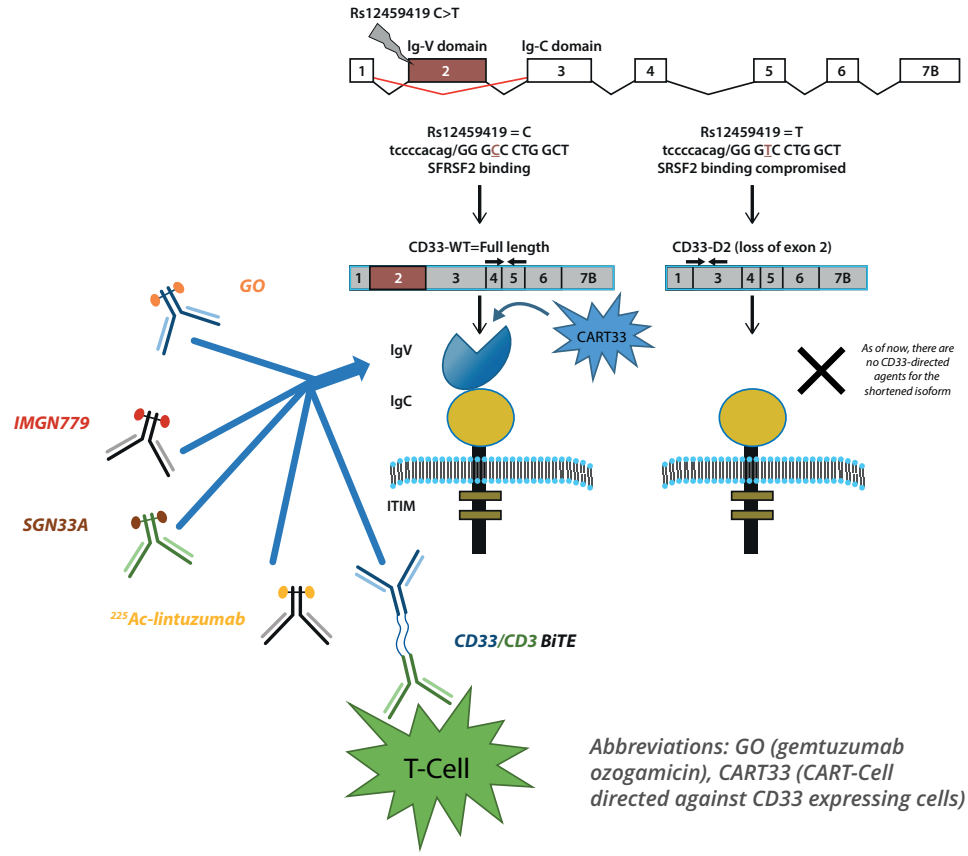
However, despite these efforts, outcomes surrounding the disease remain abysmal. In particular, for younger patients, complete remission (CR) rates of greater than 80% are achievable, however, the 5-year overall survival (OS) still remains relatively low at ~40% in comparison to other cancers due to 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

Mohammed Gbadamosi

Jatinder Lamba

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.

References

1. Dombret, H. & Gardin, C. An update of current treatments for adult acute myeloid leukemia. Blood 127, 53–62 (2016).
2. Thein, M. S., Ershler, W. B., Jemal, A., Yates, J. W. & Baer, M. R. Outcome of older patients with acute myeloid leukemia: An Analysis of SEER Data over 3 Decades. Cancer 119, 2720–2727 (2013).
3. Paul, S. P., Taylor, L. S., Stansbury, E. K. & McVicar, D. W. Myeloid specific human CD33 is an inhibitory receptor with differential ITIM function in recruiting the phosphatases SHP-1 and SHP-2. Blood 96, 483–90 (2000).
4. Ravetch, J. V & Lanier, L. L. Immune inhibitory receptors. Science 290, 84–89 (2000).
5. Hamann, P. R. et al. Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody - Calicheamicin conjugate for treatment of acute myeloid leukemia. Bioconjug. Chem. 13, 47–58 (2002).
6. Bross, P. F. et al. Approval summary: Gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin. Cancer Res. 7, 1490–1496 (2001).
7. Castaigne, S. et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): A randomised, open-label, phase 3 study. Lancet 379, 1508–1516 (2012).
8. Petersdorf, S. H. et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood 121, 4854–4860 (2013).
9. Sutherland, M. S. K. et al. SGN-CD33A: a novel CD33-targeting antibody–drug conjugate using a pyrrolobenzodiazepine dimer is active in models of drug-resistant AML. Blood (2013). doi:10.1182/blood-2013-03-491506
10. Kovtun, Y. et al. IMGN779, a Novel CD33-Targeting Antibody-Drug Conjugate with DNA Alkylating Activity, Exhibits Potent Antitumor Activity in Models of AML. Mol. Cancer Ther. (2018). doi:10.1158/1535-7163.MCT-17-1077
11. Jurcic, J. G. et al. Phase I Trial of the Targeted Alpha-Particle Nano-Generator Actinium-225 (225Ac)-Lintuzumab (Anti-CD33; HuM195) in Acute Myeloid Leukemia (AML). Blood 118, 768 (2011).
12. Jurcic, J. G. et al. Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML). Blood 128, 4050 (2016).
13. Aigner, M. et al. T lymphocytes can be effectively recruited for ex vivo and in vivo lysis of AML blasts by a novel CD33/CD3-bispecific BiTE antibody construct. Leukemia 27, 1107–1115 (2013).
14. Kenderian, S. S. et al. CD33-specific chimeric antigen receptor T cells exhibit potent preclinical activity against human acute myeloid leukemia. Leukemia 29, 1637–1647 (2015).
15. Lamba, J. K. et al. CD33 splicing polymorphism determines gemtuzumab ozogamicin response in de novo acute myeloid leukemia: Report from randomized phase III children's oncology group trial AAML0531. J. Clin. Oncol. 35, 674–2682 (2017).

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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.

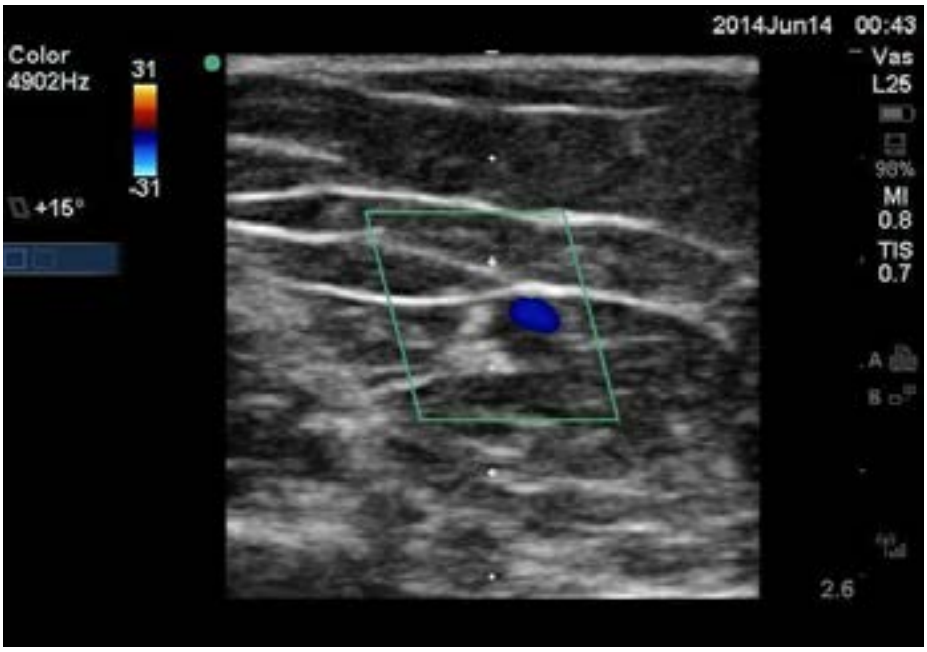

Figure 1: Short axis view of a peripheral vessel visualised with Colour Doppler (blue). The scale on the right of the screen demonstrates a total depth of 2.6 cm. A guide (white dots) in the centre of the screen marks each 0.5cm of depth. Therefore the depth of the vessel is between 1-1.5cm deep to the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

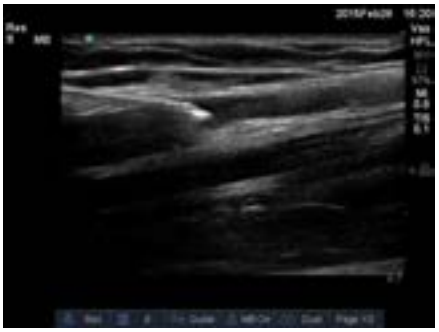

Figure 2: Long axis view of a peripheral vessel. The hyperechoic needle is visualized approaching from the top left of the screen into the vessel lumen.

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

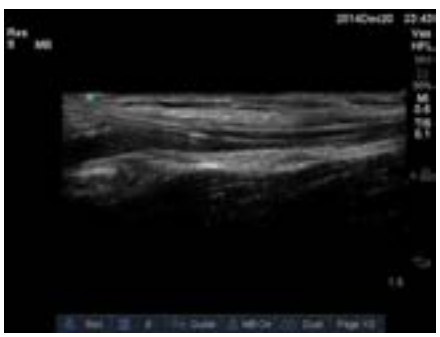

Figure 3: In this long axis view of a peripheral vessel the catheter has been threaded and is seen within the lumen of the vessel.

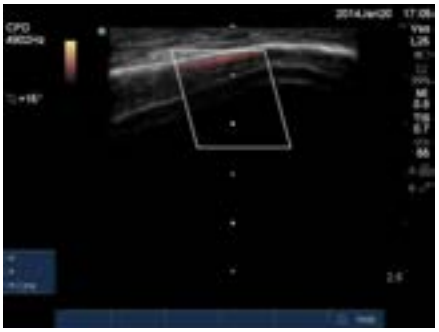

Figure 4: Power Doppler (orange) confirms placement of an intraosseus line within the distal tibia. The bright white line of the tibia cortex (in long axis view) is visualised at the top of the screen, with flow confirmation from a 10cc saline flush immediately distal (below) to the hyperechoic cortex.

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/

References:

1 Fields, J.M., Piela, N.E., Au, A.K., Ku, B.S., Risk factors associated with difficult venous access in adult ED patients. Am J Emerg Med. 2014 Oct; 32(10):1179-82.

2 Au, A.K., Rotte, M.J., Grzybowski, R.J., Ku, B.S., Fields, J.M., Decrease in central venous catheter placement due to use of ultrasound guidance for peripheral intravenous catheters. Am J Emerg Med. 2012 Nov;30(9):1950-4.

3 Schoenfield, E., Shokoohi, H., Boniface, K. Ultrasound-guided peripheral intravenous access in the emergency department: a patient-centered survey. West J Emerg Med. 2011 Nov;12(4):475-7.

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Regenerative medicine to trump cancer

A group of academic experts from the U.S. and the UK share their views on effective regenerative medicine-based strategies against cancer

Among vertebrates, adult urodele amphibians retain the capability to regenerate complex structures such as limbs, tail, jaws, eyes and a variety of internal organs following an insult[1]. Similarly, but with a more limited potential, reptiles possess the capability to regrow a fraction of their tail dropped as a self-defence mechanism to elude a predator's grasp. The strategies used by these highly regenerative organisms to restore organ function typically involve the crucial role of connective tissue-associated fibroblasts that undergo de-differentiation[2].

The undifferentiated phenotype acquired by resident fibroblasts is the source of a complex embryonic structure called blastema, where the correct pattern for tissue growth is ensured by the positional identity of every single cell and by the continuous interplay between neighbouring cells[3]. This means that a precise recapitulation of specific embryonic developmental steps is required for successful tissue regeneration. Pro- and anti-inflammatory signals are timely induced following an insult, for instance, axolotl limb amputation and sustained throughout the process of regeneration, due to the transient presence of macrophages[4].

This precise process is perpetuated until tissue restoration is completed and most interestingly, without incurring abnormalities or genetic aberrations. Rather, it has been observed that such a regeneration-permissive environment can reverse tumorigenicity by reprogramming tumour cells[5]. As an example, the administration of chemical carcinogens induces cancer in regeneration-incompetent tissues (i.e. the newt dorsal iris), but not in those capable of regeneration (i.e. the newt ventral iris)[6]. Specifically, despite a low frequency, malignant transformations can be observed together with the formation of invasive epithelial tumours, this phenomenon is generally followed by spontaneous remission as tumour cells are induced to reorganise into non-cancerous tissues[7].

We thus hypothesise that the adult mammal's susceptibility to cancer development has been determined by the loss of an advanced regenerative capability during the course of evolution, with the consequent lack of an associated control system. A better understanding of this evolutionary process can help conceive effective regenerative medicine-based strategies against cancer.

In adult mammals, only a rudimentary regenerative potential is evident in the form of quiescent cells, known as endogenous stem cells, because this feature is not sufficient to spontaneously regenerate a whole functional organ following an injury. On the other hand, we think that mammalian embryos keep the memory of the ancestors, as the controlled series of processes that resemble blastema formation described in amphibians are identified during embryonic tissue development as well. To state some common characteristics, embryos harbour an enormous number of undifferentiated cells, with a great proliferation rate, specific differentiative potential and a proper identity leading to morphogenesis (see Figure 1)[8].

Similar to the blastemal environment of urodeles, the mammalian embryonic environment critically supports normal tissue development and precludes malignant transformations. In fact, besides the more efficient and frequent DNA repair mechanisms active in embryonic cells, other processes including apoptosis and senescence have also been reported as recurrent tumour suppressive systems acting to functionally remove cells at a risk of aberrant growth during embryogenesis[9].

The above mentioned transient mechanisms, with characteristics that disappear at birth, have also been associated with the recruitment of macrophages for the clearance of suppressed cells[10]. The latter aspect is of particular interest because the presence of such inflammatory cells to the site of action is essential for the final outcome, whether during tissue regeneration, cancer progression, or morphogenesis.

Like a wound that never heals, neoplastic transformation has been associated with persistent inflammation and abnormal macrophage differentiation[11]. The reactive species produced by these cells (i.e. reactive oxygen and nitrogen species) have been directly linked to an altered DNA repair, apoptosis and/or cell cycle checkpoint control[12]. As a consequence of an impaired wound healing process, chronic inflammation leads to fibrotic scar formation,

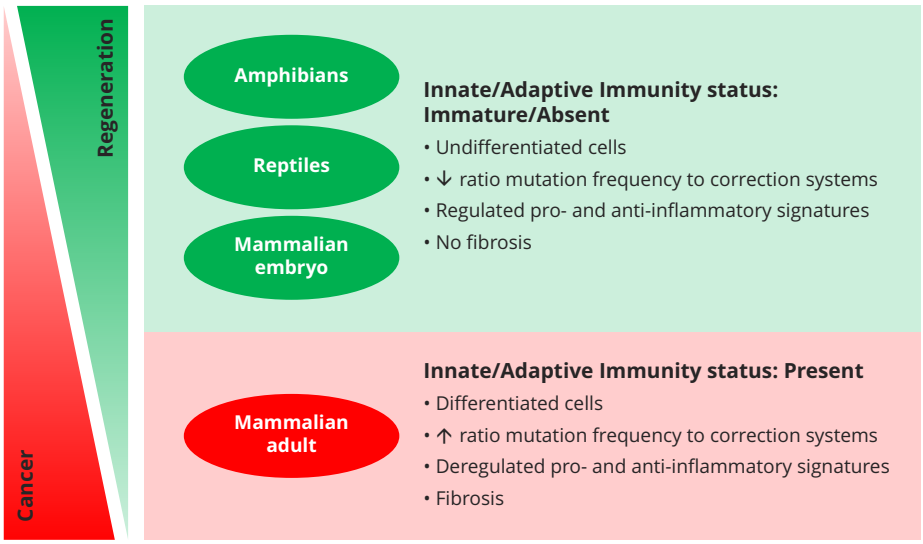

Figure 1: An overview of inter- and intra-specific differences pertinent to tissue regeneration and cancer among regenerative organisms, mammalian embryos and adult tissues. Correction systems include DNA repair, apoptotic processes and senescence.

whose role in tumorigenesis is still under debate. Some researchers consider fibrosis responsible for disruption of the anatomical polarity of a regenerating tissue and consequently for tumorigenesis following an injury, while others contemplate it as an alternative to cancer, thus protecting undifferentiated cells from uncontrolled proliferation that could represent a danger in case of chronic inflammation.

Based on these pieces of evidence, several approaches have been developed in the field of tissue engineering, which aim to reduce inflammation while avoiding scar formation and consequently to improve regeneration[13-15]. Our group recently demonstrated that the implantation of a finely functionalised collagen-based immunomodulatory material was capable of recruiting and modulating macrophage phenotype towards an anti-inflammatory status, therefore, recreating in mammals the pro-regenerative environment described in highly regenerative organisms[16].

On the other hand, conventional tumour-associated macrophages displaying an anti-inflammatory phenotype are potent suppressors of anti-tumour immunity, whereas appropriately activated macrophages have been reported to lead to cancer-related inflammation and kill tumour cells[17].

It becomes clear that within their dual role and multiple functions, macrophages hide the secret behind the uncontrolled tumorigenic condition frequently reported in adult mammals, as well as in the controlled cascade of events leading to embryogenesis. Surprisingly, embryos and highly regenerative organisms lack an established innate and adaptive immunity that is rather observed in animals with a more limited regenerative potential, including mammals, birds and reptiles[18]. The regenerating limb of newts suggests that similar to the role they play in embryogenesis and contrarily in tumorigenesis: macrophages are mainly required to mediate immunosurveillance and the clearance of senescent cells generated during blastema formation[19] and to prevent the lysis of dedifferentiating cells induced by NK cells[20].

In a nutshell, embryonal macrophages know how to create and support the microenvironment needed to guarantee tissue homeostasis and morphogenesis, while keeping it oncosuppressive. Understanding the interactions occurring at a microscopic level in the blastemal and embryonic tissues and keeping in mind the phylogenetically conserved properties between amphibians and mammals, we will be able to develop effective regenerative medicine-based strategies to fight cancer.

References

1 Stocum, D.L. Mechanisms of urodele limb regeneration. Regeneration 4, 159-200 (2017).

2 Odelberg, S.J. in Seminars in cell & developmental biology, Vol. 13 335-343 (Elsevier, 2002).

3 Brockes, J.P. Amphibian limb regeneration: rebuilding a complex structure. Science 276, 81-87 (1997).

4 Godwin, J.W., Pinto, A.R. & Rosenthal, N.A. Macrophages are required for adult salamander limb regeneration. Proceedings of the National Academy of Sciences 110, 9415-9420 (2013).

5 Tsonis, P. Effects of carcinogens on regenerating and non-regenerating limbs in amphibia. Anticancer research 3, 195-202 (1983).

6 Oviedo, N.J. & Beane, W.S. in Seminars in cell & developmental biology, Vol. 20 557-564 (Elsevier, 2009).

7 Fior, J. Salamander regeneration as a model for developing novel regenerative and anticancer therapies. Journal of Cancer 5, 715 (2014).

8 Blau, H.M. & Pomerantz, J.H. Re "evolutionary" regenerative medicine. Jama 305, 87-88 (2011).

9 Pawelec, G., Goldeck, D. & Derhovanessian, E. Inflammation, ageing and chronic disease. Current opinion in immunology 29, 23-28 (2014).

10 Storer, M. et al. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155, 1119-1130 (2013).

11 De Visser, K.E., Eichten, A. & Coussens, L.M. Paradoxical roles of the immune system during cancer development. Nature reviews cancer 6, 24 (2006).

12 Schäfer, M. & Werner, S. Cancer as an overhealing wound: an old hypothesis revisited. Nature reviews Molecular cell biology 9, 628 (2008).

13 Godwin, J.W., Pinto, A.R. & Rosenthal, N.A. in Seminars in cell & developmental biology, Vol. 61 71-79 (Elsevier, 2017).

14 Godwin, J.W. & Rosenthal, N. Scar-free wound healing and regeneration in amphibians: immunological influences on regenerative success. Differentiation 87, 66-75 (2014).

15 Corradetti, B. The immune response to implanted materials and devices. The Immune Response to Implanted Materials and Devices (2017).

16 Corradetti, B. et al. Immune tuning scaffold for the local induction of a pro-regenerative environment. Scientific reports 7, 17030 (2017).

17 Mantovani, A., Allavena, P., Sica, A. & Balkwill, F. Cancer-related inflammation. Nature 454, 436 (2008).

18 Mescher, A.L. Macrophages and fibroblasts during inflammation and tissue repair in models of organ regeneration. Regeneration 4, 39-53 (2017).

19 Yun, M.H., Davaapil, H. & Brockes, J.P. Recurrent turnover of senescent cells during regeneration of a complex structure. Elife 4, e05505 (2015).

20 Godwin, J., Kuraitis, D. & Rosenthal, N. Extracellular matrix considerations for scar-free repair and regeneration: insights from regenerative diversity among vertebrates. The international journal of biochemistry & cell biology 56, 47-55 (2014).

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Working together to treat and prevent Alzheimer's disease and related dementias

Dr Richard Hodes, Director of the National Institute on Aging within the U.S. National Institutes of Health, explores the importance of working together to treat and prevent Alzheimer's disease and related dementias

For some time, scientists have understood that Alzheimer's disease develops by way of a complex cascade of events taking place over time inside the brain. These events, influenced by both genetic and non-genetic factors, contribute to changes in the brain that disrupt functioning and are at the centre of the notorious devastation caused by this mind-robbing disease.

Driven by the growing ageing population at risk for Alzheimer's and related dementias (including Lewy body dementia and frontotemporal dementia) and the staggering costs they impose on individuals, families and society, the sense of urgency to develop an effective treatment has never been greater. Estimates indicate that some 46.8 million people age 60 and older lived with dementia worldwide in 2015, a number expected to grow to 74.7 million people in 2030 and to 131.5 million in 2050 (Prince et al., 2013).

The National Institute on Aging (NIA) at the National Institutes of Health (NIH), which leads the U.S. biomedical research effort on Alzheimer's and related dementias, is spearheading an ambitious research agenda to better understand, diagnose, prevent and treat these diseases, with a goal of finding effective treatments by 2025. Thanks to extraordinary boosts in Congressional appropriations for Federal research in recent years, we can now pursue the answers to many fundamental questions – as well as test some of these hypotheses in translational and clinical studies – that we couldn't address in the not-too-distant past.

We are now better positioned to squarely focus our attention on the heterogeneity of disease – how dementia manifests differently among individuals and across groups – and to set our sights on a precision medicine approach, targeting disease-relevant processes and delivering the right treatments at the right stage of the disease for each person affected. While, ultimately, we want to prevent or slow Alzheimer's disease and related dementias, we are working towards serving the needs of all patients at all stages of the disease.

NIH funding has been applied to a broad multidisciplinary programme where research moves through a pipeline from studies of basic mechanisms to an application in clinical trials and studies. Our efforts are broad and far-reaching, directed to:

- Enabling precision medicine research through advances in genomic sciences and deep molecular phenotyping of existing cohorts and the launch of new diverse cohorts;
- Using an open science research model of the Accelerating Medicines Partnership for Alzheimer's Disease to hasten the discovery of the next generation of therapeutic targets and biomarkers;
- Creating new translational infrastructure programmes to enable rapid sharing of data and research models and enhance research rigour and reproducibility;
- Developing emerging therapeutics in academic centres and in the small business community; and
- Making advances in disease monitoring, assessment and care, powered by the revolution in mobile technology, which are helping us bring in people living with AD/ADRD and their caregivers, as direct partners in research.

Several efforts focus on "open science," a participatory approach to research in which progress is accelerated by making research data, methods and tools available to all qualified investigators. NIH has been taking a leadership role in promoting the broad availability of research data for quite some time. With the rise of big data and new analytical approaches that can help us to better understand human wellness and disease in a person-specific manner, this focus is vital to our progress.

Reflecting from the halfway mark to the 2025 national goal, we recognise more clearly than ever that Alzheimer's disease and related dementias are complex and challenging foes. Yet our scientific capabilities and momentum are growing rapidly. We are closing in on the research advances that may ultimately contribute to an end to a public health crisis that has penetrated the United States and the world in a way that few other conditions have.

> "The National Institute on Aging (NIA) at the National Institutes of Health (NIH), which leads the U.S. biomedical research effort on Alzheimer's and related dementias, is spearheading an ambitious research agenda to better understand, diagnose, prevent and treat these diseases, with a goal of finding effective treatments by 2025."

We also need public support – none of these efforts will be successful unless we engage the public and secure the commitment of people from all walks of life to participate in clinical research.

NIA is uniquely positioned to keep the momentum in discovery going and to push forward not only an agenda but concrete, specific guidance and efforts to turn the tide for the better for millions of affected people – and their families, friends and communities – who need solutions. ■

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Neurodegenerative disorders in the U.S.

The vital work of the National Institute on Deafness and Other Communication Disorders (NIDCD) and The National Institute of Neurological Disorders and Stroke (NINDS) are explored here by Open Access Government, with a special focus on neurodegenerative disorders

By way of an introduction, The National Institute on Deafness and Other Communication Disorders (NIDCD) is part of the National Institutes of Health (NIH) in the United States. NIDCD essentially supports and conducts research in the normal and disordered processes of hearing, taste, smell, voice, balance, speech and language.

Dr Judith Cooper, Ph.D., the current Acting Director, NIDCD sums up the work of the organisation extremely well, which has been running for over 30 years: "The National Institute on Deafness and Other Communication Disorders (NIDCD) has supported basic and clinical research and research training on communication and sensory disorders. As we head toward new frontiers in scientific discovery and precision medicine, the NIDCD is well positioned to support innovative studies to produce more sensitive, effective and individually tailored interventions for communication disorders."

Hearing loss research

The current Acting Director goes on to reveal that the NIDCD's robust programme of basic and clinical research focuses, in part, on the identification of genes involved in hearing loss to lead to earlier diagnosis and treatment, as well as new therapies. These fascinating areas of the NIDCD are explained by Dr Judith Cooper in her own words.

"Nearly 30 million adults in the United States could benefit from using hearing aids, but only one in four has used them. The NIDCD supports innovative clinical and translational research to lay the foundation for making hearing health care more accessible and affordable. Current research includes identifying barriers to care and assessing novel service delivery and screening models.

"Researchers are also applying cochlear implant technology to develop other neural prostheses. These devices will, for example, provide a sense of hearing for people whose auditory nerve is removed or damaged; normalise balance by electrically stimulating the vestibular nerve; and help patients with severe speech and physical impairments express themselves using speech synthesised from brain-computer interfaces."

> "While there is currently no cure for Rett syndrome, treatment today focuses on the management of symptoms, plus medication to treat breathing irregularities and motor difficulties, as well as antiepileptic drugs to control seizures. It is said that occupational therapy, physiotherapy and hydrotherapy may prolong mobility."

Voice, speech and language

Another aspect of NIDCD research aims to improve the identification and treatment of voice, speech and language disorders such as specific language impairment, spasmodic dysphonia and stuttering. On the NIDCD website, Dr Judith Cooper details further aspects of the ongoing research where voice, speech and language are concerned.

"Other ongoing research is focused on ways to improve communication in children with autism spectrum disorder (ASD), including the 25 to 30% of children with ASD who remain functionally non-verbal beyond age five. The NIDCD has long supported the NIH Autism Centers of Excellence Program, which funds large research projects, some of which focus on developing effective interventions to help children with ASD better communicate.

"NIDCD-supported research also addresses voice,

speech, and language impairments linked to injury, stroke, and neurodegenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis (ALS). These communication problems – such as aphasia, dysarthria, and apraxia – often lead to increased isolation and poor quality of life."

Neurodegenerative disorders – Rett syndrome

Picking up on the mention above by Dr Judith Cooper concerning neurodegenerative disorders, we know there is a further example of this because research around Rett syndrome is conducted by The National Institute of Neurological Disorders and Stroke (NINDS) and other institutes of the National Institutes of Health (NIH).

NINDS seeks out fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. On Rett syndrome, for example, we know that the discovery of the gene for this in 1999 provides a basis for further genetic studies in the field. We find out on the NINDS website that understanding the cause of this disorder is essential "for developing new therapies to manage specific symptoms, as well as for providing better methods of diagnosis."

Going into further detail, it is worth pointing out that Rett syndrome is a childhood neurodevelopmental disorder that primarily affects females. The first symptom tends to be the loss of muscle tone and other early symptoms can include a slowing of development, diminished eye contact and problems crawling or walking. As the syndrome progresses, a child will lose the use of their hands and the ability to speak. Unfortunately, the inability to perform motor functions is possibly the most debilitating feature of Rett syndrome, interfering with each body movement, including speech.

While there is currently no cure for Rett syndrome, treatment today focuses on the management of symptoms, plus medication to treat breathing irregularities and motor difficulties, as well as antiepileptic drugs to control seizures. It is said that occupational therapy, physiotherapy and hydrotherapy may prolong mobility. Special equipment and aids such as braces to arrest scoliosis, splints to modify hand movements may be required by some children.

NIH: Supporting basic medical research in the U.S today

Looking at the wider picture, we know that NINDS has a long history of supporting the research and development of gene therapies for neurological disorders and that their work requires a balance of basic, translational and clinical research. The NIH supports most basic medical research in the U.S today, although it is worth mentioning that each NIH Institute and Centre has a well-defined mission with respect to disease, indeed, a number of NIH components support complementary programmes of basic neuroscience research that advance the missions of all concerned.

References

https://www.nidcd.nih.gov/about

https://www.ninds.nih.gov/

https://www.ninds.nih.gov/Disorders/All-Disorders/Rett-Syndrome-Information-Page

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Rett syndrome: Research on severe neurodevelopmental disorders

Jennifer J. McComas, PhD and Alefyah Shipchandler from the University of Minnesota discuss the current state of the evidence for communication intervention for individuals with Rett syndrome

Researchers who investigate habilitative treatments for severe neurodevelopmental disorders rely on human participants agreeing to serve as the subjects of our experiments. Some families consent to participate because they have experienced something like this: they gave birth to a healthy baby and watched that baby hit developmental milestones for the first six or more months of life, only to observe their child, who has developed fine motor and some early vocal language, go through a period of regression in which they lose motor and communication skills.

Without motor and communication skills, it is nearly impossible to know their cognitive abilities, but most experts report cognition is also severely impaired. Although this condition is rare, affecting approximately one in 10,000 girls born worldwide (it is exceedingly rare in boys), it is nevertheless devastating. The neurodevelopmental disorder, now known as Rett syndrome (RTT), was first described by an Austrian pediatrician[1], but for decades, individuals with RTT were misdiagnosed as having autism due to similarities in behavioural phenotype[2]. In 1999, Huda Zoghbi and her colleagues discovered that genetic mutations in the gene MECP2[3,4], located on the X chromosome, cause RTT. Systems that experience impairment often include speech, motor skills, breathing, cardiac function, chewing, swallowing and digestion.

Although extensive research on the genetic basis and medical treatments for RTT in non-human populations has occurred in the past 20 years[5,6,7,8], the goal of that research has been a better understanding of the causal mechanisms, potential treatments and cures for the disorder. Far less experimental research has been conducted in the area of treatment of communication deficits. Yet, while families wait for effective treatment of symptoms or a cure, they are in need of empirically validated interventions that will allow their daughters with RTT to communicate their wants and needs.

Persons with multiple disabilities, including severe physical and communication disabilities, often need assistive technology in the form of augmentative and assistive communication (AAC) devices to communicate. Eye-gaze technology that involves an eye-tracking device and a computer-based programme that produces vocal output is an emerging technology for individuals with severe motor impairments[9] and is increasingly recommended for individuals with RTT[10,11,12].

Despite claims of individuals with RTT using eye-gaze technology to converse with their families[12] and to read[13], there is little published empirical evidence of effective use of eye-gaze devices by individuals with RTT. As such, the National Institute on Deafness and Other Communication Disorders (NIDCD) within the National Institutes of Health (NIH) in the United States, funded our research project designed to develop a reinforcement-based intervention model for addressing the complex communication needs in RTT. As part of that project, we examined the published peer-reviewed empirical literature on the use of a behavioural intervention to teach or improve communication of individuals with RTT and our findings were somewhat surprising.

A systematic search was conducted in the following electronic databases: PsychINFO, PubMed and Academic Search Premier. In all databases, "Rett syndrome" was inserted into the search field along with one of the following: "behavioural + intervention," "communication + intervention," "educational + intervention," "habilitative + intervention," and "augmentative communication," for a total of five search term pairs.

From the resulting 310 publications, chapters, non-peer-reviewed papers (e.g., dissertations) and non-English articles were excluded. In addition, articles that focused on genetics, reports of general characteristics of RTT, medical interventions and interventions conducted with non-human subjects were excluded. Finally, any article in which communication was not reported as a dependent variable or that did not describe a procedure

	Bartolotta et al (2012)	Byiers et al (2014)	Elefant, et al (2004)	Evans et al (1999)	Hetzroni et al (2002)	Koppenhaver et al (2001)	Sigafoos et al (1996)	Simacek et al (2017)	Simacek et al (2016)	Smith et al (1993)	Stasolla et al (2014)	Sullivan et al (1995)	Van Acker et al (1995)	Vessoyan et al (2018)	Wigram et al (2005)	TOTAL
Total (out of 9)	**3/9**	**6/9**	**3/9**	**4/9**	**7/9**	**4/9**	**7/9**	**9/9**	**8/9**	**4/9**	**6/9**	**3/9**	**7/9**	**4/9**	**1/9**	
Context & setting	N	N	N	Y	Y	N	N	Y	Y	N	N	N	Y	Y	N	**6/15**
Participants	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	**15/15**
Intervention agent	N	N	N	N	N	Y	Y	Y	N	Y	N	Y	N	N	N	**5/15**
Description of practice	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	**13/15**
Implementation fidelity	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N	N	**2/15**
Internal validity	N	Y	N	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N	**7/15**
Outcome measures/ dependent variables	N	Y	N	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N	**7/15**
Data analysis	N	Y	N	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N	**7/15**
Conceptualisation	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	**14/15**

Table 1. Rating of each quality indicator for each article

related to teaching or improving a communicative response was excluded. A total of 15 studies were identified for evaluation.

Next, we evaluated each of the 15 studies using the Council for Exceptional Children (CEC): Standards for Evidence-Based Practice in Special Education[14]. In addition, an indicator of conceptualisation underlying the study[15] was included in the review. The CEC's standards for evidence-based practice contain sub-features of each indicator. For an indicator to be considered "met," the study needed to address all the relevant sub-features of the indicator. For example, quality indicator five 'Implementation Fidelity' includes three sub-features pertaining to adherence, dosage and duration[14].

For an indicator to be scored as Yes (Y), all sub-features needed to be adequately addressed. One rater independently evaluated all 15 articles according to the CEC standards, and a second rater independently evaluated eight of the 15 articles using the same criteria. Inter-rater agreement for the nine indicators was 100% across all articles that were evaluated by both raters.

All 15 studies addressed non-vocal forms of communication and targeted either motor responses or eye gaze as their target behaviours, with some including both. Target communicative responses included unaided responses (e.g., signs, gestures) or technology aided responses that involved either low technology (e.g. pictures, micro-switches, 2D symbols, 3D objects) or high technology (e.g., speech generating devices [SGD] activated by eye-gaze). Of the fifteen studies, two studies utilised eye-gaze technology[16,17].

Results of the evaluation of the nine quality indicators for evidence-based practice described by the CEC (#1-8) and research described by Gersten and colleagues (#9) are presented in Table 1. The ratings of the quality indicators varied widely across the 15 studies. All 15 studies met the criteria for describing participants, all but one met the criteria for conceptualisation and all but two met the criteria for describing the practice. Only one study met the criteria for all nine indicators[18] and 1/3 of the studies (five of 15) met the criteria for at least seven

Image: © Leszek Czerwonka | Dreamstime.com

Young girl with Rett syndrome

of the nine indicators. Four studies (1/4) met criteria for three or fewer of the nine indicators.

In our experience, families affected by RTT have been exceptionally generous with their time and energy in voluntarily participating in research projects, despite the challenges they encounter caring for a loved one with severe multiple disabilities. As researchers, we owe it to these families and to our science to conduct rigorous investigations and disseminate our procedures and results in a way that is replicable by other researchers. In our role as reviewers for publication outlets and funding recommendations, we must take stock of the body of evidence and demand continuous improvement in the quality of evidence pertaining to treatment for critical skills such as communication.

In summary, within the body of work to date, the claims vary widely pertaining to the utility of high-technology devices that involve eye-gaze for individuals with RTT. As the field matures, more studies that meet the quality standards of evidence-based practices and research and that improve understanding for whom and under what conditions particular technologies and practices are effective are imperative for continued progress in the field[19,20].

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References

Note: * Indicates the article was included in the review

1 Rett, A. (1966.) [On an unusual brain atrophy syndrome in hyperammonemia in childhood]. Wein Med Wochenschr, 116, 723-6.

2 Percy, A. K. (2011). Rett Syndrome: Exploring the Autism Link. Archives of Neurology, 68, 985-989. http://doi.org/10.1001/archneurol.2011.149.

3 Amir, E. R., Van Den Veyve,r B. I., Wan, M.,Tran, Q. C., Francke, U., & Zoghb,i Y. H. (1999). Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nature Genetics, 23(2), 185-8.

4 Nuzzo, R. (2006). Profile of Huda Y. Zoghbi. Proceedings of the National Academy of Sciences of the United States of America, 103, 3017-3019.http://doi.org/10.1073/pnas.0509604103

5 Gogliotti, R., Senter, R., Fisher, N., Adams, J., Zamorano, R., Walker, A.,... Niswender, C. (2017). MGlu potentiation rescues cognitive, social, and respiratory phenotypes in a mouse model of Rett syndrome. Science Translational Medicine, 9, 1-11.

6 Ghorbel, R., Fendri-Kriaa, R., Ben Salah, N., Belguith, G., Ammar-Keskes, N., Rouissi, L.,... Fakhfakh, N. (2018). First report of an unusual novel double mutation affecting the transcription repression domain of MeCP2 and causing a severe phenotype of Rett syndrome: Molecular analyses and computational investigation. Biochemical and Biophysical Research Communications, 497, 93-101.

7 Na, S. E., Morris, J.M., Nelson, D. E, & Monteggia, M. L. (2014). GABAA Receptor Antagonism Ameliorates Behavioral and Synaptic Impairments Associated with MeCP2 Overexpression. Neuropsychopharmacology, 39, 1946-1954.

8 Percy, A. K., Lane, J., Annese, F., Warren, H., Skinner, S. A., & Neul, J. L. (2018). When Rett syndrome is due to genes other than MECP2. Translational Science of Rare Diseases, 3, 49-53. http://doi.org/10.3233/TRD-180021

9 Borgestig, M., Sandqvist, J., Parsons, R., Falkmer, T., & Hemmingsson, H. (2015). Eye Gaze Performance for Children with Severe Physical Impairments Using Gaze-Based Assistive Technology – a Longitudinal Study. Assistive Technology, 28, 93-102.

10 Djukic A., & McDermott V.M., (2012). Social Preferences in Rett Syndrome. Pediatric Neurology, 46, 240-242.

11 International Rett Syndrome Foundation n.d. https://www.rettsyndrome.org/about-rett-syndrome/communication

12 LaRiviere, J. A. (2015). Eye gaze technology for girls with Rett syndrome: From trials to conversations. Closing the Gap newsletter, 4-13. http://www.dbmhresource.org/uploads/2/2/5/7/22571778/closing_the_gap_lariviere_eye_gaze_december_2014_1.pdf [Accessed August 28, 2018].

13 Fabio, R., Castelli, I., Marchetti, A., & Antonietti, A. (2013). Training communication abilities in Rett Syndrome through reading and writing. Frontiers in Psychology, 4, 911.

14 Cook, B., Buysse, V., Klinger, J., Landrum, T., McWilliam, R., Tankersley, M., Test., D. Council for Exceptional Children: Standards for Evidence-Based Practices in Special Education. (2014). Teaching Exceptional Children, 46, 206-212.

15 Gersten, R., Fuchs, L., Compton, D., Coyne, M., Greenwood, C., & Innocenti, M. (2005). Quality Indicators for Group Experimental and Quasi-Experimental Research in Special Education. Exceptional Children, 71, 149-164.

16 Simacek, J., Reichle, J., & McComas, J. (2016). Communication Intervention to Teach Requesting Through Aided AAC for Two Learners With Rett Syndrome. Journal of Developmental and Physical Disabilities, 28, 59-81.

17 Vessoyan, K., Steckle, G., Easton, B., Nichols, M., Mok Siu, V., & Mcdougall, J. (2018). Using eye-tracking technology for communication in Rett syndrome: Perceptions of impact. Augmentative and Alternative Communication, 1-12. DOI: 10.1080/07434618.2018.1462848.

18 Simacek, J., Dimian, F. A., & McComas, J. J., (2017). Communication Intervention for Young Children with Severe Neurodevelopmental Disabilities via Telehealth. Journal of Autism and Developmental Disorders, 47, 744-767.

19 Chen, S-H. K., & O'Leary, M. (2018). Eye Gaze 101: What Speech-Language Pathologists Should Know About Selecting Eye Gaze Augmentative and Alternative Communication Systems.

20 Townend, G., Peter, M., Smeets, E., Berg, R., Berg, M., & Curfs, L., (2016). Eye Gaze Technology as a Form of Augmentative and Alternative Communication for Individuals with Rett Syndrome: Experiences of Families in The Netherlands. Journal of Developmental and Physical Disabilities, 28, 101-112.

*Bartolotta, T., & Remshifski, P. (2012). Coaching Communication Partners: A Preliminary Investigation of Communication Intervention During Mealtime in Rett Syndrome. Communication Disorders Quarterly, 34, 162-171.

*Byiers, J. B., Dimian, A., & Symons, J. F. (2014). Functional Communication Training in Rett Syndrome: A Preliminary Study. American Journal on Intellectual and Developmental Disabilities, 119, 340-350.

*Elefant, C., & Lotan, M. (2004). Rett Syndrome: Dual Intervention - Music and Physical Therapy. Nordic Journal of Music Therapy, 13, 172-182. 10.1080/08098130409478114.

*Evans, I., & Meyer, L. (1999). Modifying adult interactional style as positive behavioural intervention for a child with Rett syndrome. Journal of Intellectual and Developmental Disability, 24, 191-205.

*Hetzroni, O., Rubin, C., & Konkol, O. (2002). The use of assistive technology for symbol identification by children with Rett syndrome. Journal of Intellectual and Developmental Disability, 2002, 27, 57-71.

*Kopperhaver, A. D., Erickson A. K., Harris, B., McLellan, J., Skotko, S. B., Newton, A. R. (2001). Storybook-based communication intervention for girls with Rett syndrome and their mothers. Disability and Rehabilitation, 23, 149-159.

*Sigafoos, J., Laurie, S., & Pennell, D. (1996). Teaching children with Rett syndrome to request preferred objects using aided communication: Two preliminary studies. Augmentative and Alternative Communication, 12, 88-96.

*Smith, T., Kleystrand, M., Lovaas, O. (1993) Behavioral treatment of Rett's disorder: Ineffectiveness in three cases. American Journal of Mental Retardation, 100, 317-22.

*Stasolla, F., De Pace, C., Damiani R., De Leone, A., Albano, V., & Perilli, V. (2014). Comparing PECS and VOCA to promote communication opportunities and to reduce stereotyped behaviours by three girls with Rett syndrome. Research in Autism Spectrum Disorders, 8, 1269-1278.

*Sullivan, M., Laverick, W., & Lewis, D. (1995). Brief report: Fostering environmental control in a young child with Rett syndrome: A case study. Journal of Autism and Developmental Disorders,25, 215-221.

*Van Acker, R., & Grant, H S. (1995). An Effective Computer-Based Requesting System for Persons with Rett Syndrome. Journal of Childhood Communication Disorders,16, 31-38.

*Wigram, T., & Lawrence, M. (2005). Music therapy as a tool for assessing hand use and communicativeness in children with Rett Syndrome. Brain and Development, 27, S95-S96.

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Cutting-edge technology synergy in the personalised nanomedicine space: Focus on 3D printing nanomedicines

Cecilia Van Cauwenberghe from Frost & Sullivan's TechVision Group explains the role of cutting-edge technology synergy in the personalised nanomedicine space, with a special focus on 3D printing nanomedicines

When it comes to understanding cutting-edge technology synergy, let's start by looking at how 3D printing is meeting nanotechnology.

Two-photon polymerization (TPP) based 3D printing technology revolutionised many industries by allowing printing objects at nanoscale resolution. By using a near-infrared femtosecond laser, TPP-based 3D printing technique solidifies photoresist for the assembly of ultra-precise 3D nanostructures. In fact, it is the laser power that determines the final resolution, along with the exposure time and the efficiency of TPP initiators. According to a very recent publication (Zhu et al., 2018), the principal challenge to a broader spectrum of biomedicine applications of this technology is associated with the ease of aggregation and precipitation of nanomaterials when they are used in printable inks, hence demanding complex stabilisation procedures. Most active pharmaceutical ingredients (APIs), especially new chemical entities (NCEs), exhibit poor solubility. Therefore, overcoming solubility issues by using new technologies such as nanotechnology appears promising.

How is 3D printing empowering nanomedicine?

Inkjet printing and drug nanonization procedures have been successfully combined at the research level (Cheow et al., 2015). Similarly, various nanosuspensions have been utilised as inks in two well-renowned research studies (Palo et al., 2015; Pardeike et al., 2011). However, a more recent review (Preis and Rosenholm, 2017) comments that although in all these cases, the active agents have been formulated as a nanosuspension, even more advantages could arise by incorporating the agent into a nanocarrier, further formulated into an ink for 3D printing of high precision, personalised therapeutics. According to the authors, the utilisation of nanostructures as drug carriers, along with the simultaneous incorporation of a stabiliser in the ink, can facilitate printability.

> "3D printing has allowed the generation of a broad spectrum of customised implants, principally spinal and craniofacial implants, as well as, cardiovascular stents. Similarly, this technology has also facilitated the generation of multiple cell types via 3D bioprinting by originating a variety of cell patterns in a restrained space, while preserving cell function and viability within the printed construct."

Printers designed for bioprinting are usually pressure regulated, instead of thermally or piezo-electrically regulated to avoid damage on thermo-labile ingredients. Nevertheless, more sensitive substances, such as biomolecules, can be affected, even by shear forces. Therefore, the incorporation of these molecules into a nanocarrier can significantly enhance bioavailability and stability during print processing (Giner-Casares et al., 2016).

How is 3D printing supporting regenerative medicine?

3D printing technology is paving the way for personalised medicine by enabling individual configuration (Shafiee and Atala, 2016). 3D printing technology is being widely used to create biofunctional scaffolds, in which nanocarriers are introduced for monitoring and control of stem cell behaviour after transplantation

(Rosenholm et al., 2016). Moreover, the same approach can be used to design personalised drug-eluting implants through the creation of a biomimetic bone-specific environment (Van Cauwenberghe, 2015).

Therefore, 3D printing technology can be used to mimic different biological microenvironments that may potentially function as powerful tools for studying cancer metastasis and assessing drug response sensitivity, among many other applications. Interestingly, fluorescent nanoparticle inks can be used as biomarkers or labels to enhance biomedical imaging techniques. 3D printing has allowed the generation of a broad spectrum of customised implants, principally spinal and craniofacial implants, as well as, cardiovascular stents. Similarly, this technology has also facilitated the generation of multiple cell types via 3D bioprinting by originating a variety of cell patterns in a restrained space, while preserving cell function and viability within the printed construct.

Final remarks

The future landscape for 3D printed nanomedicines is a revealing perspective. The development of highly sophisticated drug delivery platforms and realistic diagnostic systems that enable the delivery of precise and personalised medicine solutions is certainly being energised by the introduction of 3D printing technologies. Printable nanomedicines are expected to have a major impact on the nanomedicine market over the coming two to three years. The regenerative medicine space has been substantially energised with the advent of stem cells. 3D printing platforms constitute promising tools due to their ability to conform structures and devices with atomic- scale precision and accuracy. Fundamental building blocks are able to fold, join, build and grow by themselves, perfectly well-matched to building nanostructures. Binding can be specifically tailored so that customised parts can be combined to bind with each other and construct exotic structures. Novel techniques focus on printing a grid-like 3D structure laden with stem cells to enhance the discovery of personalised nanomedicines is something that has gained an increased amount of attention.

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References

1 Cheow, W.S., Kiew, T.Y. and Hadinoto, K., 2015. Combining inkjet printing and amorphous nanonization to prepare personalized dosage forms of poorly-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics, 96, pp.314-321.

2 Giner-Casares, J.J., Henriksen-Lacey, M., Coronado-Puchau, M. and Liz-Marzan, L.M., 2016. Inorganic nanoparticles for biomedicine: where materials scientists meet medical research. Materials Today, 19(1), pp.19-28.

3 Palo, M., Kolakovic, R., Laaksonen, T., Määttänen, A., Genina, N., Salonen, J., Peltonen, J. and Sandler, N., 2015. Fabrication of drug-loaded edible carrier substrates from nanosuspensions by flexographic printing. International journal of pharmaceutics, 494(2), pp.603-610.

4 Pardeike, J., Strohmeier, D.M., Schrödl, N., Voura, C., Gruber, M., Khinast, J.G. and Zimmer, A., 2011. Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. International journal of pharmaceutics, 420(1), pp.93-100.

5 Preis, M. and Rosenholm, J.M., 2017. Printable nanomedicines: the future of customized drug delivery?

6 Rosenholm, J.M., Zhang, J., Linden, M. and Sahlgren, C., 2016. Mesoporous silica nanoparticles in tissue engineering–a perspective. Nanomedicine, 11(4), pp.391-402.

7 Shafiee, A. and Atala, A., 2016. Printing technologies for medical applications. Trends Mol. Med. 22 (3), 254–265.

8 Zhu, W., Webster, T.J. and Zhang, L.G., 2018. How can 3D printing be a powerful tool in nanomedicine?

9 Van Cauwenberghe, C., 2015. Trends in Nanomedicine - Nano-based science paving the precision medicine era. Frost & Sullivan TechVision Analysis. D6C0.

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The regenerating spiny mouse and its potential for human therapy discovery

Discovering cures for human diseases or how to recover from damage or trauma to tissues is the fundamental goal of medical researchers, but it is a daunting task. Nevertheless, recent studies have shown the remarkable potential of the spiny mouse in addressing these crucial issues

How can we induce the regrowth of myelin to stop the debilitating effects of multiple sclerosis? How can we induce the regeneration of cardiomyocytes after a heart attack or the regrowth of axons after spinal cord damage?

The classical approach to this regrowth problem in mammals is to study a model organism that can recover from this type of degeneration or trauma and learn how they do it.

Following the hypothesis that regenerative mechanisms are conserved throughout the vertebrates, we could then extrapolate these finding to develop therapies for humans. Traditionally, lower vertebrates such as zebrafish, newts and salamanders have provided model systems with which to study tissue regeneration and many important insights have come from these studies. However, we have recently discovered an adult mammal that can already regenerate several of its tissues and organs, so studying this organism will allow us to speed up the therapeutic discovery process.

This organism is the spiny mouse of the genus *Acomys*. We have shown that it can perfectly regenerate a hole punched through the ear and after removing large pieces of skin. In these instances, the epidermis, dermis, hairs, sebaceous glands, erector pili muscles, cartilage and skeletal muscle of the panniculus carnosus regenerate.

The skin can also regenerate perfectly after a burn injury, the kidney and spinal cord have greatly reduced fibrosis after damage, which permits improved recovery, and so does the heart after a myocardial infarction.

The spiny mouse can thus regenerate each of the three types of muscle: smooth, skeletal and cardiac and here I describe the circumstances under which this may provide some important avenues for extrapolation to humans.

Smooth muscle: In the dermis, there are two structures that contain smooth muscle cells, namely the vasculature and the muscles that raise hairs when we are cold or frightened.

Cutting out a piece of skin removes both of these smooth muscle tissues (erector pili muscles Fig 1A stained with smooth muscle actin) and in the spiny mouse, the newly regenerated skin contains both of these structures, which have regenerated anew (regenerated erector pili muscle Fig 1B).

The lab mouse (or human) only scars and no hairs are regenerated so there will obviously be no regeneration of these erector pili muscles. This suggests that in the spiny mouse, the regeneration of smooth muscle erector pili muscles is induced by the new hair follicles and unravelling the molecular mechanisms (for example, which growth factor induces smooth muscle differentiation) and cellular origin (dermal fibroblasts or hair follicle stem cells) will be an important avenue for further discovery. This may lead to ideas for treatments for diseases in which there is smooth muscle degeneration in the lung, the gut or the bladder, for example.

Skeletal muscle: When the full thickness skin is removed, the skeletal muscle layer at the bottom of the skin, known as the panniculus carnosus, is also removed. This type of injury, where a hole is created in skeletal muscle, normally creates permanent damage in mammals because skeletal muscle needs a connective tissue sheath to induce or guide its regeneration. This is known as a volumetric muscle loss.

This defect is not regenerated in the lab mouse but in the spiny mouse, amazingly, the defect is regenerated and embryonic myosins and other myogenic transcription factors are induced again in a recapitulation of development (Fig 1C). Being able to induce the regeneration of a volumetric muscle loss in humans after trauma would be of major significance.

Lab mouse skeletal muscle can regenerate, however, if the connective tissue surrounding the muscle fibres is not removed and the muscle is

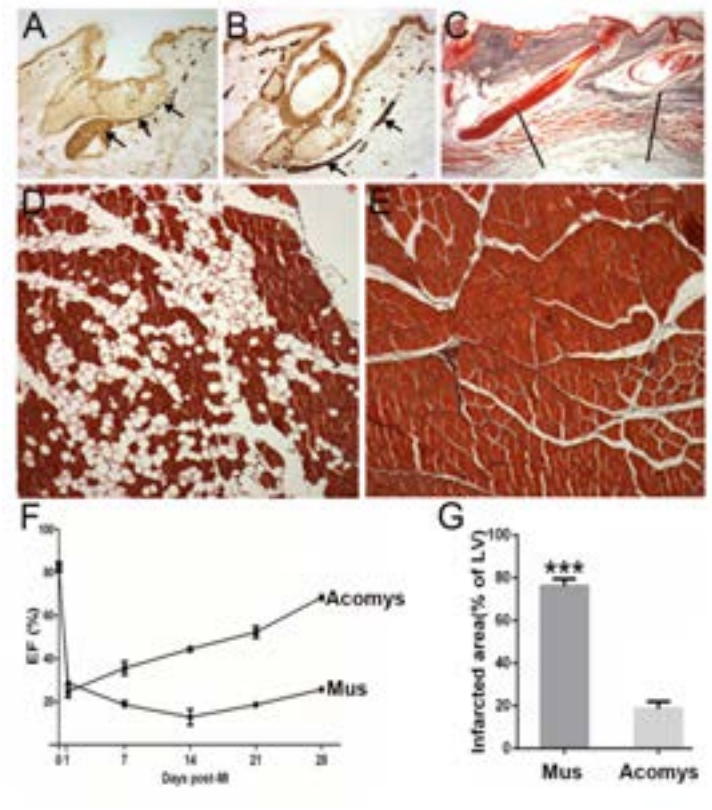

Fig. 1. **A**. Section of a normal hair follicle in spiny mouse skin stained with a smooth muscle actin antibody showing the erector pili muscle (arrows). **B**. Section of a regenerated hair follicle in the centre of a spiny mouse wound stained with a smooth muscle actin antibody showing the regenerated erector pili muscle (arrows). **C**. Section through the regenerated skin (day 35) of a spiny mouse wound showing the regenerated panniculus carnosus skeletal muscle (between the black lines). **D**. Structure of lab mouse tibialis anterior skeletal muscle after five repeated rounds of regeneration. Many muscle fibres have failed to regenerate and instead produced fat cells. **E**. Structure of spiny mouse tibialis anterior muscle after the same five regeneration events. The muscle has regenerated perfectly. **F**. Ejection fraction measurements over four weeks after myocardial infarction in spiny mouse (Acomys) and the lab mouse (Mus). The *Mus* heart shows no recovery of EF and is permanently damaged by the infarc, but the *Acomys* data shows a good recovery to near-normal EF levels by 28 days. **G**. The size of the scar area in the *Mus* and *Acomys* ventricle wall following an MI. There is clearly a very much reduced damaged area in *Acomys* compared to *Mus*.

injected with snake venom. Under these conditions, the skeletal muscle stem cells, the satellite cells, proliferate and redifferentiate back into myonuclei.

When we repeat this regenerative process five times then the lab mouse muscle starts to fail in its regenerative capacity, probably because it runs out of stem cells and gradually replaces the muscle fibres with fat tissue (Fig 1D).

In contrast, the spiny mouse muscle after repeated rounds of regeneration will continue to perfectly replace myofibres without any signs of fat tissue (Fig 1E).

In the disease of muscular dystrophy, the affected muscles are in a permanent state of regeneration and the myofibres gradually fail to be replaced by more muscle and fat regenerates instead exactly in the case of the repeated regenerating lab mouse (Fig 1D). As a result of the replacement of myofibres with fat, the performance of the muscle in humans declines over time and produces the terrible muscular wasting we see with this disease. Learning how to perfectly regenerate muscle fibres repeatedly as the spiny mouse can (Fig 1E) may have important implications for the treatment of muscular dystrophy.

Cardiac muscle: Following a myocardial infarction (heart attack), the lab mouse and the human heart undergoes a wave of cardiomyocyte cell death and the fibroblasts at the damaged site lay down a collagenous scar. The result is a reduced pumping power, measured as ventricular ejection fraction (Fig 1F).

In an attempt to counteract this loss, the remaining ventricle wall thins and expands, making itself much more liable to a further damage.

Remarkably, the spiny mouse heart after a myocardial infarction rapidly recovers its pumping performance in terms of the ejection fraction (Fig 1F) and there is a vastly reduced scar present at the site of damage (Fig 1G). It effectively regenerates its cardiomyocytes after a heart attack and discovering the molecular basis of this would have a huge impact on human health as this is the biggest killer in the Western world.

We can see that the adult spiny mouse is a remarkable animal model that can regenerate each of its three types of muscle, as well as more complex structures. Discovering the reason for this property may provide some answers to very significant human healthcare problems.

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Warnings and forecasts of hazardous tropical weather in the United States

In this special interview, Dr Michael Brennan, Branch Chief at the Hurricane Specialist Unit within the National Hurricane Center (NHC) speaks to us about their work in issuing the best watches, warnings, forecasts and analyses of hazardous tropical weather, including hurricanes

Michael Brennan, PhD, is the Branch Chief of the Hurricane Specialist Unit at the National Oceanic and Atmospheric Administration's (NOAA's) National Hurricane Center (NHC) in Miami, United States (U.S.). The Hurricane Specialist Unit issues tropical cyclone forecasts and warnings for the Atlantic and Eastern North Pacific hurricane basins.

Dr Brennan served as a senior hurricane specialist at NHC from 2008 to 2018, a position where operational duties include the issuance of the track, intensity and wind radii forecasts and associated watches and warnings for tropical cyclones. Dr Brennan's current research interests include quantifying the impact of supplemental observations on model forecasts of tropical cyclone track and intensity. He also conducts training on a variety of topics related to tropical cyclones as well as forecast uncertainty and messaging. Dr Brennan also serves as a reviewer for several scientific journals and is currently an associate editor for the AMS journal Weather and Forecasting.

In this fascinating interview, he explains to us the work the NHC on the very latest hazardous tropical weather systems, including their science-based environmental predictions delivered to the U.S. and the global community. He also shares something of their mission to save lives, mitigate property loss and improve economic efficiency by issuing the best watches, warnings, forecasts and analyses of hazardous tropical weather that occur within the North Atlantic and eastern North Pacific basins.

We discover that these areas are monitored constantly for signs of cyclone development and once a tropical cyclone forms, NHC issues an advisory package, which is their standard forecast of the track and intensity of the storm out to five days and the forecast of how big the storm out is to three days. NHC issues that every six hours, so it is constantly updated with the latest data and model information. Dr Brennan then develops this crucial aspect of NHC's work.

"Within this, the human forecaster still has a very significant role in the forecast process, which they do by analysing the storm and its current state and providing that information as input it into numerical models. NHC forecasters try to maintain continuity with our previous forecasts as much as possible so that we provide users with a consistent forecast that evolves over time in a predictable way."

The conversation then moves to explore Dr Brennan's observations on the type of science-based environmental predictions NHC delivers to the U.S. and the global community, a point he keenly explains to us in his own words.

"We start off by forecasting tropical cyclone formation and make probabilistic forecasts four times a day, every six hours and we provide two probabilities. The first is that the system will go and become a tropical cyclone over the next 48 hours and then over the next five days.

"That approach is mainly based on observational data, satellite imagery, what we see in other observations such as ships, weather balloons, radar or aircraft data, for example. Numerical weather prediction model guidance can provide information about whether a particular system will go on and develop or what the environment looks like in terms of large-scale conditions

Image courtesy of Mike Trenchard, Earth Sciences & Image Analysis Laboratory, Johnson Space Center.

From his vantage point high above the earth in the International Space Station, Astronaut Ed Lu captured this broad view of Hurricane Isabel

being favourable for a system to go on and form or not.

"Once we identify a tropical cyclone, the prediction we make of the track and intensity of the storm are heavily dependent on numerical modelling. This modelling has made great scientific advancements during the last 20 to 30 years in terms of forecasting the circulation of the atmosphere and the tropical cyclone track. This is largely due to the progress that has been made with numerical modelling to analyse the current state of the atmosphere through smarter ways of using observations, especially with satellites."

Dr Brennan adds that with all of the interaction between the atmosphere and the ocean, a tropical storm or hurricane will extract heat from the ocean, so there is an interplay here that has to be captured to forecast intensity. In terms of improving intensity forecasts, this is an area where less progress is being made, but during the last decade or so hurricane research has certainly progressed and intensity forecast errors have decreased. This is an important point that Dr Brennan details further to us.

"The Hurricane Forecast Improvement Project [(1)] follows on from the 2004/05 hurricane season, after which Congress made a major investment in numerical modelling and research to try and improve intensity forecasts. We are seeing progress in this area now, even though we are not where we want to be, but one of the biggest challenges we face here is rapid intensification or weakening where the storm strengthens or weakens.

"For example, in the 2017 season in the Atlantic basin, we had 39 instances of rapid intensification within the first 24 hours of the forecast period, and we were able to successfully forecast six of those 39. 10 years ago, that number of successful forecasts would probably have been zero."

Continued on page 41 ➔

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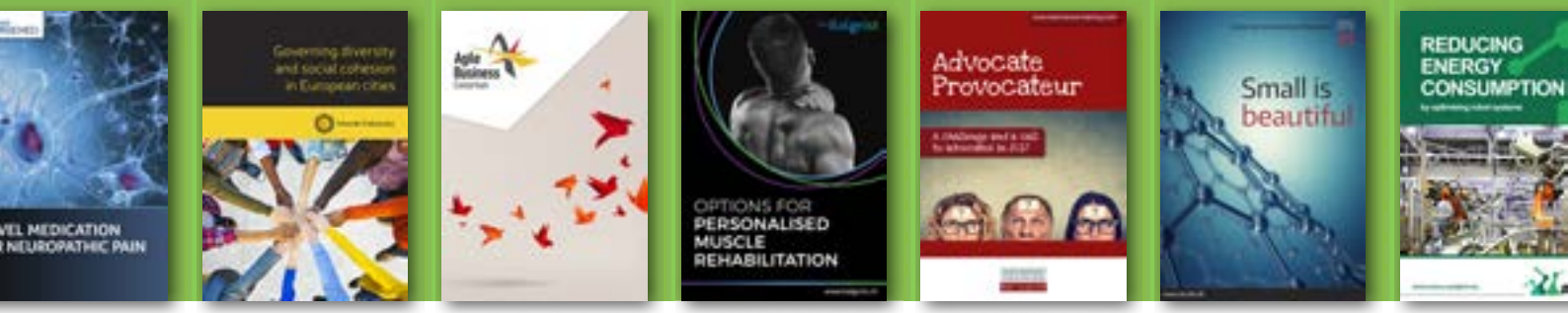

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← *Continued from page 39*

The NHC's mission

In essence, the NHC's mission is to make better forecasts for tropical storms and hurricanes, save lives, mitigate property loss and improve economic efficiency, Dr Brennan is keen to elaborate on these areas. He explains that many populations live in hurricane-prone areas, such as on islands or at coastal location areas and are, therefore, vulnerable to the effects of storm surge, wind and heavy rainfall. He also details NHC's work in outreach on training, in terms of helping communities to be prepared for adverse weather.

"A big part of NHC's job is not just to make forecasts, but to communicate aspects of our work, as well as training the emergency management community to use the information we provide to enable them to make the best decisions they can when it comes to evacuation.

"Another aspect of our work is helping communities to know what their level of risk is when it comes to storm surge, for example, which is the push of water from the ocean by the hurricane winds onto land. It is what drives most evacuation decisions in the U.S. when it comes to a hurricane.

"Our modelling work is helping communities to reassess their risk from a storm surge, so they can develop evacuation zones so they can map out, plan and have evacuation routes and shelters plus determine how much time they need to get people out."

Dr Brennan tells us that warnings are typically issued 36 hours before tropical storm force winds arrive, but for some communities, evacuation decisions are made three or four days in advance of the storm, depending on how many people they have to move, how far they have to go and where they are all going to go.

In closing, Dr Brennan stresses that hurricanes are events which can change communities for generations to come. For example, look at what happened at the Caribbean islands, including Puerto Rico, which were devastated by tropical cyclones in 2017, Dr Brennan outlines. The importance of all inhabitants of areas that can be affected by tropical storms and hurricanes to be prepared is a crucial point, Dr Brennan argues.

> "Within this, the human forecaster still has a very significant role in the forecast process, which they do by analysing the storm and its current state and providing that information as input it into numerical models. NHC forecasters try to maintain continuity with our previous forecasts as much as possible so that we provide users with a consistent forecast that evolves over time in a predictable way."

"While the forecast has gotten better, we still have a very large number of people that are vulnerable to tropical storms and hurricanes in the Atlantic Basin, so our mission is to make the best forecast possible. We also need to help people to be as prepared as much as possible before a storm, to protect them, so they know what their vulnerability and risk are.

"It is important to have a plan in place for what they are going to do when a storm approaches, well in advance. This is important because hurricane apathy sets in quite quickly in areas that have not been affected by hurricanes, but everybody has to be prepared for what could happen every year." ■

[1] www.hfip.org

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Hurricane hazards and climate science research in the U.S.

Ning Lin, Associate Professor at Princeton University's Dept. of Civil & Environmental Engineering details her fascinating research on hurricane and climate science by refining methods in risk analysis in this in-depth interview

The experience of Prof Ning Lin from Princeton University is very impressive in terms of her published work and research interests. She is currently leading a multi-year multi-institutional National Science Foundation (NSF) projection on hurricane hazards and risk analysis. She also has an NSF CAREER project on hurricane hazard modelling and application to engineering structure design considering climate change.

In this interview, she reveals her thoughts on research into hurricane and climate science by refining methods in risk analysis. We know that Ning Lin's theoretical risk assessment framework combines physical data with statistics to simulate storms' activity, hazards and risk. This approach projects future hurricane risk and investigates the same from a historical perspective. Prof Ning Lin also describes her research on developing multi-hazard vulnerability models to better predict the damage of hurricane wind and storm surge to residential communities.

Hurricane hazards and risk analysis research

As the interview beings, Prof Ning Lin introduces us to her work on hurricane and climate science by refining methods in risk analysis. Her research group aims to establish a physics-based probabilistic TC risk assessment framework that integrates the analysis of storm activity, hazards, and risk. She explains that they employ a holistic approach to study the impact of climate change on hurricanes, wind, surge and rainfall hazards induced by hurricanes, as well as public policy.

Due to the limitation of historical records and the complexity of the problem, Prof Ning Lin's group apply physics-based statistical methods to their work. This way, large numbers of synthetic but physically possible storms, characterised by their various track, intensity, and size are simulated (with their annual frequencies estimated), under observed or climate-model projected future climate conditions. The hazards induced by the storms are then estimated, to a large extent, with physical models.

Prof Ning Lin observes that this approach has its advantages. One is that while hurricanes often produce multiple hazards such as extreme winds, storm surge and heavy rainfall it is difficult to perform a direct statistical analysis to estimate the joint probability of such events, as the data is very limited, particularly for specific locations. The physics-based approach can generate a large number of physically correlated hazard events for more reliable statistical analysis. The other advantage is that, unlike the direct statistical method, a physics-based approach does not assume that the climate is stationary and so it can be better applied in the context of a changing climate.

Developing multi-hazard vulnerability models

The conversation then moves to her work on refining vulnerability models that describe the damage to coastal communities under the joint forces of strong wind, storm surge, and rainfall flooding. Prof Ning Lin's research into hazards and vulnerabilities is unique because it specifically models the physical correlation of hurricane hazards (strong wind, storm surge and heavy rainfall) and thus their joint impact. In this vein, it can be applied to policymaking, including urban planning and federal and insurance bodies in coastal risk mitigation, because they need to find systematic strategies to be ready for any potential hazards. Prof Ning Lin explains this further and details her research in this area.

"Recent disasters, such as Hurricanes Sandy, Harvey, and Irma underscore the significant vulnerability of the U.S. to hurricanes. We investigated the structural damage caused by these hurricanes and developed vulnerability models, which describe the relationship between damage severity and hazard intensity. Then we can combine, on one hand, the hazard information and on the other, vulnerability information to quantify the risk. Along with my colleagues, we are seeking solutions to predict and prepare for these events.

"In terms of policymaking, the federal government in the U.S. has a policy in place on flooding but there are various issues there that could be improved. Together with Howard Kunreuther of Wharton risk centre at the University of Pennsylvania, we are trying to work with policymakers in the National Flood Insurance Program to better account for the effect of climate change so that the policy as a tool will better support coastal communities.

"We are also working with policymakers in New York City, through the New York City Panel on Climate Change (NPCC), to ensure that they have up-to-date knowledge on hurricane hazards and climate change, so they can use that information to develop policy, for example, in the area of construction.

Work with the National Science Foundation (NSF)

Turning to her work with the NSF, one example of this is Hazard SEES: An Integrated Approach to Risk Assessment and Management in Responding to Land Falling Hurricanes in a Changing Climate. This project is developing a new framework for managing and assessing hurricane risk and will apply to all hurricane-afflicted coastal communities. Here, research is taking place in the coastal communities of New York, New Jersey, North Carolina and Florida to discover and compare hurricane hazards and to estimate how they might evolve in the future. As such, engineering and policy strategies for coping with these hazards can be developed.

While Prof Ning Lin is developing her own model as part of this project, she collaborates with other scientists of varied skill sets, such as Michael Oppenheimer, a Professor of Geosciences and International Affairs at Princeton and Guy Nordenson, an Architecture Professor at Princeton. The scientists involved in this project are developing their own types of models and it brings together various disciplines including atmospheric science, civil engineering, architecture, plus economics and public policy in a holistic way. "In this respect, very good progress is being made because people involved in this project have had to move out of their comfort zone", Prof Ning Lin observes. For example, Guy Nordenson at Princeton leads a 'Structures of Coastal Resilience' study that includes hurricane and climate science into engineering design for coastal resilience, she notes.

Closing thoughts

In closing, we learn that climate change models are surrounded by much uncertainty, so Prof Ning Lin is exploring ways to improve the models and reduce their uncertainties. Such an approach will help us to better understand uncertainties in climate projections and, therefore, improve hazard projections.

In addition, a better design strategy can save much investment and at the same time, ensure that communities remain both safe and alive, as focused by her NSF CAREER project. In closing, Prof Ning Lin shares her views on the importance of design when it comes to tolerating severe weather and also her ambitious plans for the future.

"If you elevate your house, you may get a higher wind impact. If your house is built at a lower level, then you may experience a storm surge impact. Also, storm surge and rainfall flooding can come together as evidenced by Hurricane Harvey, or perhaps not at the same time, but one after the other. A very interesting topic I am addressing is how do we deal with multi-hazards, not only from a scientific modelling perspective but also in terms of a strategy – that is how we could deal with them and consider them together.

> "Recent disasters, such as Hurricanes Sandy, Harvey, and Irma underscore the significant vulnerability of the U.S. to hurricanes."

"Our methodology has been applied to a number of different locations, such as New York City, Shanghai and Dubai. We are currently applying our modelling to the entire East Coast and the Gulf Coast of the U.S. This way, we can investigate variations in the hazards and risk from location to location. This is a promising aspect of our on-going work. I would envision that in the future, our study will go beyond the U.S. and encompass a scale that is global in its scope."

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Toxicology: Chemicals and their impact on human health

Brian Berridge, Associate Director of the National Toxicology Program (NTP), details how NTP studies the health impacts of chemicals and other factors in this fascinating interview

The National Toxicology Program (NTP) was established in 1978 by the U.S. Department of Health and Human Services (although it was called the Department of Health, Education and Welfare at that time) due to a growing concern about the effects of various substances in the environment which could directly or indirectly contribute to diseases and illness. In short, their goal today is to supply information on harmful substances, prevent disease and disability due to exposure and to improve the health of the general population in the United States (U.S.).

To find out more about NTP's excellent work in the U.S., we were fortunate to speak with Brian Berridge, Associate Director of the National Toxicology Program who provides compelling insights into the organisation's work. He details the first goal of the NTP as identifying potential hazards associated with chemicals and non-chemical agents that the general population might be exposed to. This includes industrial chemicals, consumer goods, food additives, pharmaceuticals, radiofrequency radiation, infectious agents and a full range of possible agents. Brian then draws our attention to NTP's second goal, which is to develop and validate novel methods used to study and characterise these potential hazards.

The conversation then moves to how the NTP's work in the U.S. addresses the human health effects of chemical agents in the environment. Brian underlines that they largely try to understand the biological activity of the agents they study, some of which are nominated by regulatory agencies and policymakers because they are interested in understanding the potential health effects of environmental exposures. Brian explains this point further in his own words.

"Some of those nominations come from regulators, policymakers or the general public and some are generated from within the NTP. Largely, we use a variety of test methods such as in vitro culture systems, in silico computational methods and animal studies to try and get a sense of biological activity in terms of hazards associated with these kinds of agents."

"All of the data NTP generates is captured in a variety of forms and it is all made public on our website and databases. We also produce formal reports, publish peer review manuscripts in scientific journals and give many presentations at scientific meetings."

"The bottom line here is that we take on the things that folks are concerned about and we study them in a variety of ways, with testing and modelling systems, so we can then report that out for consumption by policymakers, regulators, the general public and the scientific community."

> "In terms of the methods being developed at NTP, as time has gone by the range of agents has become broader. We don't just look at chemicals any more, but we also look at pharmaceuticals and non-traditional agents such as radio frequency radiation associated with cell phones as well as exposure to lighting conditions for those in shift work."

We now turn our thoughts on why the NTP was set up in the U.S. in 1978 and consider something of its journey from then to the present day. Brian believes the original intent was to create a focus within the U.S. government to take on a responsibility for carrying out some of this testing and also to coordinate amongst other agencies who were doing a similar type of work. Brian adds that

a fundamental interest of the public is cancer risks, an activity that had largely taken place in the National Cancer Institute. After the NTP was established in the late 1970s, it was given some responsibility for taking that on, Brian notes.

"Over the years, our interests and efforts have become broader, so NTP took on and developed methods for evaluating immune system toxicity, as well as developmental and reproductive effects. As time has gone on, scientists have realised that not everybody is equally prone to these effects. Individual susceptibility has, therefore, become a much more important part of our work.

> "All of the data NTP generates is captured in a variety of forms and it is all made public on our website and databases. We also produce formal reports, publish peer review manuscripts in scientific journals and give many presentations at scientific meetings."

"In terms of the methods being developed at NTP, as time has gone by the range of agents has become broader. We don't just look at chemicals any more, but we also look at pharmaceuticals and non-traditional agents such as radio frequency radiation associated with cell phones as well as exposure to lighting conditions for those in shift work. These are agents beyond traditional chemicals that potentially have public health effects."

Finally, we ask Brian if there any specific research initiatives that he would like to highlight as an example of NTP's work in the U.S. He draws our attention to the traditional testing of chemicals of public health concern for which there has been long-term exposure. He then details NTP's work around more short-term concerns, such as a chemical spill in the Elk River, West Virginia back in 2014 where a more rapid response was required and ultimately delivered.

"This population was exposed to very high concentrations of an industrial chemical which got into the water supply, so you can imagine that caused a fair bit of concern. NTP got its resources and capabilities together pretty quickly and carried out a number of studies over a short period of time to generate information that would help the folks there to understand what the potential hazards were.

"The other part of our business is about developing and validating novel methods and as such, we are the host for the NTP's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Essentially, their role is to facilitate the adoption of novel methods that do not use animals.

"We also contribute to a programme called Toxicology in the 21st Century (Tox21) which has been running since 2008. The aim of this initiative is to develop high-throughput methods to rapidly test whether substances in our environment adversely affect human health. The number of things that are being put into the environment, such as the products we consume or industrial chemicals has far outpaced our ability to test them in traditional ways. We had to develop high-throughput methods to understand things that we really need to focus on that represent a true risk versus those that are less of a problem.

"One last thought is that NTP, as is the case with a lot of scientific efforts, tries to keep pace with both the needs and the opportunities. Accordingly, we're constantly assessing novel approaches, assessing our portfolio for public health relevance and adjusting to changing expectations." ■

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Polychlorinated biphenyls (PCBs): A persistent environmental health problem

Carolyn R. Klocke, Postdoctoral Scholar and Pamela J. Lein, Professor at University of California, Davis both argue that polychlorinated biphenyls (PCBs) are a persistent environmental health problem today

Polychlorinated biphenyls (PCBs) are a family of synthetic chemicals that were produced in large quantities for industrial and commercial applications beginning in the late 1920s through the late 1970s. PCB mixtures were synthesised globally and identified under several trade names, including Aroclor® (United States and United Kingdom), Clophen® (Germany), Phenclor® (France) and Kanechlor® (Japan). Chemically, PCBs are biphenyls with variable chlorine atoms substituted for the hydrogen atoms in the benzene rings. There are 209 possible PCB compounds – each of which is referred to as a congener – that are named according to the number and position of chlorine substitutions (i.e., lower-chlorinated congeners have lower number designations and higher-chlorinated congeners that have higher number designations).

Image: Wisconsin Department of Natural Resources

PCB Cleanup site at Sheboygan Falls, Wisconsin, United States, circa 1990

While concern regarding adverse health outcomes associated with occupational exposures to PCBs arose as early as the 1930s, by the 1960s and 1970s there was significant alarm about the human health risks of PCBs in the environment. The manufacturing, use and disposal of PCBs had resulted in widespread PCB contamination of air, water and soil, and because PCBs are highly resistant to degradation, they had accumulated in the human food chain and were readily detected in human tissues, including breast milk.

These observations, coupled with emerging data linking environmental PCB levels to increased cancer risk in humans and animal models, impelled the United States Congress to institute a ban on PCB production in 1979. This was followed by a global ban on the production and use of PCBs by the Stockholm Convention on Persistent Organic Pollutants in 2001.

In the decades following the ban on PCB production, environmental PCB levels decreased significantly. During this time, basic research scientists identified the biological mechanisms by which PCBs cause cancer and regulatory scientists established "safe" exposure levels for PCBs in the environment and human food supplies based on attributable cancer risk. It was widely believed that the PCB problem was solved and that further research on PCBs was not warranted. However, emerging research on PCBs over the past decade has revealed a number of unexpected findings that suggest the mainstream understanding of PCB exposures and PCB toxicity may be too limited and that PCB regulations focused on cancer outcomes may not be protective of vulnerable populations.

One surprise from current research is that while environmental levels of PCBs are decreasing globally, levels have stabilised or may be increasing in some geographic regions. One explanation is the accelerated release of "legacy" PCBs from ageing products. For example, higher than expected

levels of PCBs in the air over the city of Chicago are thought to be due in part to the release of PCBs from ageing paints and caulking materials used to construct municipal buildings during the era when PCBs were intentionally added to these construction materials. The release of legacy PCBs from paints and caulking materials may also explain why PCB levels in the indoor air of elementary schools in the United States exceed the 2009 public health guidelines set by the United States Environmental Protection Agency. Additionally, novel PCBs that were not part of the original industrial mixtures have been detected in the environment and in human tissues. The toxic potential of most of these contemporary PCBs, many of which are lower chlorinated congeners, is largely unknown.

Historically, consumption of contaminated food was thought to be the primary source of PCB exposure in humans, with fish, meat and dairy products comprising the main dietary sources of PCBs. However, recent studies documenting PCB contaminants in the air of major cities and indoor air of municipal buildings, including schools, suggest that inhalation may be a significant and underappreciated source of human exposure. While sources of airborne PCBs, which include both legacy PCBs as well as the lower chlorinated contemporary PCBs, are not yet completely understood, some studies have demonstrated that PCBs can be unintentionally produced during the synthesis of yellow and green paint pigments. Once dried, volatile PCBs can be released into the air (a phenomenon also referred to as "off-gassing") to be inhaled by humans. Whether the toxic effects of PCB are different if they are inhaled from the air vs. ingested with food remains to be determined.

Another evolution in our understanding of the environmental health impacts of PCBs is the realisation that the developing brain is a vulnerable target of PCBs. PCBs interfere with the growth and maturation of neurons in the developing brain, which shifts the developmental trajectory of the brain in a manner that disrupts normal patterns of connections between brain regions. The magnitude of this effect differs depending on the specific PCB congener involved and whether it is a higher- or lower-chlorinated congener. Interestingly, a pathological change that is common to many neurodevelopmental disorders, including autism and attention deficit hyperactivity disorder (ADHD), is altered connectivity in the brain, and recent studies report that elevated maternal PCB levels are associated with increased risk of having a child with autism or ADHD.

The recent discovery of PCB contamination in the indoor and outdoor air has also raised concern regarding the effects of exposure to airborne PCBs on the developing lung. Lung development continues long after birth, so there is the possibility that inhalation of PCBs interferes with lung development and growth. Since PCBs are known to interfere with neuronal development, it is hypothesized that the inhalation of airborne PCBs may interfere with innervation of the lung, resulting in increased airway hyperreactivity, a hallmark characteristic of asthma. It has been hypothesized that airborne PCBs contribute to the unexplained and perplexing increase in childhood asthma since the 1960s.

Collectively, epidemiologic studies and experimental data from animal models suggest that further investigation of PCBs is warranted to understand how the changing patterns of PCB exposure are contributing to non-cancer outcomes, specifically neurodevelopmental disorders and potentially pediatric asthma. Such work is required to ensure that regulatory policies targeting PCBs are protective of the most vulnerable members of society.

UCDAVIS VETERINARY MEDICINE

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U.S. efforts to promote food security and provide humanitarian assistance

The vital work of the US Agency for International Development (USAID) is examined here by Open Access Government, with a focus on their efforts to promote food security and provide humanitarian assistance in other countries, such as Ethiopia

The US Agency for International Development (USAID) leads efforts in international development and humanitarian terms to reduce poverty, save lives, strengthen democratic governance and help people progress beyond assistance. Their incredible scope of work ranges from preventing the next global epidemic, helping a farmer access tools to grow their business or responding to a devastating earthquake. By way of background, 35th President of the United States (U.S.), John. F. Kennedy created the organisation by executive order in 1961 to lead the government's efforts in international development and humanitarian assistance.

The USAID's work covers many areas, such as economic growth and trade, environment and global climate change, gender equality and women's empowerment, working in crises and conflict, as well as water and sanitation. Another area of their work concerns food security, which we will now look at in further detail. We know that given the scarcity of resources and other challenges, there is a need to be more efficient in how this demand is met. They believe that ensuring a sufficient supply of food for people requires aligning short-term assistance with a long-term development strategy to assist countries to feed their own inhabitants.

In essence, food security can be defined as people having both physical and economic access to sufficient food to cater for dietary needs and to enable a productive and healthy life, at all times. We learn that food insecurity can often be traced back to poverty and has far-reaching consequences on the ability of families, communities and countries to develop. Also, we find out that extended undernourishment stunts growth increases susceptibility to illness and slows cognitive development.

In addition, the growth of the agriculture sector is highly effective in reducing poverty and as such, USAID strongly believes in investing in smallholder farmers who depend on agriculture to feed their families and make a living. There was a spike in world food prices back in 2008 which hurt economies across the world and this led to destabilising riots in no less than 30 countries. To feed a population that is expected to grow to 9 billion people by 2050, USAID points out that the world will somehow have to double its current level of food production, albeit with less water and land.

At the G-8 Summit in L'Aquila, Italy in 2009, the U.S. rallied global leaders to address the root causes of global food insecurity. This meeting set the foundation for the U.S. government's global hunger and food security initiative, Feed the Future, which is making a significant contribution towards a concerted global effort to combat global poverty, hunger and malnutrition. Led by USAID, Feed the Future plays on the strengths of agencies across the U.S. government and leverages resources with multilateral organisations, NGOs, research institutions, the private sector other stakeholders to step up inclusive agricultural growth.

Feed the Future, in collaboration with 10 other U.S. government agencies and departments, aims to do the following:

- Invest in cutting-edge scientific and technological agricultural research;
- Develop agricultural markets;

Image: © Sjors737 | Dreamstime.com

Ethiopia, Afar region, a group of semi-nomadic cattle farmers severely effected by drought and massive loss of livestock. This boy will walk for hours to find a water and food source.

- Help farmers access capital.
- Offer extension services;
- Develop sustainable agriculture strategies;
- Provide emergency food assistance.

So, we know that through efforts like Feed the Future, USAID, in summary, are: "Advancing global food security by helping to improve the most basic of human conditions: the need that families and individuals have for a reliable source of quality food and sufficient resources to purchase it. This, in turn, supports global stability and prosperity." [1]

Finally, let's take a look at a recent example of how the USAID is providing assistance, which in this case is to support the inhabitants of the Federal Democratic Republic of Ethiopia. As many people in Ethiopia have left their homes due to escalating conflict or natural disaster and are facing severe food insecurity as a result, the U.S. announced in July this year an additional $170 million in humanitarian assistance to support them.

The funding will provide emergency food and nutrition assistance, life-saving medical care, shelter and safe drinking water. It will also fund programmes to improve sanitation and hygiene to treat and stop the spread of preventable diseases. It is estimated that 8.5 million people in Ethiopia are in need of urgent humanitarian assistance, a situation that has escalated due to the insecurity and large-scale displacement along the border of Oromiya and Southern Nations Nationalities and Peoples region. We learn that the number of people displaced along the Gedeo and West Guji zones has risen to almost one million since April 2018. This newly displaced population is on top of the 1.6 million Ethiopians who have been pushed away from their homes by drought conflict and as such, require immediate and vital humanitarian assistance.[2] ■

References

[1] https://www.usaid.gov/what-we-do/agriculture-and-food-security

[2] https://www.usaid.gov/news-information/press-releases/jul-24-2018-united-states-announces-170-million-humanitarian-assistance-ethiopia

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Climate Hazards Group: Strengthening defences against food in-security

The Climate Hazards Group contributes to Food Security Outlooks that strengthen food security

The Climate Hazards Group (CHG) brings together a cooperative team of multidisciplinary scientists and food security analysts from the University of California, Santa Barbara, the U.S. Geological Survey (USGS), Africa and Central America to develop data sets, tools and forecasts that help guide effective disaster responses and long-term development plans in food-insecure countries.

Working closely with partners in the USGS, NOAA CPC, NOAA ESRL, NASA, USDA and the Famine Early Warning Systems Network (FEWS NET), the team uses climate and hydrologic models together with satellite-based Earth observations to provide six-to-eight month food security outlooks for the world's most vulnerable populations. The CHG supports critical planning and timely humanitarian assistance that ultimately saves lives and livelihoods.

When climate variability and shifting climatic trends converge to produce severe droughts, fragile food insecure populations may face rapid-onset food crises as resources diminish, prices rise and household incomes decline. In vulnerable areas, these unanticipated climate shocks may devastate herds and harvests and degrade local food stocks. Unfortunately, the number of very hungry people continues to grow at an alarming rate over the past few decades, with more than 76 million people experiencing life-threatening conditions in 2017 and 2018.

Many of these extremely food insecure people live in Africa, which experienced a recent sequence of severe droughts associated with an extreme El Niño and La Niña. To monitor these droughts, the CHG has developed the Climate Hazard Group InfraRed Precipitation with Station data (CHIRPS) data product.

CHIRPS harnesses the power of satellite technology, which is able to provide regular, detailed observations of entire regions. With each pass of the satellite, observers gain comprehensive information about how precipitation interacts with the geography. When combined with station data, CHIRPS allows for the rapid identification of hydrologic extremes, such as the terrible El Niño-related droughts in Ethiopia and Southern Africa in 2015-16, or the La Niña-related droughts in East Africa in 2016-2017.

Recent research (a, b, c) by the CHG has linked these droughts to very warm sea surface temperatures in the eastern and western Pacific Ocean. Very warm east Pacific waters (associated with the 2015-16 El Niño) contributed to rainfall deficits and very poor growing seasons in Ethiopia and Southern Africa.

In 2016, the global climate transitioned to a La Niña event, presenting cool east Pacific conditions and very warm waters in the western Pacific and eastern Indian Ocean - perfect conditions for producing back-to-back droughts in Kenya, Somalia and eastern Ethiopia. Recognition of the dangers posed by these warmer waters helped the CHG and partners effectively predict droughts (d) in 2015, 2016 and 2017.

The CHG team has helped document predictable sequences in these extremes (a). Several times over the

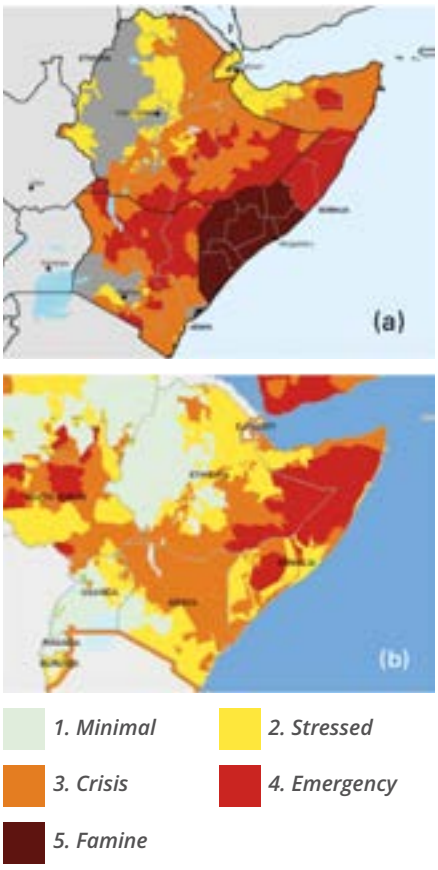

Figure 1. Integrated Food Insecurity Phase Classification (IPC) Maps showing the levels of food insecurity for (a) July-September 2011 and (b) June-September 2017. From this WMO report.

past twenty years, a strong El Niño has occurred, followed by a La Niña. In 1997-2001, 2008-2011, and 2015-2017, successive El Niños and La Niñas produced multi-year increases in drought and food insecurity. These insights have helped FEWS NET, working with its network partners, successfully provide "food-security early-warning advisories with a six-to-eight months month lead-time (d)."

In 2010-11, such a pattern contributed to a very intense drought over Somalia, Ethiopia and Kenya, with more than 12 million people requiring assistance. Sadly, in Somalia, a combination of armed conflict and poor food access and availability led to the deaths of more than 250,000 people.

In October of 2016, the CHG began providing advance warning of another similar drought for East Africa. By June 2017, 27 million East Africans required urgent food assistance. This drought led to a United Nations appeal for $4.4 billion in funding – twice the amount requested in 2011.

Indeed, "the improved early-warning systems and multi-agency responses employed during this drought, as well as improved humanitarian access thanks to less-adverse patterns of conflict, meant that famine was averted, unlike the case in 2010-2011 in Somalia" (d).

In 2011, Somalia food prices reached catastrophic levels. In 2017, the timely arrival of aid helped stave off meteoric increases, averting famine (Figure 1).

The CHG and FEWS NET partners also helped provide early warning for the 2015-16 drought in Southern Africa. Predictions for a strong El Niño led to pessimistic food-security outlooks beginning in July of 2015. By January 2016, nearly five months before the end-of-season crop harvests, analyses of seasonal rainfall to date and historical El Niño rainfall performance led to a consensus FEWS NET agro-climatological assumption that crop performance in most Southern Africa countries was likely to fall below average. By June of 2016, the early warning community estimated that some 40 million people in the region needed humanitarian assistance.

Figure 2. CHG members. Chris Funk, Greg Husak, Joel Michaelsen, Alkhalil Adoum, Gideon Galu, Tamuka Magadazire, Seth Peterson, Laura Harrison, Diriba Korecha, Shraddhanand Shukla, Chris Shitote, Frank Davenport, Diego Pedreros, Emily Williams, Pete Peterson, Marty Landsfeld, Sari Blakeley, Will Turner, Juliet Way-Henthorne, Mario Rodriguez and Amy McNally

Communication, collaboration, capacity

These early warning successes have made an important contribution to the implementation of the United Nations' Sustainable Development Goals, particularly to Goal 2 and the challenge of ending hunger and achieving food security for all.

Close working relationship between climate scientists and food security analysts have enabled scientists to respond to the analytical needs of food security experts. These effective communication systems have facilitated the production of well-targeted briefs, reports and web-based interventions delivered to high-level decision-makers in both donor countries and organisations, and in the affected countries.

A unique and valuable component of the CHG team is its international composition (Figure 2). Almost half of the members of the CHG team live in Africa or Latin America. These scientists work closely with local stakeholders, decision-makers and science institutions to increase disaster preparedness and guide long-term "climate-smart" development. Building on the CHG's commitment to developing data sets and tools, as well as harnessing the tremendous potential of satellite-based Earth observations, these capacity-building efforts are strengthening defences along the frontlines of climate variation and change.

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Energy technologies and manufacturing: America at the forefront of innovation

When it comes to energy technologies and manufacturing, America aims to be at the forefront of innovation, as Open Access Government finds out

In September 2018, the U.S. Department of Energy (DOE) shared the news that 42 projects were selected to support advanced vehicle technologies, with a total amount of $80 million in funding to support this. It is hoped that these projects will facilitate more affordable mobility, reduce dependence on foreign sources of critical materials, strengthen domestic energy security and enhance the country's economic growth.

This important aspect of the DOE's work supports their ambition to invest in early-stage research of transportation technologies that can provide businesses and families with a greater choice in how their mobility needs are met. Commenting on this important part of DOE policy, U.S. Secretary of Energy Rick Perry says: "Improving the affordability of transportation for American consumers and businesses keeps our economy moving. By investing in a broad range of technologies, DOE is ensuring America remains at the forefront of innovation."

When it comes to batteries and electrification, the funding for these projects totals $31.9 million. These projects set out the technologies which will recharge multiple electric vehicles speedily and at considerably high "extreme" power levels. Materials and the research projects total $8.4 million and these intend to develop models that predict corrosion in multi-material joints

for materials in high-temperature combustion environments that can be used to accelerate the introduction of new materials into advanced vehicles, as well as lightweight vehicle structures.

Another part of this funding for transportation technologies concerns projects worth $10.1 million around engines and fuels. We find out that these projects will research advanced multi-mode (spark ignition/compression ignition) engines with co-optimised fuels for bio-derived blendstocks for diesel engines for medium- and heavy-duty vehicles, as well as light-duty vehicles.

> "Improving the affordability of transportation for American consumers and businesses keeps our economy moving. By investing in a broad range of technologies, DOE is ensuring America remains at the forefront of innovation."

One last example is the $3.4 million funding in place for off-road and fluid power systems, the projects of which will focus on improving the energy efficiency of off-road vehicles used in agriculture, construction and mining applications. (1)

Manufacturing

Other energy technologies supported by DOE include LED bulbs and solar panels, as well as electric vehicles which were discussed earlier in this article. When it comes to manufacturing in the U.S., this is the lifeblood of the economy because it provides jobs for hard-working families and also helps to increase U.S. competitiveness, according to the DOE. In addition, the DOE is supporting manufacturers to increase their productivity in energy by implementing energy efficiency measures. (2)

Research & development consortia

Staying on the subject of manufacturing, it's worth noting here that the DOE's Advanced Manufacturing Office (AMO) brings together a number of actors to pursue coordinated early-stage R&D in high-priority areas around energy in manufacturing. These include manufacturers, small businesses, universities, national laboratories, as well as state and local governments. While these consortia have distinct technology focus areas, they are all working towards the common goal of securing the country's future by means of manufacturing innovation, collaboration and education.

In addition, AMO's five institutes are part of Manufacturing USA, which is a network of regional institutes, each of which has a specialist technology focus area. We know that these institutes facilitate the transition of information, innovative advanced materials and process technologies to industry. This approach enables manufacturing scale-up and helps to develop national capabilities that enable workforce development and future global leadership in advanced manufacturing. (3)

Closing thoughts

Finally, it's worth noting that the energy technologies and manufacturing discussed here are just two examples that strongly support the overall mission of the DOE, which is: "to ensure America's security and prosperity by addressing its energy, environmental and nuclear challenges through transformative science and technology solutions." (4). Certainly, the DOE is working towards ensuring America's Energy Future by various means, including the ones described here.

References

1 https://www.energy.gov/articles/department-energy-announces-80-million-investment-advanced-vehicle-technologies-research

2 https://www.energy.gov/energy-economy/manufacturing

3 https://www.energy.gov/eere/amo/research-development-consortia

4 https://www.energy.gov/about-us

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Clean energy: The U.S. Energy Department's priorities for wave, tidal and hydropower resources

The work of the U.S. Energy Department is examined here by the Editor of Open Access Government Jonathan Miles in respect to clean energy and the remarkable potential of wave, tidal and hydropower resources

The U.S. Department of Energy began its life in 1977, but it traces its lineage to the Manhattan Project effort to develop the atomic bomb in World War II and to a number of energy-related programmes that were dispersed throughout various Federal agencies.

At the time of writing, the Department is led by Secretary of Energy Rick Perry who serves as the 14th United States Secretary of Energy. This article will examine some aspect of the Energy Department's work, with a focus on clean energy, including their support for the development of wave, tidal and hydropower resources.

Clean energy

One area of the U.S. Department of Energy's work concerns clean energy; indeed, we find out that a revolution of this kind is taking place across America, supported by the steady expansion of the country's renewable energy sector. We know that the clean energy industry generates hundreds of billions of dollars in economic activity and is expected to continue to grow at a rapid pace during the years ahead. The economic opportunity for the countries that invent, manufacture and export clean energy technologies is tremendous.

We go on to learn that the responsible development of all the U.S.'s rich energy resources will help to ensure the country's continued leadership in the field of clean energy. The energy resources here include solar, wind, water, geothermal, bioenergy and nuclear. Looking ahead, the Energy Department aims to carry on driving strategic investments in the transition to a cleaner, more secure and domestic energy future.

Water

Untapped sources of energy in America include wave, tidal and hydropower resources which have a vast potential to expand electrical generation in the future. As such, the Energy Department is determined to drive forward critical research and development efforts from these clean energy resources.

> "The Energy Department announced $116 million in funding for 263 research and development grants for 184 small businesses in 41 states - including four grants for water power projects. Funded through DOE's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, Phase I grants enable small businesses to research the technical feasibility innovations that advance the Department's mission."

This policy ambition includes investments in existing hydropower facilities to enable the necessary infrastructure to produce electricity and leading marine and hydrokinetic technology advancements to generate energy from water.

On wave and tidal energy, we know that the efforts of the Water Power Program's marine and hydrokinetic research and development (R&D) focus on advancing technologies that capture energy from America's rivers and oceans. In contrast to hydropower, marine and hydrokinetics represent an emerging industry with hundreds of potentially viable technologies. As such, the Program is leading efforts to evaluate technical and economic viability; prove functionality; and generate cost, performance and reliability data for a number of devices.

Also, we are told that marine and hydrokinetic energy technologies convert the energy of waves, rivers, tides and ocean currents into electricity. The Department of Energy's Marine and Hydrokinetic 101 video reveals how these technologies work and underline some of the Water Power Program's R&D efforts in this area. This Program consists of three categories: market acceleration and deployment; technology development; plus, resource assessment and characterisation.

> "We know that the clean energy industry generates hundreds of billions of dollars in economic activity and is expected to continue to grow at a rapid pace during the years ahead. The economic opportunity for the countries that invent, manufacture and export clean energy technologies is tremendous."

Research and development

In recent news, we learn that the Energy Department announced $116 million in funding for 263 research and development grants for 184 small businesses in 41 states – including four grants for water power projects. Funded through DOE's Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs, Phase I grants enable small businesses to research the technical feasibility innovations that advance the Energy Department's mission.

One example of the research funded here is for Creare, LLC of Hanover, New Hampshire, who plan to develop a technology for low-cost desalination that concerns the process of removing salt from seawater in coastal regions afflicted with water scarcity by harnessing power from the ocean and tidal currents. Another example is Resolute Marine Energy, Inc. of Boston, Massachusetts, who intend to research a wave energy-powered, fresh water production solution that can solve water security problems facing underserved markets in a cost-effective manner. Such small businesses are playing a very important part in spurring innovation and creating jobs in the U.S. economy.

The importance of clean electric power

In closing, it is worth highlighting the that clean electric power is vital to the Energy Department's aim to meet their interdependent security, economic and environmental goals. While supporting aggressive emission reductions, the traditional market drivers such as reliability, safety and affordability must be enhanced and maintained, as we are told in Chapter 4 – Advancing Clean Electric Power Technologies. We also find out how the current portfolio of electric production is characterised and the importance of technological advances to meet energy needs in America.

"The current portfolio of electric production includes a combination of coal, nuclear (with five new reactors under construction), hydro, growing natural gas and rapidly advancing renewable generation sources. Complementing this evolving generation mix, technologies to enable higher efficiencies, pollution control and carbon capture and storage are essential aspects of the RDD&D portfolio."

"A combination of flexible technology options will be required to meet increasing power needs in the U.S. and globally. The Quadrennial Technology Review focuses on technological advances to meet U.S. energy needs and challenges, recognising that these also offer opportunities for cooperative research that will expedite the international deployment of these technologies." ■

For more information on the Energy Department's extraordinary range of work, please visit: www.energy.gov.

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Radioiodine in the environment: The importance of natural organic matter

Peter H. Santschi, Regents Professor at the Department of Marine Sciences, Texas A&M University – Galveston discusses radioiodine in the environment, focussing on the importance of natural organic matter

There is a single stable isotope of iodine, ^{127}I, and two environmentally relevant iodine radionuclides, ^{131}I and ^{129}I, both of which have been primarily introduced into the environment because of human activity since the dawn of the nuclear age. ^{131}I has a half-life of just eight days (the duration required for it to radiologically decay to half of its mass) but is a threat to human health immediately following a nuclear accident, such as Chernobyl or Fukushima, because of its high inventory, and bio-concentrates in the thyroid gland. Because of its short half-life, ^{131}I levels usually fall below detection in environments contaminated by nuclear event shortly after the release (about two months).

In contrast, ^{129}I is much less of an immediate health risk because it has a much longer half-life (16 million years), however, it is problematic as a contaminant associated with nuclear waste disposal. Another important reason that ^{129}I is a key risk driver is that there is the uncertainty regarding its biogeochemical fate and transport in the environment and such uncertainty requires that conservative assumptions about its associated risk must be included in our risk models. Its risk is considerably higher than that of ^{99}Tc, which receives most of the attention in the US [Fig. 1].

As a consequence of some of these characteristics, ^{129}I has a very low Drinking Water Standard, DWS, which is set at 0.04 Bq/L, the lowest of all radionuclides in the US Federal Register. Thus, ^{131}I is a significant and immediate health hazard associated with large-scale nuclear events, whereas ^{129}I poses a challenge in terms of environmental remediation and the long-term stewardship of nuclear waste (Kaplan et al., 2014).

Stable iodine is a required nutrient for human health. About 90% of the iodine in the human body exists in the 14-g thyroid gland, where it is an essential component of several thyroid hormones. When radioiodine enters the human body, it mimics the behaviour of stable iodine and concentrates on the thyroid gland but can be a carcinogen.

The World Health Organization (2006), reported that the Chernobyl nuclear power plant accident resulted in 5,000 thyroid cancer cases of people who were under 18 years old at the time of the accident. Radioactive iodine was deposited in pastures eaten by cows who then concentrated it in their milk which was subsequently drunk by children. This was further exacerbated by a general iodine deficiency in the local diet causing more of the radioactive iodine to be accumulated in the thyroid. Since radioactive iodine is short-lived, if people had stopped giving locally supplied contaminated milk to children for a few months following the accident, it is likely that most of the increase in radiation-induced thyroid cancer would have been averted.

Iodine exists in multiple oxidation states, primarily as molecular iodine (I_2), iodide (I^-), iodate (IO_3^-) or organic iodine (org-I). The mobility of iodine in the environment is dependent upon its speciation and a series of redox, complexation, sorption, precipitation and microbial reactions. Over the last 15 years, there have been significant advances in iodine biogeochemistry and geobiology, largely spurred by a renewed interest in the fate of radioiodine in the environment and advances in detecting these various species at environmentally relevant concentrations. The biogeochemistry of iodine, with particular emphasis on the microbial processes responsible for volatilisation, accumulation, oxidation and reduction of iodine, are reviewed in Yeager et al. (2017).

The key environmental factor influencing radioiodine's fate and transport in the environment is natural organic matter (NOM) that consists of residues of decaying plant matter and freshly produced exudates from microbes (Santschi et al., 2017a). Recently, great progress has been made in understanding the impact NOM compounds and microbial processes on the fate of different radionuclides in Japanese and U.S. soils. It has been shown that NOM not only influences the fate and

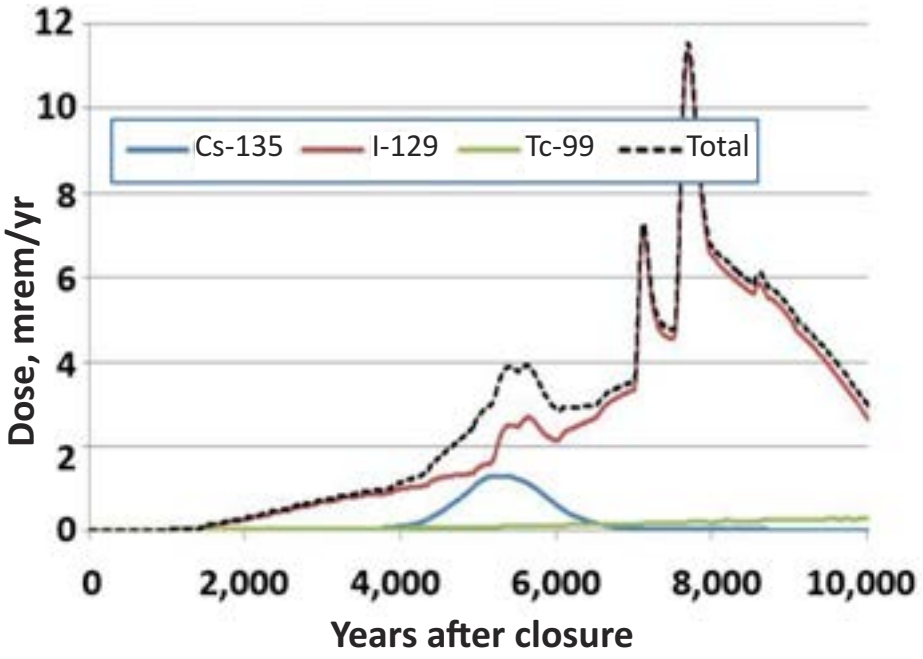

Fig. 1. Example of calculated risk associated with the disposal of low-level waste in cementitious waste forms (WSRC-STI-2007-00306)

transport of radioiodine but also many other radionuclides. However, there still remains great uncertainty in predicting NOM-radionuclide interactions because of a lack of understanding of radionuclide binding to the wide array of specific binding sites (organic moieties) within NOM, as NOM is polymeric, polyfunctional, containing pH and redox reactive moieties that can be controlling radionuclide behaviour in the environment.

The architecture of macromolecular organic matter requires that thermodynamic constants for binding to macromolecular organic matter will have distribution functions rather than discrete values, which is a challenge for modellers. While radionuclide-NOM studies have been conducted using model organic compounds or elevated radionuclide concentrations, the results of such studies might provide compromised information related to true environmental conditions.

Therefore, sensitive techniques are required not only for the detection of radionuclides and their different species, at ambient and/or far-field concentrations, but also for potential trace organic compounds that are chemically binding these radionuclides (Santschi et al, 2017b). Recent analytical chemistry advances (based on GC-MS and AMS) have demonstrated that iodine forms strong bonds with NOM by covalently binding to aromatic functionalities. These recent studies have led to a more mechanistic understanding of radioiodine biogeochemistry.

Different from other high risk radionuclides (Cs, Sr, and U) that have been attenuated, ^{129}I continues to leave the source at a rate that may have been exacerbated by the initial remediation actions (Kaplan et al., 2014) that ignored the strong pH and redox control of its organoiodine formation and mobilisation/immobilisation that is opposite to that of many metal radionuclides.

In another example, the Fukushima Prefecture surficial soil ^{127}I content was significantly and positively correlated to soil OM content, regardless of land use type and showed strong correlations (negative to pH, positive to Eh) to soil ^{127}I content, suggesting that soil OM might be an important factor affecting iodine biogeochemistry. These observations have far-reaching implications for remedial actions and demonstrate the need for additional understanding of the impact of NOM interactions on the fate and transport of radioiodine.

Acknowledgements

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References

Kaplan, D. I., et al. 2014. Critical Reviews of Environmental Science and Technology, 44(20), 2287-2335.

Santschi, P.H., et al. 2017a. Appl. Geochem., 85, 121-127.

Santschi, P.H., et al. 2017b. J. Environ. Radioactivity, 171, 226-233.

Yeager, C.M., et al. 2017. Advances in Applied Microbiol., 101, 83-136.

Cancer consequences of the Chernobyl accident: 20 years after Journal of Radiological Protection (. vol 26(2), pages 125- (on-line doi:10.1088/0952-4746/26/2/001).

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Ocean sciences in the United States

The role of the National Science Foundation (NSF) in supporting the ocean sciences in the United States is examined here by Open Access Government

The National Science Foundation (NSF) is an independent federal agency in the U.S. that supports fundamental research and education across all fields of science and engineering.

This article looks at the work of NSF's Division of Ocean Sciences (OCE), within the NSF, who exist to support research, education and infrastructure that advance our understanding of the global oceans and ocean basins, including their interactions with the integrated Earth system and human beings. Within this division is the Marine Geosciences Section, which has a Chemical Oceanography section and one for Marine Geology and Geophysics (MG&G).

Firstly, the Chemical Oceanography Program supports research into the chemistry of the oceans and the role of the oceans in global geochemical cycles. Areas of interest here include:

- Chemical exchanges between the oceans and other parts of the Earth system;
- Chemical composition, speciation and transformation;
- Internal cycling in oceans, seas and estuaries plus and;
- The use of measured chemical distributions as indicators of biological, physical and geological processes.

Secondly, the Marine Geology and Geophysics Core Program is concerned with all aspects of research around the geology and geophysics of the present ocean basins and margins, plus the same for the Great Lakes. This Program supports science that includes the following fascinating areas, to name a few:

- The structure, composition, evolution and tectonics of the oceanic lithosphere;
- Marine hydrogeology, seeps and gas hydrates, water-rock interaction and hydrothermal vent and fluid formation and geochemistry;
- Marine sedimentology and coastal processes, stratigraphy, sediment transport and diagenesis;
- Paleoceanography, paleoclimate and sea level change;
- Submarine volcanology, petrology and geochemistry of the oceanic crust and upper mantle and;
- Marine geohazards (such as earthquakes, mass wasting, geological aspects of tsunamis).

Added to this, we know that the Marine Geology and Geophysics Program is concerned with supporting new ideas and cutting-edge research. Field, analytical, and laboratory experimental projects; methods development; modelling; and the re-analysis and/or synthesis of existing data are supported by this Program. Also, the Program interfaces with NSF programs across the geosciences and across the Agency. [1]

New connections between climate change and warming oceans

In recent news from the field, NSF recently highlighted the work of scientists from the University of Toronto who have drawn new connections between climate change and the warming oceans.

Uli Wortmann, a professor in the Department of Earth Sciences in the Faculty of Arts & Science at the University of Toronto and co-author of the study explains more about what this study reveals in his own words. "Our study shows that global warming is not only about extreme weather events, or hotter summers, but it has the potential to alter the ocean structure with unknown consequences for fisheries.

"We show that the last time large amounts of CO_2 were injected into the atmosphere, not only did the planet get hot – which is known as the so-called Paleocene-Eocene Thermal Maximum, about 55 million years ago – but it also changed the chemistry of the ocean quite markedly."

The research discovers that as the oceans warm, oxygen decreases while hydrogen sulfide increases,

which makes the oceans toxic and puts marine species at risk. [2]

How calcifying organisms will respond to ocean acidification

Another piece of research highlighted by NSF's Division of Ocean Sciences (OCE) suggests that size is the key factor that predicts how calcifying organisms will respond to ocean acidification. Allison Barner, who carried out the research while completing her PhD in integrative biology at Oregon State University shares her thoughts on ocean acidification. "Decades of research have shown that calcifying species are negatively affected by ocean acidification…But even closely related species can have different responses to acidification and not much was known about the drivers that shape this variation."

Added to this, we learn that around 30% of the carbon dioxide in the air ends up in the sea, where it causes a reduction in carbonate ions – a key building block for a variety of calcifying organisms, including not only the algae in the study but also animals such as oysters, mussels, sea stars and corals. As well as running experiments that simulated future ocean acidification conditions, Barner and colleagues measured a suite of properties for each species, including its habitat distribution along the Oregon coastline and its size, surface area and shape.

"All of the species had declining calcification with short-term increases in acidification," says Barner, who now works as a postdoctoral scholar at the University of California, Berkeley. "And the findings supported the hypothesis that organismal size is the best predictor of an individual's physiological performance under acidified conditions. Importantly, we can rule out the scenario that each species might have a different response to ocean acidification." [3]

The links between carbon and plankton

One project, announced in June this year concerns a joint project between the National Aeronautics and Space Administration (NASA) and the National Science Foundation (NSF) which aims to study the life and death of microscopic plankton, tiny plant and animal organisms that play a vital part in removing carbon dioxide from the atmosphere and the oceans.

While the major pathways of how carbon moves through the ocean are known, how much of it is transferred along these pathways and how much they depend on ecosystem characteristics, are not as well known. Providing us with more detail on this, Mike Sieracki, a Biological Oceanography program director in NSF's Division of Ocean Sciences (OCE) says: "The carbon that humans are putting into the atmosphere is warming Earth…Much of that carbon goes into the ocean and is transported to the deep sea, where it will not return to the atmosphere for a long time. This project will help us to understand the biological and chemical processes that remove that carbon, and to monitor these processes as climate changes." [4]

Closing remarks

Many further examples of NSF supported research could be discussed here if space allowed, such as how a new study challenges scientists' presupposition about the carbon cycle [5] or how nutrient pollution makes ocean acidification worse for coral reefs [6]. In closing, we have seen some fantastic examples of just one area that the NSF supports when it comes to basic research and the people to create knowledge that transforms the future of our world. [7] ■

References

[1] https://www.nsf.gov/funding/programs.jsp?org=OCE

[2] https://news.artsci.utoronto.ca/all-news/scientists-draw-new-connections-climate-change-warming-oceans/

[3] https://today.oregonstate.edu/news/size-main-factor-predicting-how-calcifying-organisms-will-respond-ocean-acidification

[4] https://www.nsf.gov/news/news_summ.jsp?cntn_id=245753&org=OCE&from=news

[5] http://news.fsu.edu/news/science-technology/2018/07/18/in-the-oceans-twilight-zone-tiny-organisms-may-have-giant-effect-on-earths-carbo-cycle/

[6] https://www.hawaii.edu/news/2018/06/07/nutrient-pollution-worse-for-coral-reefs/

[7] https://www.nsf.gov/about/

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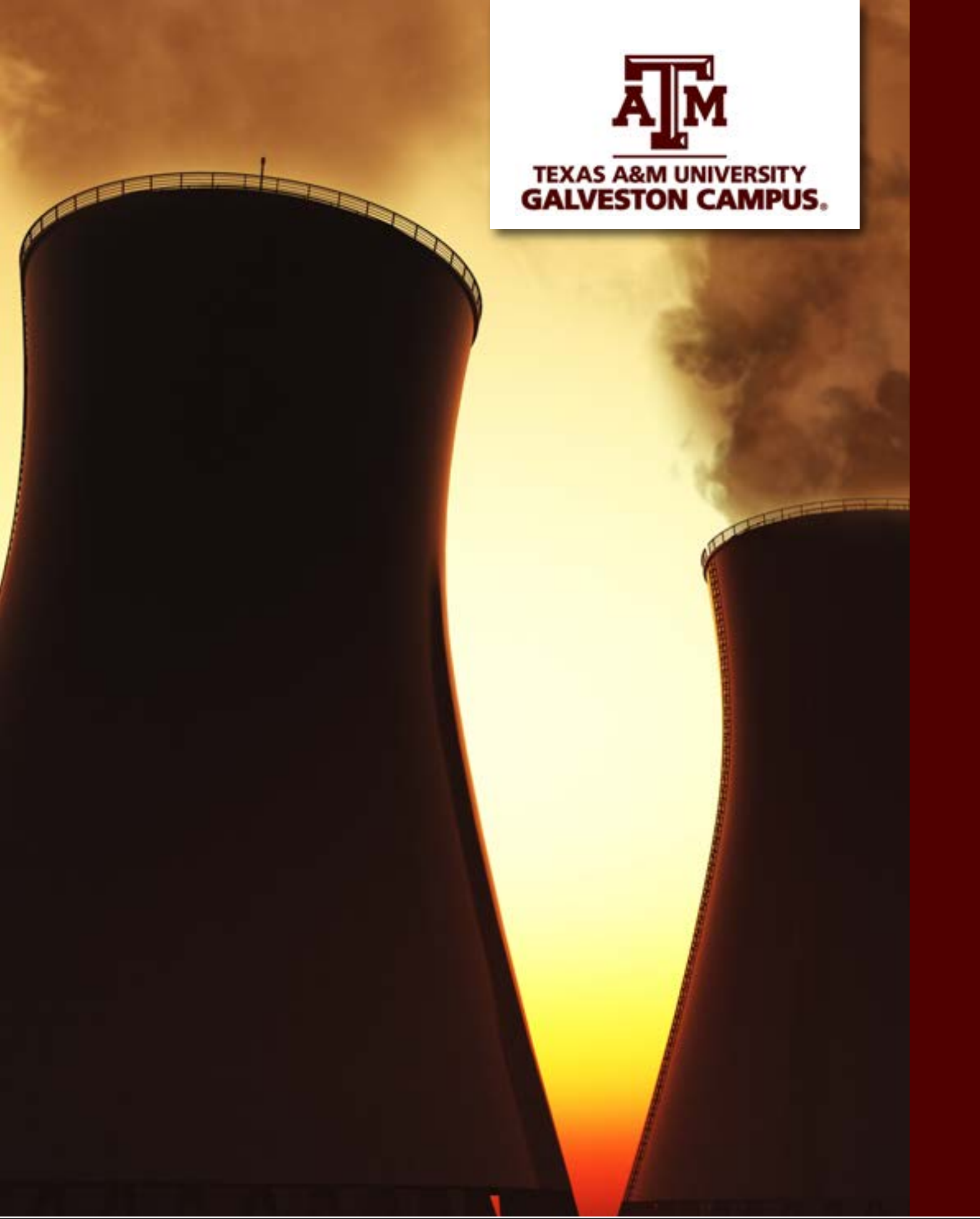

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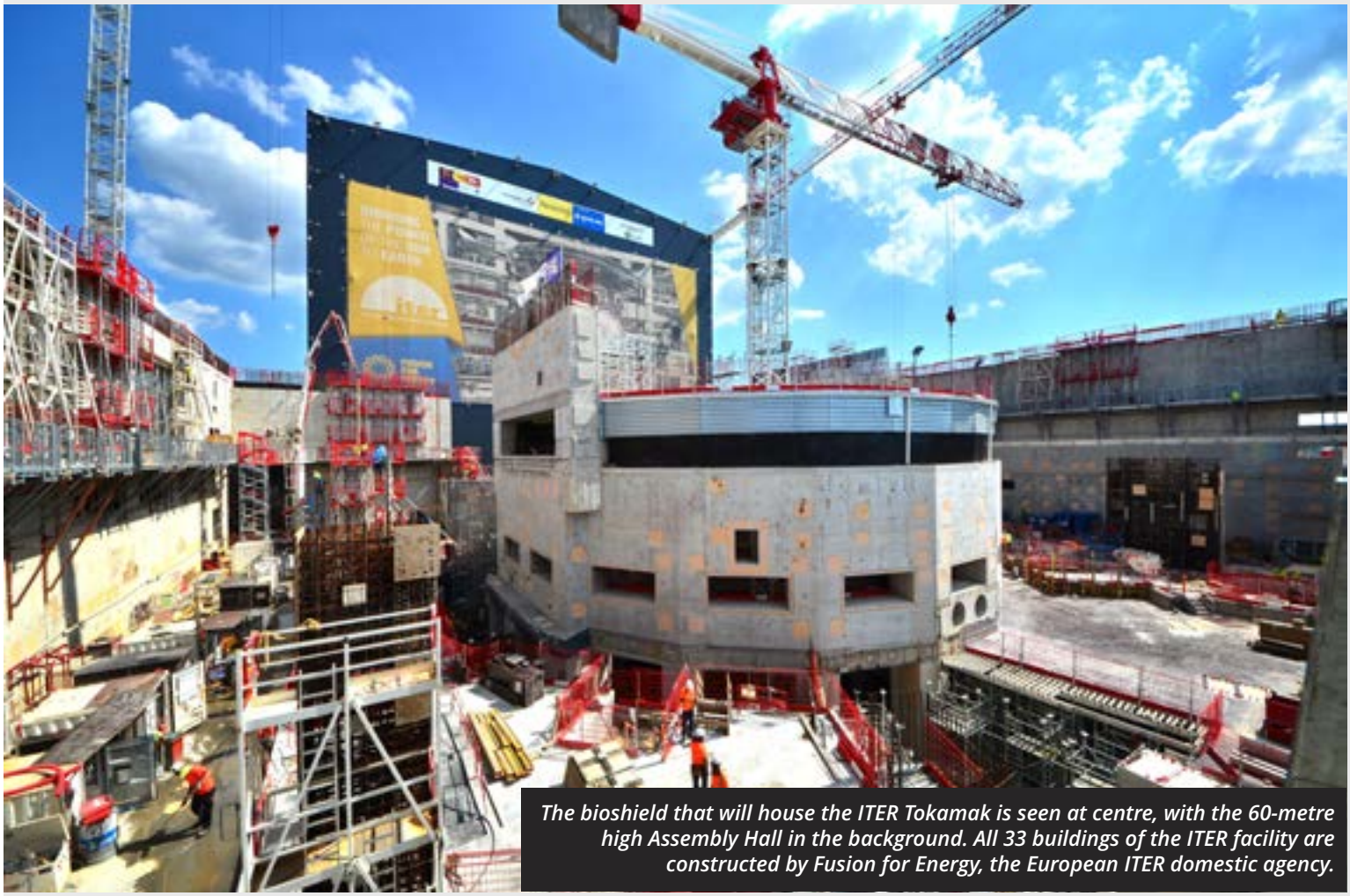
WHY SHOULD WE CARE ABOUT RADIOIODINE IN THE ENVIRONMENT?

Peter H. Santschi from the Department of Marine Sciences at Texas A&M University – Galveston and **Daniel I. Kaplan** from Savannah River National Laboratory share their views on radioiodine in the environment.

In this analysis, the focus is given to the pathways, from source to human risk and presents questions about radioiodine mobility in the environment today.

One of the many fascinating facts revealed here is that according to an article published in Scientific American (Fischetti, 2011), risk factors (in number of premature deaths, including accidents, per 100 gigawatts power produced per year) for nuclear power are extremely low (0.7), compared to fossil fuels such as natural gas (719), crude oil (937) and coal (1200).

Click here to read the full ebook



The bioshield that will house the ITER Tokamak is seen at centre, with the 60-metre high Assembly Hall in the background. All 33 buildings of the ITER facility are constructed by Fusion for Energy, the European ITER domestic agency.

Fusion energy: Global procurement to build a star on earth

Laban Coblentz, Head of Communication, ITER provides an overview of fusion energy, focussing on the first industrial-scale fusion reactor

In the 1990s, when the ITER Project was in the early design stage, the prospect of building the first industrial-scale fusion reactor – a star on earth – had every ITER Member country lobbying to host the facility. The economic benefits were obvious and attractive. The chance to push the boundaries of innovation in many technologies, from robotics and power electronics to cryogenics, superconducting magnets, and materials science, promised major advancements for industrial suppliers.

Fierce competition led to compromise. Each Member chose critical pieces of the ITER Tokamak and its support systems as its spheres of responsibility. Most complex ITER components involve partnerships among multiple nations. Nine companies in eight countries have fabricated superconductor strand for ITER's giant magnets. The magnets themselves, each several hundred tons, are in fabrication in Hefei, China; San Diego, California; St. Petersburg, Russia; La Spezia, Italy; Kobe, Japan; and on the ITER worksite in Cadarache, France.

China has completed all of the winding packs for Poloidal Field magnet #6, at the Institute of Plasma Physics of the Chinese Academy of Sciences (ASIPP) manufacturing facilities in Hefei.

In its heavy engineering facility in Hazira, Indian contractor Larson & Toubro is manufacturing segments of the upper cylinder of the Cryostat: The giant "refrigerator" that will house the ITER Tokamak.

A segment of the colossal Central Solenoid magnet, "the beating heart of ITER," under fabrication at General Atomics near San Diego, California, USA.

Port stub extensions for the ITER Tokamak are being supplied by the Efremov Institute in St. Petersburg, Russia.

The first toroidal field magnet was completed last year at Mitsubishi Heavy Industries near Kobe, Japan.

A true "visit to ITER", therefore, requires a global tour. This article shows a small sample of the ITER fabrication centres around the world. Together, 35 countries are committed to making fusion energy – the power of the sun and stars – a reality on Earth. ■

To continue your virtual tour of ITER, visit www.iter.org

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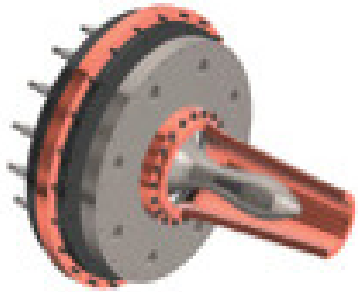
Plasma-Jet-Driven-Magneto-Inertial-Fusion (PJMIF) – A status report

Professor Y. C. Francis Thio and Dr. Douglas Witherspoon from HyperJet Fusion Corporation, Chantilly, Virginia in the U.S. present the latest exciting developments around Plasma-Jet-Driven-Magneto-Inertial-Fusion (PJMIF)

In the previous article in this series[1], the fusion approach, Plasma-Jet-Driven-Magneto-Inertial-Fusion (PJMIF) was briefly introduced and described. We now report on the current status of its development.

While coaxial plasma guns have been used to accelerate plasma since the 1950's, notably in space propulsion as plasma thrusters, the challenges of applying plasma guns as a driver for fusion are unique. The mass density and momentum flux density (the ram pressure) of the plasma jets required for fusion application is typically several orders of magnitude higher than for conventional applications. The jet Mach number (ratio of directed jet speed to internal sound speed) needs to be greater than ten so that the jet avoids excessive expansion, and the liner formed from the jets are highly compressible, while plasma jets launched by conventional plasma guns have Mach number of the order of unity. The jet-to-jet variation in mass, mass density, velocity, temperature and the arrival time of the jets at a particular radius of the reactor chamber needs to be very low.

Our initial 3D computer simulations show that jet-to-jet variation in mass of no more than 5% can be tolerated to maintain good symmetry and peak pressure; we may eventually find that even lower jet-to-jet variations will be required. A stringent requirement is the compactness of the jets. An aspect ratio of the jets (length-to-diameter ratio) of less than unity is required for high energy gains required for a fusion power plant. A typical aspect ratio of jets launched by conventional plasma guns is 10 or more.



The coaxial plasma gun developed by HyperV Technologies and Hyperjet Fusion is shown above. It consists of the following elements:

1. The outer electrodes and the inner electrodes, in between which the plasma slab is accelerated by the huge magnetic field generated by the currents flowing in the electrodes interacting with the current in the plasma slab;

2. A gas valve that injects the working gas into the region between the electrodes at the breech;

3. A pre-ionization system that pre-ionizes the initial gas slab;

4. A capacitor module that stores the energy and creates the huge pulse of current;

5. A set of six high-current, low-jitter, fast switches that discharges the capacitor module and;

6. The transmission manifold that carries the current from the capacitor module to the electrodes.

The following component technologies have been demonstrated:

a. A gas valve that can open and close in 600 μs, driven by a capacitor storing about 1 kJ of energy, and dispense a controlled amount of argon gas up to 1 mg or more with a mass variation of less than 2% from valve to valve;

b. A pre-ionization system that uses an array of 20 capillary discharges with about 1 kJ of stored energy;

c. A switching and triggering system that limits the gun-to-gun variation of the launch time of the jets to about 1 μs;

d. launching an argon plasma of up to 1 mg to velocities exceeding 50 km/s with an energy efficiency of about 25% and;

e. A plasma jet with a density exceeding 10^{16} ions/cm^3 over a length of about 10 cm but with a total length including a lower-density tail of about 1 metre.

A conical array of 7 guns have been installed on the Plasma Liner Experiment (PLX) at Los Alamos National Lab-

Table 1. A brief history of PJMIF

Period	Description	Institutions
1996 - 1999	Invention, theoretical development of the PJMIF concept by Thio[2].	Massey U. (Auckland, NZ), LANL, NASA Marshall Space Flight Center (MSFC).
1999 - 2004	Early experimental exploration by NASA MSFC[3,4]. Concept adopted by NASA for a conceptual system study as the baseline fusion propulsion approach for a human mission to Callisto, a moon of Jupiter[5]. Invention of the coaxial plasma gun with contoured electrodes as a low-cost driver for PJMIF by Thio.	NASA MSFC, U. Alabama in Huntsville (UAH), U. Wisconsin–Madison.
2004 - 2009	Contoured-electrode coaxial plasma gun reduced to practice by Witherspoon at HyperV Technologies with technical contributions from Thio[6]. Further exploration of the PJMIF concept by a number of research groups, stewarded by the U.S. Department of Energy (DOE) Office of Fusion Energy Sciences (FES).	HyperV Technologies, U. Wisconsin-Madison, GA, MIT, Far-Tech, Tech-X, Voss Scientific, Prism Computational Sciences.
2009 - 2014	Los Alamos National Laboratory (LANL) joined the development of PJMIF and constructed the Plasma Liner Experiment (PLX), sponsored by FES[7].	LANL, HyperV, UAH, U. New Mexico (UNM), Brookhaven National Lab (BNL), Tech-X.
2015 - Present	PJMIF selected for development by the DOE Advanced Research Projects Agency–Energy (ARPA-E)[8], and attracted private investments of Strong Atomics, LLC and one other investor. HyperJet Fusion formed to lead PJMIF development. HyperV Technologies functionally merged with HyperJet Fusion. PJMIF development initiated independently at Xi'an Jiaotong University, Xi'an, Shaanxi, China[9].	LANL, HyperV, HyperJet, UAH, UNM, Tech-X, BNL, Xi'an Jiaotong University (XJTU).

oratory (LANL), and experiments to merge the jets launched from these guns to form a piece of the plasma liner have been performed. The initial results[8] show the formation of a series of shocks between merging jets, in qualitative agreements with our 3D computational results.

The experience with the first version of the coaxial guns indicates that considerable improvements on the gun are necessary to field 36 guns in a spherical array to perform a high-quality liner-formation experiment. Development is in progress at HyperJet Fusion of an upgraded coaxial plasma gun to improve on the earlier gun-performance metrics as follows:

a. To reduce the open-and-close time of the gas valve;

b. To reduce the energy required to drive the gas valve to below 0.2 kJ;

c. To have a pre-ionization system that is more convenient and efficient and;

d. To reduce the total length of the jet including the low-density tail by more than a factor of two and increase the density by a corresponding factor over the densest part of the jet.

Our plan is to field 36 of the upgraded plasma guns on PLX at LANL during 2019 to experimentally demonstrate a fully spherical imploding plasma liner and obtain data on liner ram-pressure scaling to benchmark our models and codes.

In the next article in this series, we will present more details of the results of our preliminary experiments on merging a conical array of plasma jets we have performed so far and describe in more detail the planned 36-gun experiments on PLX, which will be the world's first attempt at merging an array of plasma jets to form and study a spherically imploding plasma liner.

References

1 Y. C. Francis Thio and F. Douglas Witherspoon, "Plasma-Jet-Driven-Magneto_Inertial_Fusion (PJMIF)," Open Access Government, pp. https://www.openaccessgovernment.org/physics-plasma-jet-driven-magneto-inertial-fusion-pjmif/47442/, 9 July 2018.

2 Y. C. F. Thio et al., "Magnetized Target Fusion in a Spheroidal Geometry with Standoff Drivers," in Current Trends in International Fusion Research – Proc. 2nd International Symposium (NRC Canada, Ottawa, 1999), p. 113.

3 Y. C. Francis Thio et al., J. Fusion Energy 20, 1 (2002).

4 Y. C. F. Thio et al., Paper AIAA 2002-4269, 38TH AIAA Joint Propulsion Conference, Indianapolis, July 2002.

5 R. B. Adams et al. "Crewed Mission to Callisto Using Advanced Plasma Propulsion Systems," NASA Technical Report, HYPERLINK "http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20030062121.pdf" http://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20030062121.pdf .

6 F. D. Witherspoon et al., Rev. Sci. Instrum. 80, 083506 (2009).

7 S. C. Hsu et al., IEEE Trans. Plasma Sci. 40, 1287 (2012).

8 S. C. Hsu et al., IEEE Trans. Plasma Sci. 46, 1951 (2018).

9 S. Liu et al., Phys. Plasmas 25, 053506 (2018).

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Promoting excellence in U.S. STEM education

The important mission of the National Science Foundation when it comes to fostering excellence in undergraduate science, technology, engineering, and mathematics (STEM) education for all students in the U.S. is placed under the spotlight by Open Access Government

The mission of the Undergraduate Education (DUE) division within the National Science Foundation (NSF) is to "promote excellence in undergraduate science, technology, engineering, and mathematics (STEM) education for all students."[1]

It is worth noting that this division falls under the work of the Education and Human Resources (EHR) division, the aim of which is nothing but the achievement excellence in U.S. science, technology, engineering and mathematics (STEM) education at every level and in all settings (both formal and informal). The thinking behind this is to foster the progress of a well-prepared and diverse workforce of engineers, scientists, technicians, mathematicians and educators. "The purpose of these activities is to enhance the quality of life of all citizens and the health, prosperity, welfare and security of the nation", they add on their website.

One important goal of the Undergraduate Education (DUE) division is to get the next generation of STEM professionals ready and to retain and attract more Americans towards STEM careers, we discover. Going into further detail, capacity-building strategies in this vein are four-fold:

1. To identify the means to prepare and support teachers who can challenge and inspire students in the STEM disciplines and provide them with effective strategies and materials for learning;

2. To invest in research on learning, to facilitate the translation of research into practice and to foster supportive learning environments and STEM pathways by various means including networking, partnerships, alliances and collaborations.

3. To make sure that the STEM community is broadly representative of America's geographic regions, individuals, types of institutions and STEM disciplines plus;

4. To identify effective ways (formal and informal) to address the STEM knowledge requirements of adults, to help them be both informed and active citizens, as well as productive members of the workforce.[2]

> "NSF INCLUDES was conceived as a sustained effort, a recognition that a problem as complex as the need to broaden participation in STEM requires a long-term, collaborative approach, After laying the groundwork through pilot projects, NSF INCLUDES is taking a significant step toward creating a national network with these new awards."

Funding to advance STEM graduate education training

In terms of a concrete example of how the mission of the Education and Human Resources (EHR) division is put into practice, we need to look no further than a recent news story that details funding announced to advance STEM graduate education training.

Announced in early September 2018, we discover that the National Science Foundation's (NSF) Innovations in Graduate Education (IGE) programme awarded $5.8 million to fund 12 new projects. These projects will pilot, test and validate innovative approaches in STEM graduate education.

Jim Lewis, NSF acting assistant director for Education and Human Resources offers his thoughts on these new investments in terms of how they will help to respond to the needs of the STEM workforce.

"These investments by NSF will help us identify advances in graduate education that address current and future STEM workforce needs. We have an opportunity to test innovative strategies in STEM graduate education to underscore the importance of interdisciplinary and broader professional training. Our goal is to identify educational methodologies and elements that will result in scientists that are ready to meet grand challenges in science and engineering."

One point to add here is that the projects discussed above encompass many divergent areas in graduate education, but what they all have in common is that they aim to investigate approaches that could be scaled for use at other institutions throughout the U.S. It is worth noting that current research areas place the spotlight on graduate students' professional identities, advancing community and industry engagement, "human-centred thinking" in engineering education and strategies that encourage diverse student success in the STEM disciplines.[3]

You can learn more about the projects discussed here at this link.

Leadership in science, technology, engineering and mathematics (STEM)

Looking at recent news from the Undergraduate Education (DUE) division, we find out that the NSF announced new awards in early September that represent the next major step for its programme, NSF INCLUDES. This endeavour concerns the development of a national network to enhance the country's leadership in science, technology, engineering and mathematics (STEM) by broadening participation in these disciplines.

We know that the U.S. innovation economy requires skilled STEM workers to maintain the country's status as a global leader in this area. This is very much supported by NSF Director France Córdova, who explains the thinking behind this programme.

"NSF INCLUDES was conceived as a sustained effort, a recognition that a problem as complex as the need to broaden participation in STEM requires a long-term, collaborative approach, After laying the groundwork through pilot projects, NSF INCLUDES is taking a significant step toward creating a national network with these new awards."

For many years, the NSF along with its partners have sought to create opportunities in the STEM disciplines for all U.S. residents, no matter who they are or where they come from so that they benefit from access to education and employment. We end this article on this vital point, in the words of Córdova.

"NSF INCLUDES addresses populations largely missing in the current science and engineering enterprise. Their inclusion is essential in helping the U.S. maintain its position as the world's leader in innovation. Through NSF INCLUDES, we are funding researchers and others who have great proposals that would move the needle."[4] ■

References

1 https://www.nsf.gov/ehr/due/about.jsp

2 https://www.nsf.gov/ehr/about.jsp

3 https://www.nsf.gov/news/news_summ.jsp?cntn_id=296518&org=EHR&from=news

4 https://www.nsf.gov/news/news_summ.jsp?cntn_id=296531&org=DUE&from=news

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Environmental undergraduate research: Creating a generation of citizen scientists one local problem at a time

On environmental undergraduate research, Professors Tom Landerholm and Kelly McDonald discuss their plan to focus all of their students on the research needed for a local river to recover

When we as citizens look around the world today there are many concerns that make us pause. The growth of populations, socio-political strife, the destruction of the natural environment, exposure to toxic materials at home, at work and to those we love. We see these changes everywhere, from local regions with unique ecologies and politics to competing needs for large swaths of oceans and rainforests, to changes in global economics and climate.

When we as scientists look around the world today we understand that now is not the time to pause. These many concerns lead to an increased need for evidence-based policy, citizen scientists and environmental stewardship. Towards this, STEM leadership across the globe calls for training students at every level in the way that working scientists and engineers do business and with a sense of stewardship. Thus, creating a new generation of citizens capable of exploring, monitoring and remediating our impacts on the world. Yet today, and not for the first time, we are faced with reduced science budgets and an increased politicising of science. So, how do we navigate through these unsettled waters? How do we tackle so many problems with so few resources? How do we give new generations the tools to address the problems of the 21st century?

The SIRIUS Project: A model for doing real science in any classroom

California State University, Sacramento is creating a model that balances these competing needs, called Sustainable Interdisciplinary Research to Inspire Undergraduate Success. This is a model for sustainable science performed at relatively low cost. This is science aimed at local, regional or global problems performed as part of the standard training for every STEM student. To do this, all students must be encouraged to inquire and discover, understand the relevance of their work beyond the classroom, fail and repeat their work – just like a working scientist.

The SIRIUS Project began by redesigning biology classes to collect and analyse real data about the American River that runs through our campus. This urban river has been listed as 'impaired' since the 1970's. We started our students with monitoring changes in ecological relationships, bacterial diversity and toxicology along the river. Following a classroom model called Course-based Undergraduate Research Experiences (CUREs), we integrated twelve courses along these three threads from our intro series through our advanced courses. Importantly, few courses modified their entire semester. Most developed a module encompassing a few weeks, usually changing concepts that they were already trying to teach into river investigations.

Since then, we have added six courses in Chemistry, Geology and Environmental Studies that allow us to collect abiotic data (temperature, pH, potential toxin levels, etc.) to go with our biological data, to compare surface water with groundwater reservoirs and to add human risk assessment to our toxicology studies. Our next goal is to incorporate all of the STEM disciplines at Sacramento State and our four local community college campuses. More STEM disciplines mean more interdisciplinary engagement and better solutions to the problems we face. Engaging all STEM undergraduates in Sacramento will give our scientist-teachers more than 6,000 pairs of hands each semester to work towards a resolution. But even this may be too narrow a view. What might the students training in policy, law, recreation studies, etc. add to the work of SIRIUS? What problems do other communities face that could be studied and, perhaps, resolved by their local educational institutions?

A diversity of inputs leads to better solutions

Scientific American (2014) points out that: "Decades of research by organisational scientists, psychologists, sociologists, economists and demographers show that socially diverse groups (that

is, those with a diversity of race, ethnicity, gender and sexual orientation) are more innovative than homogeneous groups." An important aspect of the SIRIUS Project is our specific goal to train 100% of our STEM undergraduates to do research. The traditional training of researchers involves apprentice-style training in the laboratory of an established investigator. However, limited resources mean that there is inequality in the distribution of these opportunities. Most occur after hours or during summer breaks, a time when many undergraduates must work. Most go to students who have financial help from families, excel academically and already know about the benefits of research. This has severely limited the diversity in STEM, from the professorship down to each graduating class. Hence, redefining these opportunities is critical to this innovative diversity.

Help getting started and the sky is now the limit

SIRIUS is a project that can, essentially, be replicated by any college or university. Once the CUREs are established, the research can evolve and be sustained with normal course budgets. Each institution must assess their needs and seek funding to establish their CUREs. At Sacramento State, a primarily undergraduate institution, our biggest needs were in training faculty to design and implement CUREs and in retrofitting teaching laboratories with equipment to carry out the relevant science. The Division of Undergraduate Education at the National Science Foundation (NSF) provided the time and resources for training faculty and the Major Research Instrumentation program at NSF and the Undergraduate Education Program at the W.M. Keck Foundation in Los Angeles, CA provided grants to purchase equipment.

Now our only question is: How many colleges, teachers and students does it take to change the world?

SIRIUS PROJECT
AT SACRAMENTO STATE

SACRAMENTO STATE
Redefine the Possible

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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

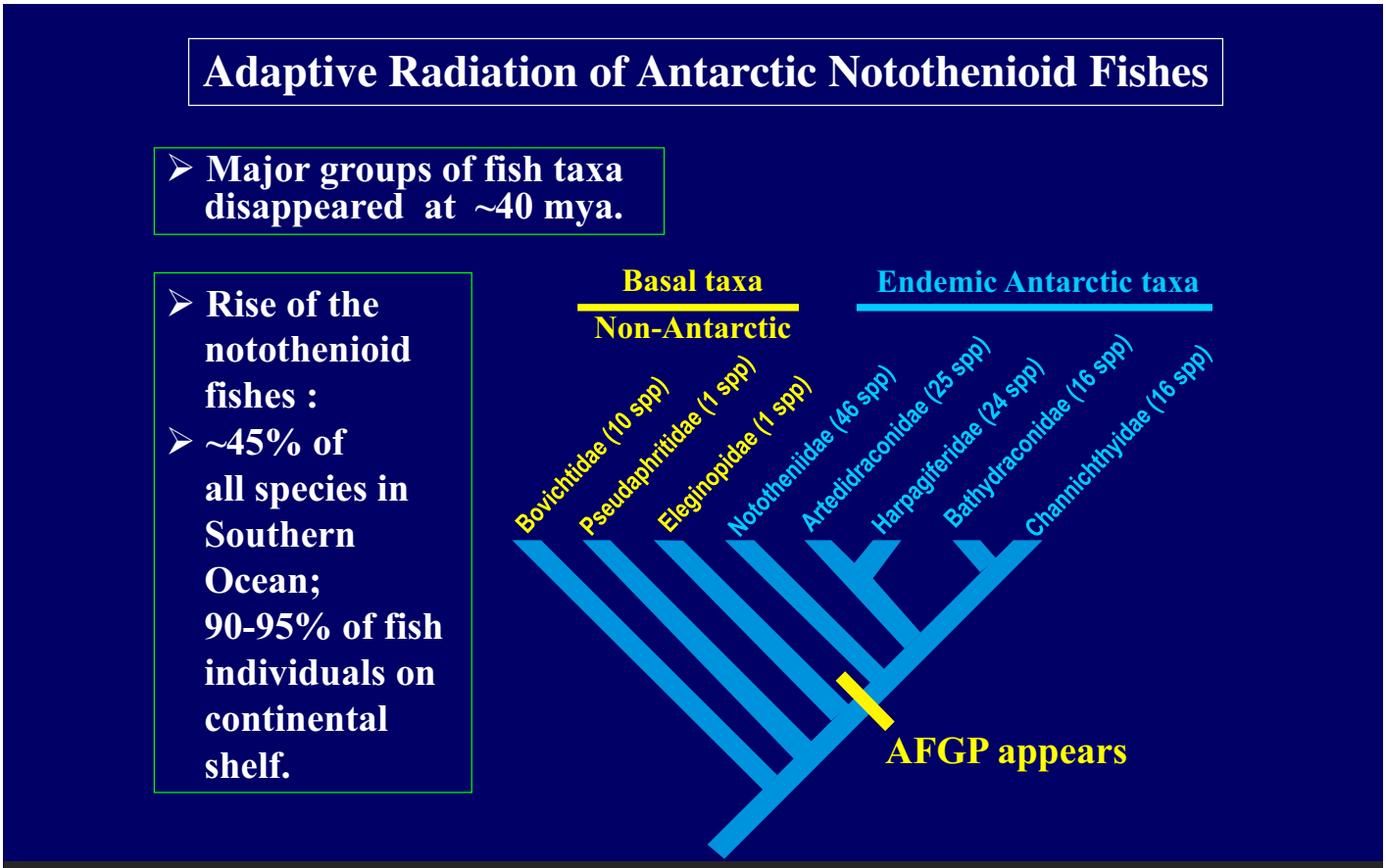

Figure 1. Cladogram of Antarctic fishes of the Suborder Notothenioidei and characteristics of the group

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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Why funding fruit fly research is essential for the biomedical sciences

Andreas Prokop, Head of the Manchester Fly Facility, explains how fruit fly research generates knowledge important for understanding many human diseases

For 30 years I have been studying the nervous system of the fruit fly *Drosophila melanogaster*, the tiny insect that hovers over our fruit bowls in summer (Prokop, 2016). You may wonder why anybody would invest professional time or public money in something that seems more of a private hobby than serious research. But I am not alone: the fruit fly has been intensively studied for over 100 years and worldwide over 10,000 scientists are currently estimated to engage in fly research; and their work has great impact: nine (arguably ten) researchers have received a Nobel Prize in 'Physiology or Medicine' for their work in *Drosophila* – the last one as recently as 2017 (Fig. 1). As I will argue here, the biomedical sciences would be very far behind their current status quo without research in fly or other simple organisms, such as the nematode worm *C. elegans* or baker's yeast.

Why the fly? A historical perspective

Kick-starting genetics

Mere serendipity set in motion the long-lasting interest in the fruit fly: in 1910, studies on evolution by Thomas Hunt Morgan led to the almost accidental finding that genes lie on chromosomes. This started the era of genetics – with *Drosophila* research leading the field unravelling how genes are organised, become mutated or interact with each other (Allchin, 1997; Brookes, 2001; Kohler, 1994).

Genetics as a tool

In the middle of the 20th century, researchers started to use *Drosophila* genetics to address the essential question of how genes work and determine biology. In the same way, as mutations in humans cause inherited diseases that tell us something about the biological relevance of those genes, mutations can be used in *Drosophila* research as a tool to dissect and understand biological processes. The fly was ideal because genetic manipulation techniques were well established, its generation cycle of only 10 days allowed fast progress, and the ease of keeping big numbers of flies facilitated systematic 'mutational screens' to search for new genes that contribute to biological processes (Fig. 2). *Drosophila* became "a boundary object par excellence, residing in the interstices of two major disciplines, genetics and embryology" (Keller, 1996).

Together with the advent of molecular biology (to decipher and manipulate genes) and advances in biochemistry (to study the protein products of genes), fly research turned into a gold mine for discovery. For example, genes that mediate embryonic development, nervous system function or even the ability to learn were discovered and studied, pioneering fundamental understanding of those processes (Mohr, 2018).

> "Fly research turned into a gold mine for discovery... genes that mediate embryonic development, nervous system function or even the ability to learn were discovered and studied"

A translational path to humans

Through parallel work in vertebrate animals, in particular the mouse, it became increasingly clear that fundamental concepts discovered in the fly seemed to apply to all animals: genes studied in mammals turned out to be very similar in structure and function to their fly equivalents; in some cases, it was even shown that genes from fly and mouse were interchangeable. The scale of this 'evolutionary conservation' became clear when the human and fly genomes were sequenced and compared. Ethan Bier and colleagues reported at the time that 77% of 714 distinct human disease genes matched unique *Drosophila* sequences (Reiter et al., 2001). The fundamental truth behind this statement was unequivocally documented by a systematic study

T. H. Morgan *H. J. Muller* *E. B. Lewis* *C. Nüsslein-Volhard* *E. Wieschaus*

R. Axel *J. A. Hoffmann* *J. C. Hall* *M. Rosbash* *M. W. Young*

Fig. 1: Researchers awarded the Nobel Prize for work on Drosophila in 1933, 1946, 1995, 2004 (only marginally for fly work), 2011 and 2017.

in yeast using 414 strains with lethal mutations, of which almost half could be 'cured' by introducing the equivalent human gene (Kachroo et al., 2015; Leslie, 2015). Therefore, the fundamental processes of biology and the genes involved are ancient; organisms that shared their last common ancestor a billion years ago have maintained many of these fundamental functions to astonishing degrees. This concept of 'deep homology' explains the above mentioned Nobel laureates: through their work, they have laid foundations for a fundamental understanding of biological processes which can explain to us what goes wrong in human disease and pave the translational path into the quest for cures.

The importance of *Drosophila* research is undiminished

The last decades have brought new strategies for research in mice and other vertebrate animals that have now turned also these organisms into true boundary objects. The fairly recent advent of CRISPR technology is seen as the magic silver bullet that has finally closed the experimental gap to research in smaller invertebrate models. However, I would argue that this is a dangerous misconception likely leading to increased research costs, the unnecessary use of animals and a slow-down in scientific advance.

> "In the middle of the 20th century, researchers started to use *Drosophila* genetics to address the essential question of how genes work and determine biology. In the same way, as mutations in humans cause inherited diseases that tell us something about the biological relevance of those genes, mutations can be used in *Drosophila* research as a tool to dissect and understand biological processes."

Hugo Bellen was cited to have said: "You get 10 times more biology for a dollar invested in flies than you get in mice" (Levitan, 2015). To illustrate this point, keeping 400 fly stocks requires one stand-alone incubator and £100 a month to pay for food vials and four to six hours of work (Fig. 3); maintaining the same number

of mouse strains readily accessible would take at least £12,000 a month and a vast housing facility.

Furthermore, CRISPR technology certainly has enormously accelerated mouse research, but it is also well established in *Drosophila* and has enhanced the possibilities of fly research to the same degree. Many more arguments can be listed (Prokop, 2015), but I would like to focus here on one last, enormously important aspect: the fact that biology is complex.

Thus, to understand inherited diseases, it is often not sufficient to gain important knowledge of the affected genes and their products; it requires an understanding of the usually complex functional networks in which they operate (Prokop, 2016). An important strategy to unravel complex genetic networks is the simultaneous manipulation of two or more genes in the same individual – a task that is routinely performed in a fly laboratory, but enormously laborious and time-consuming in mice.

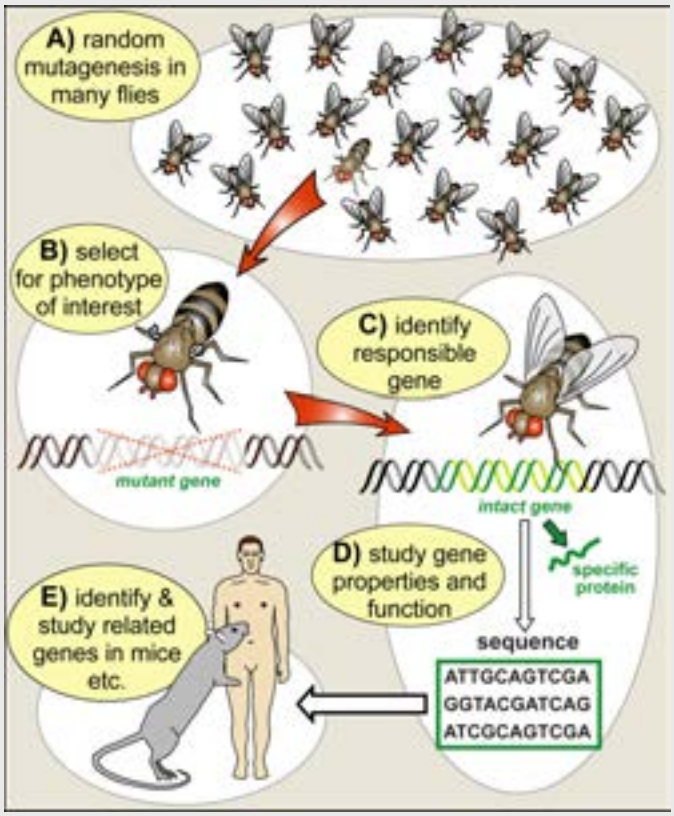

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Fig. 2: Flies as an efficient starting point of a translational pipeline towards medical research

> "Work in fly gives access to flexible experimentation, where try-and-error is a feasible strategy to overcome the challenging enigmas posed by biological complexity."

Furthermore, experiments, even if based on well-informed rationale, often fail. In fly, such failure is unfortunate but can be easily absorbed, since time and money invested are usually low, with alternative experiments being set up in a matter of days or weeks rather than months or beyond. Hence, work in fly gives access to flexible experimentation, where try-and-error is a feasible strategy to overcome the challenging enigmas posed by biological complexity.

Conclusions

Understanding biology is the lifeblood for translational research into human disease and, as I have argued here, *Drosophila* research is a powerful generator of such understanding. Certainly, the fly is NOT a mini-human. For example, it cannot be used to study arthritis or fibrosis, but it can be used to understand fundamental concepts of extracellular matrix regulation underlying those problems. In the context of Alzheimer's disease, flies are unsuited to study personality loss but can be used to address the still unresolved important question of how this condition triggers nerve cells to die. In any case, the choice of experimental models should always be carefully justified. Consequently, funding panels should, in my opinion, more often question the uses of higher animals where fundamental concepts could be pioneered more efficiently in simpler models – thus spending research money responsibly and speeding up the discovery process. ■

The author, Andreas Prokop, is Professor for Neurobiology at The University of Manchester. As academic head of the 'Manchester Fly Facility' he drives a science communication initiative advocating the wider awareness of fly research. Part of this initiative is the 'droso4schools' project aiming to establish *Drosophila* also as a powerful teaching tool in school biology lessons. The author would like to thank Tom Millard for his helpful comments on the manuscript.

References

Allchin, D. (1997). Thomas Hunt Morgan & the white-eyed mutant. In "Doing Biology (chapter 5)" (J. B. Hagen, D. Allchin, F. Singer, Eds.). Benjamin Cummings — shipseducation.net/db/morgan.htm

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Fig. 3: Maintaining and handling flies in the laboratory. (A) A ~10 cm high vial containing flies. (B) 400 different fly stocks kept in one incubator. Genetic crosses are performed under a stereo microscope (C) on CO_2-dispensing porous pads (D) to carefully inspect the immobilised flies (E).

Brookes, M. (2001/2002). "Fly: The Unsung Hero of Twentieth-Century Science." Ecco/Phoenix, - www.amazon.com/Fly-Unsung-Hero-Twentieth-Century-Science/dp/0060936797

Kachroo, A. H., Laurent, J. M., Yellman, C. M., Meyer, A. G., Wilke, C. O., Marcotte, E. M. (2015). Evolution. Systematic humanization of yeast genes reveals conserved functions and genetic modularity. Science 348, 921-5 - www.ncbi.nlm.nih.gov/pubmed/25999509

Keller, E. F. (1996). *Drosophila* embryos as transitional objects: the work of Donald Poulson and Christiane Nüsslein-Volhard. Hist Stud Phys Biol Sci 26, 313-46 - www.ncbi.nlm.nih.gov/pubmed/11613313

Kohler, R. E. (1994). "Lords of the fly. *Drosophila* genetics and the experimental life." The University of Chicago Press, Chicago, London.

Leslie, M. (2015). Yeast can live with human genes. Blog post in "Science Magazine News" - www.sciencemag.org/news/2015/05/yeast-can-live-human-genes

Levitan, D. (2015). Paul Knocks flies and NIH funding. Blog post in "FactCheck.org" - www.factcheck.org/2015/02/paul-knocks-flies-and-nih-funding

Mohr, S. E. (2018). "First in fly - *Drosophila* research and biological discovery." Harvard Univ. Press, Cambridge MA and London UK - www.hup.harvard.edu/catalog.php?isbn=9780674971011

Prokop, A. (2015). Why fly? Blog post in "droso4schools" - droso4schools.wordpress.com/why-fly

Prokop, A. (2016). Fruit flies in biological research. Biological Sciences Review 28, 10-14 - https://t.co/nyz7zxFfl3

Reiter, L. T., Potocki, L., Chien, S., Gribskov, M., Bier, E. (2001). A systematic analysis of human disease-associated gene sequences in *Drosophila melanogaster*. Genome Res 11, 1114-25 - http://www.ncbi.nlm.nih.gov/pubmed/11381037

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Developmental biology: Electrogenic cells in a gymnotiform fish

Graciela A. Unguez, PhD at Professor of Biology at New Mexico State University argues that electrogenic cells in a gymnotiform fish retain a skeletal muscle transcriptome, but they are not muscle cells in this fascinating example of developmental biology

Embryological, molecular and genetic studies in vertebrates have revealed a highly conserved process of generating skeletal muscle cells. In all species of mammals, birds, fish, reptiles and amphibians studied to date, precursor cells are induced to differentiate to form skeletal muscle by the activation of a small number of core myogenic regulatory factors (MRFs) belonging to the MyoD family of transcription factors[1-4]. All four MRF members, i.e., MyoD, myogenin, myf5 and MRF4/myf6, have been isolated and studied in different vertebrate embryos.

Although the number of copies of these MRFs and their temporal expression patterns during muscle differentiation can differ considerably between species, it is clear that formation of skeletal muscle cells requires MRFs[1-4]. Parallel studies using different vertebrate systems are providing fundamental knowledge of the transcriptional and signalling mechanisms of the MRF-dependent myogenic programme.

Reports that some MRFs are detected in non-contractile cells like the electrical conductive cells of the heart (or Purkinje fibres) in birds and frogs[5], the myoid cells of the thymus and myofibroblasts in mouse[6-7] and the electrogenic cells (or electrocytes) of the electric organ (EO) in electric fish[8] are considered rare exceptions. We investigated the transcriptional regulation of the electrocyte phenotype by MRFs in the gymnotiform *Sternopygus macrurus*. Specifically, we determined the expression profiles of target muscle genes with MRF binding sites tested for activation by MRFs.

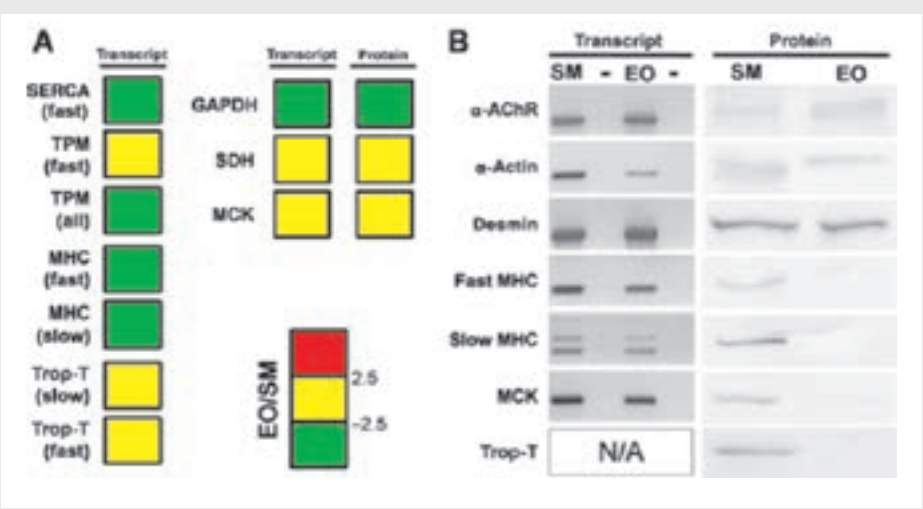

Figure 1. Some muscle genes exhibit post-transcriptional regulation in S. macrurus myogenic tissues. The abundance of contraction-associated and metabolic transcripts was determined in EO relative to skeletal muscle (SM) by quantitative RT-PCR. The expression of metabolic proteins was determined in EO relative to SM using western blotting. Coloration indicates a higher abundance in EO (>2.5 times, red) or in muscle (>2.5 times, green), or a similar abundance in the two tissues (<2.5 times difference between EO and SM, yellow).

Our analysis showed similar levels of these muscle transcripts in EO and skeletal muscle (Fig. 1)[9]. The detection of transcripts for these contraction-associated genes in EO was unexpected given that protein expression studies using mammalian antibodies against muscle creatine kinase, troponin-T and all isoforms of sarcomeric myosin heavy chain failed to detect these proteins in EO lysate (Fig. 1) and mature electrocytes (Fig. 2)[9].

We have also performed an expression analysis using qRT-PCR informed by deep RNA sequencing of transcriptomes of muscle and EO tissues from adult *S. macrurus*[10]. Our data showed that:

- Components associated with the homeostasis of the sarcomere and sarcomere- sarcolemma linkage was transcribed in EO at levels similar to those in muscle; and

- MRFs associated with activation of the skeletal muscle programme were not differentially expressed between these tissues.

Together, these data indicate that the down-regulation of the muscle pheno-

type in EO is not predominantly controlled at the transcriptional level by MRFs. Instead, electrocytes in *S. macrurus* appear to have evolved from striated muscle cells wherein the muscle programme may be under the regulation of non-coding RNAs (long non-coding RNAs, microRNAs) to repress the gene expression that gives rise to the contractile phenotype.

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References

1 Pownall ME, Gustafsson MK, Emerson CP Jr. (2002). Myogenic regulatory factors and the specification of muscle progenitors in vertebrate embryos. Annu Rev Cell Dev Biol. 18:747-83.

2 Rescan PY (2001). Regulation and functions of myogenic regulatory factors in lower vertebrates.

Comp Biochem Physiol B Biochem Mol Biol. 130:1-12.

3 Watabe S. (2000). Myogenic Regulatory Factors. In Johnston, ed., Fish Physiology: Muscle Development and Growth Vol. 5, Academic Press, pp. 19-42.

4 Mok GF and Sweetman D (2011). Many routes to the same destination: lessons from skeletal muscle development. Reproduction 141 301–312.

5 Takebayashi-Suzuki K, Pauliks LB, Eltsefon Y, Mikawa T (2001) Purkinje fibers of the avian heart express a myogenic transcription factor program distinct from cardiac and skeletal muscle. Dev Biol 234:390–401.

6 Grounds MD, Garrett KI, Beilharz MW (1992) The transcription of MyoD1 and myogenin genes in thymic cells in vivo. Exp Cell Res 198:357–361.

7 Mayer DC, Leinwand LA (1997) Sarcomeric gene expression and contractility in myofibroblasts. J Cell Biol 139:1477–1484.

8 Neville CM, Schmidt J (1992) Expression of myogenic factors in skeletal muscle and electric organ of Torpedo californica. FEBS Lett 305:23–26.

9 Guth R, Pinch M and Unguez GA. (2013). Invited Review: Mechanisms of muscle gene regulation in the electric organ of Sternopygus macrurus. J Exp Biol. 216:2469-2477.

10 Pinch M, Güth R, Samanta MP, Chaidez A, Unguez GA. (2016). The myogenic electric organ of Sternopygus macrurus: a non-contractile tissue with a skeletal muscle transcriptome. PeerJ, 4(1828).

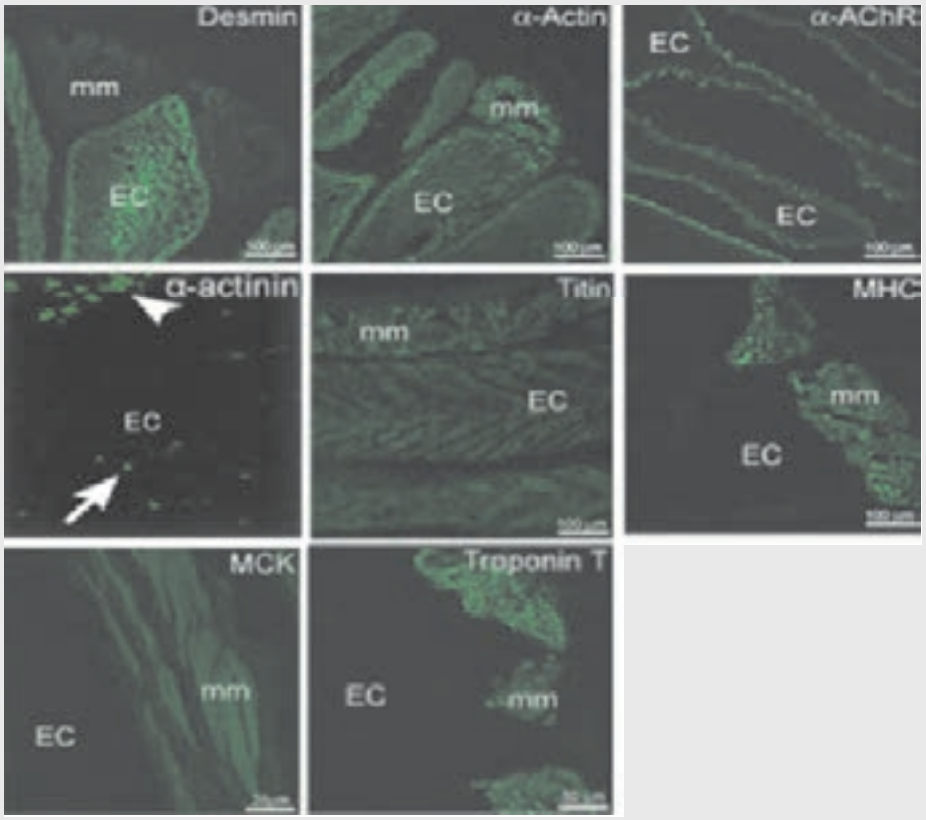

Figure 2. Muscle proteins in electrocytes of S. macrurus. Immunolabeling for muscle proteins (green) reveals staining of electrocytes (ECs) (arrow in α-actinin panel) for desmin, α-actinin, α-acetylcholine receptor (AChR), α-actinin, and titin but not for myosin heavy chain (MHC), muscle creatine kinase (MCK) or troponin-T. mm, skeletal muscle fibers.

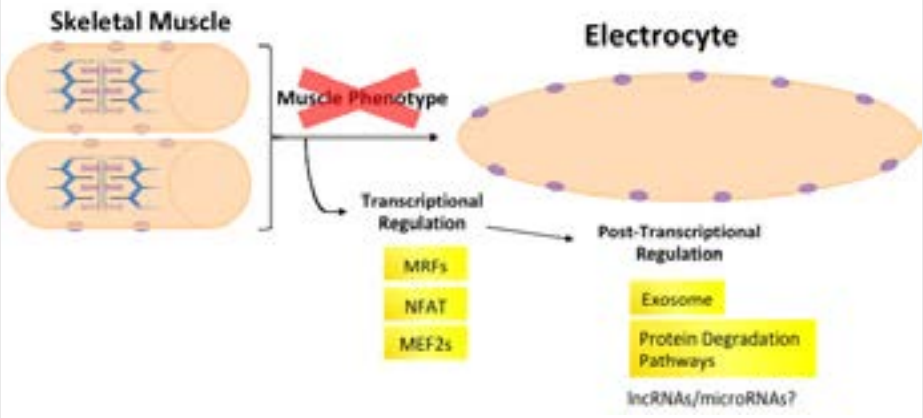

Figure 3. Overview of expression of transcripts associated with regulation of muscle gene expression in muscle and EO of S. macrurus. Electrocytes are large, cigar-shaped, multi-nucleated and do not contain sarcomeres, but express all transcripts that code for sarcomeric proteins, muscle-specific transcription factors, and protein-degradation genes at levels sim ilar to those in muscle.

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High-resolution face completion with multiple controllable attributes

New technology is helping computer systems learn to accurately fill in the gaps in high-resolution facial images – and offer users multiple options for customisation

When we look at an incomplete object with some missing parts, our visual system can immediately fill in the gaps and perceive the object as being whole. In psychology, this is known as the law of closure.

Perceptually completing objects seems to be an intuitive task for human observers, but it can be very challenging for a computer system.

We investigate the problem of constructing completion models for facial images both efficiently and effectively and at high resolutions.

Given samples drawn from an unknown data-generation process, the goal of completion models is to learn the underlying data distribution so that when some samples are corrupted, a trained model can recover the missing data and generate completed samples that are indistinguishable from real ones.

Completion models can be applied to various areas, such as dialogue analysis, audio reconstruction etc. Image completion, in particular, is an important field of completion models, not only because it has many practical applications but also because it is a challenging task due to the high-dimensional data distribution of images.

With the rapid development of social media and smartphones, it has become increasingly popular for people to capture, edit and share photos and videos.

Sometimes, data is "missing" in the pictures or video frames and we need a system that is able to learn ways to generate the missing contents and complete images, with user-chosen constraints, from an initial set of exemplary images.

For instance, faces can be occluded by dirty spots on a camera lens. Users may want to remove unwanted parts from images, such as whelk or dark eye circles.

Finally, before sharing images, many users prefer replacing parts of their faces (e.g. eyes or mouths) with more aesthetic components so that the modified images look more attractive or have more natural expressions.

Image completion is a technique to replace target regions, either missing or unwanted, of images with synthetic content so that the completed images look natural, realistic and appealing.

Image completion can be divided into two categories: generic scene image completion and specific object image completion (e.g. human faces).

Due to the well-known compositionality and reusability of visual patterns, target regions in the former usually have a high chance of containing similar patterns in either the surrounding context of the same image or images in an external image dataset. Target regions in the latter are more specific, especially when large portions of essential parts of an object are missing (e.g. facial parts in Figure 1).

So, the completion entails fine-grained understanding of the semantics, structures and appearance of images and this is a more challenging task.

Face images have become one of the most popular sources of images collected in people's daily lives and transmitted on social networks. Much progress has been made since the recent resurgence of deep convolutional neural networks (CNNs), especially the generative adversarial network (GAN). Data distribution-based generative methods learn the underlying distribution governing the data generation with respect to the context. We address three important issues in our work.

First, previous methods are only able to complete faces at low resolutions (eg 128×128).

Second, most approaches cannot control the attributes of the synthesised content. Previous works focused on generating realistic content. However, users may want to complete the missing parts with certain properties (eg facial expressions).

Figure 1: Face completion results of our method on CelebA-HQ. Our model directly generates completed images based on the input contextual information, instead of searching for similar exemplars in a database to fill in the "holes" like traditional methods. Images in the left most column of each group are masked with grey colour, while the rest are synthesised faces.

Top: Our approach can complete face images at high resolution (1024×1024).

Bottom: The attributes of completed faces can be controlled by conditional vectors. Attributes ("Male", "Smiling") are used in this example. The conditional vectors of column two to five are [0, 0], [1, 0], [0, 1] and [1, 1] in which '1' denotes the generated images have the particular attribute while '0' denotes not. Images are at 512×512 resolution. All images best viewed enlarged.

Third, most existing approaches require post-processing or complex inference processes. Generally, these methods synthesise relatively low-quality images from which the corresponding contents are cut and blended with the original contexts. In order to complete one image, other approaches need to run thousands of optimisation iterations or feed an incomplete image to CNNs repeatedly at multiple scales.

To overcome these limitations, we introduce a novel approach that uses a progressive GAN to complete face images in high resolution with multiple controllable attributes (see Figure1).

Our network is able to complete masked faces with high quality in a single forward pass without any post-processing. It consists of two sub-networks: a completion network and a discriminator.

Given face images with missing content, the completion network tries to synthesise completed images that are indistinguishable from uncorrupted real faces, while keeping their contexts unchanged.

The discriminator is trained simultaneously with the completion network to distinguish completed "fake" faces from real ones. Unlike most existing works that use the Encoder-Decoder structures, we propose a new architecture based on the U-Net that better integrates information across all scales to generate higher quality images.

Moreover, we designed new loss functions, inducing the network to blend the synthesised content with the contexts in a realistic way.

Additionally, the training methodology of growing GANs progressively is adapted to generate high-resolution images. Starting from a low resolution (i.e. 4×4) network, layers that process higher-resolution images are incrementally added to the current generator and discriminator simultaneously.

A conditional version of our network is also proposed so that appearances (e.g. "Male" or "Female") and expressions (eg smiling or not) of the synthesised faces can be controlled by multi-dimensional vectors (Figure1).

In experiments, we compared our method with state-of-the-art approaches on a high-resolution face dataset CelebA-HQ. We showed that our system can complete faces with large structural and appearance variations using a single feed-forward pass of computation with mean inference time of 0.007 seconds for images at 1024×1024 resolution. The results of both qualitative evaluation and a pilot user study showed that our approach completed face images significantly more naturally than existing methods, with improved efficiency.

Video: https://youtu.be/B2vWbRAMkXc

References

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Zeyuan Chen, Shaoliang Nie, Tianfu Wu and Christopher G Healey. High-resolution face completion with multiple controllable attributes via fully end-to-end progressive generative adversarial networks. arXiv preprint arXiv:1801.07632, 2018.

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Maternal education and Specific Language Impairment in children: Not a robust relationship

It has long been held that a mother's education is a key factor in the development of their child's language. However, the link may not be as strong as previously thought, writes Mabel L Rice

Children develop language as they interact with parents, siblings, and people in the neighbourhood. For decades, the extent of mother's education has been recognised as an important indicator of the resources of the home related to children's social, cognitive and vocabulary development[1].

Recently, the New York Times featured an article on its front page that tied higher levels of maternal education to maternal age, due to the additional years of schooling, which in turn delays the start of families but adds to the family financial resources. The age that women become mothers also varies by geography and in the U.S., these factors are also linked to socioeconomic status and urban versus rural residency. In turn, these differences are linked to political decisions and public health policies.

Given the current spotlight on maternal education, it is time to revisit what is known about the relationship of maternal education with children's language acquisition and whether it plays a role in risk for Specific Language Impairment (SLI), defined as a language disorder that delays the mastery of language skills in children who have no hearing loss or other developmental delays.

It would be tempting to think that maternal education could play a large role in children's language acquisition, broadly across all dimensions of language, or in accounting for SLI or providing ways for a child to overcome SLI. Such interpretations would not be consistent with available evidence, however, which shows a more complicated picture of the relationship between maternal education and children's language acquisition.

Effects of maternal education differ depending on the dimension of language studied. For example, relations between maternal education and children's language differ for words compared to grammar. Comparing the relationship of maternal education and language outcomes in children with and without SLI reveals surprising outcomes that work against simple models of causality or ways to overcome SLI.

Mothers' education and children's word learning

The best evidence comes from long-term longitudinal studies of children with and without SLI. In a study of 240 children with SLI and 279 unaffected children that included longitudinal measures from two-and-a-half to 21 years of age, across all participants children of mothers with higher education had higher performance on vocabulary tests over time[2]; however, the effect was weak, accounting for 1.3% of the variance on the vocabulary test.

A study of 1,255 twins at four and six years of age reported that children of mothers with higher levels of education had higher scores across multiple outcome measures (vocabulary and grammar)[3]. On the other hand, an epidemiological study of 1,766 24-month children reported that risk for late appearance of words was not associated with particular strata of parental educational levels or socioeconomic resources[4]. Perhaps a longer span of word learning is more sensitive to influences of maternal education, or perhaps the effects are not as strong for predicting low levels of word acquisition.

Mother's education and grammar

An accumulating body of evidence suggests that maternal education does not predict grammar outcomes. In a study of 69 children at risk for delayed language acquisition, because they were treated in neonatal care units at birth, at four years of age, maternal age predicted vocabulary/semantic outcomes but did not predict grammar outcomes[5].

Another programme of study focused on the finiteness requirement of verb conjugation in English and other languages[6]. This is the requirement for well-formed sentences to mark past tense, the third person singular *-s*, conjugated forms of *BE* copula and auxiliary, and insertion of *DO* auxiliary in questions such as "What do you want?"

These grammar markers appear in the speech of toddlers, although English-speaking children tend to omit them inconsistently throughout the toddler period and beyond.

In a detailed study of toddlers' utterances, mothers' education did not predict change in their toddlers' use of these markers[7]. In addition, a longitudinal study found that mothers' education levels do not predict growth in the production of finiteness markers for children with SLI or typically developing children ages 2;6-8;9[8].

Using a similar task, a study of 130 SLI children, 100 non-specific language impairment (children with low nonverbal IQs), 73 low cognition children (passed language and hearing testing but had low nonverbal IQ) and 117 unaffected controls reported initial test levels in kindergarten for all four groups and longitudinal outcomes for the other three groups between six and 10 years. Mother's education did not predict accuracy on the grammar marker in kindergarten or growth in accuracy between six and 10 years in any of the groups[9].

Another study used tasks requiring children between the ages four and eight to make judgments of sentences similar to sentences they produce with omitted finiteness markers and compared children with SLI, younger controls and same age controls. Mothers' education did not predict growth in children's judgments of errors for any of the groups[10].

A further study documented ongoing acceptance of omitted *BE* and *DO* in questions, in children with SLI but not their unaffected peers aged six to 15. Mother's education did not predict performance for either group of children on this grammar task[11].

In a large sample of 16-year-old twins, the correlation of mothers' education with grammaticality judgments for the question finiteness task was .16, statistically significant but low, accounting for only .0256% of the variance[12].

Another measure of young children's early language is their mean length of utterances, measured in words and morphemes such as finiteness markers and others such as plurals and prepositions. In a longitudinal study of an SLI group and a younger MLU-matched group, mother's education did not predict growth for either group in vocabulary scores or MLU between three and 10 years[13].

A study of MLU in 306 children ages three to nine with SLI (170) and without SLI (136) found no evidence of an advantage in MLU growth for the children of higher educated mothers at the initial times of assessment. Further, there were low correlations between siblings within the families of the target children[14].

Revisiting the focus on mother's education

Although mother's education is surely an important factor in a family's social and economic resources and in many aspects of children's lives, it appears that the influence of this metric on children's language acquisition and the developmental trajectories of various linguistic manifestations of SLI is modest at best.

Children's acquisition of grammar, in the metrics of MLU in early childhood and in the likelihood of finiteness marking throughout childhood, appears to be unaffected by maternal education levels. This is consistent with the observation that young children around the world, across diverse levels of maternal education, acquire their native languages usually without explicit teaching. It also assures us that it is very unlikely that low levels of maternal education are the cause of SLI.

References

1. Entwisle DR, Astone NM. Some practical guidelines for measuring youths' race/ethnicity and socioeconomic status. Child Dev. 1994;65(6):1521-1540.
2. Rice ML, Hoffman L. Predicting vocabulary growth in children with and without Specific Language Impairment (SLI): A longitudinal study from 2 1/2 to 21 years of age Journal of Speech, Language & Hearing Research. 2015;58:345-359.
3. Rice ML, Zubrick SR, Taylor CL, Hoffman L, Gayan J. Longitudinal study of language and speech of twins at 4 and 6 years: Twinning effects decrease; zygosity effects disappear; and heritability increases. J Speech Lang Hear Res. 2018;61:79-83.
4. Zubrick SR, Taylor CL, Rice ML, Slegers D. Late language emergence at 24 months: An epidemiological study of prevalence, predictors, and covariates. J Speech Lang Hear Res. 2007;50:1562-1592.
5. Rice ML, Spitz RV, O'Brien M. Semantic and morphosyntactic language outcomes in biologically at-risk children. Journal of Neurolinguistics. 1999;12:213-234.
6. Rice ML. Language development: Learning from what children say. Open Access Government. 2018.
7. Hadley PA, Holt J. Individual differences in the onset of tense marking: A growth curve analysis. Journal of Speech , Language, and Hearing Research. 2006;49:984-1000.
8. Rice ML, Wexler K, Hershberger S. Tense over time: The longitudinal course of tense acquisition in children with specific language impairment. J Speech Lang Hear Res. 1998;41:1412-1431.
9. Rice ML, Tomblin JB, Hoffman L, Richman WA, Marquis J. Grammatical tense deficits in children with SLI and nonspecific language impairment: Relationships with nonverbal IQ over time. J Speech Lang Hear Res. 2004;47:816-834.
10. Rice ML, Wexler K, Redmond SM. Grammaticality judgments of an extended optional infinitive grammar: Evidence from English-speaking children with specific language impairment. J Speech Lang Hear Res. 1999;42:943-961.
11. Rice ML, Hoffman L, Wexler K. Judgments of omitted BE and DO in questions as extended finiteness clinical markers of specific language impairment (SLI) to 15 years: A study of growth and asymptote. Journal of Speech, Language, and Hearing Research. 2009;52:1417-1433.
12. Dale PS, Rice ML, Rimfeld K, Hayiou-Thomas ME. Grammar clinical marker yields substantial heritability for language impairments in 16-year-old twins. Journal of Speech, Language, and Hearing Research. 2018;61:66-78.
13. Rice ML, Redmond SM, Hoffman L. MLU in children with SLI and young control children shows concurrent validity, stable and parallel growth trajectories. J Speech Lang Hear Res. 2006;49:793-808.
14. Rice ML, Smolik F, Perpich D, Thompson T, Rytting N, Blossom M. Mean length of utterance levels in 6-month intervals for children 3 to 9 years with and without language impairments. Journal of Speech, Language, and Hearing Research. 2010;53:1-17.

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Transforming chemical discovery and innovation

The National Science Foundation's Division of Chemistry (CHE) aims to be a global leader in transforming chemical discovery and innovation, as Open Access Government finds out

The Division of Chemistry (CHE) supports research in chemical sciences and works to advance education through strategic investment in developing a globally-engaged chemistry workforce that reflects the diversity of the United States.

It encourages chemists to lead multi-disciplinary efforts to expand human knowledge and address societal problems, both short and long-term. The CHE also has a major role in communicating the value of chemistry to the public.

As part of the National Science Foundation (NSF), the CHE has awarded millions of dollars to support research initiatives in all 50 states. California has the received the most funding, with $173.9 million distributed to 251 projects.

Recent research backed by the CHE has helped scientists at the University of Oregon and Oregon State University to detect previously unknown triggers for toxicity in nanomaterials caused by an automated system designed to speed up their delivery for testing in fish.

In the early days of nanotechnology, toxicologists' hand-delivered microscopic nanoparticles using pipettes for exposure to zebrafish. Based on that approach, the four-member research team found that individually, the widely used mix of inorganic nanoparticles and surfactants - compounds that reduce surface tension in liquids to improve mixing - were not toxic.

However, automation - using devices similar to inkjet printers to rapidly inject materials employing small amounts of surfactant to control the size of the delivered droplets - created a synergistic, or multiplying, the effect that triggered toxicity. In testing, there was an 88% mortality rate among zebrafish embryos.

While it is not yet clear if the new-found toxicity could pose a threat to human health, the research, which was published in the journal ACS Nano, has been described as a "wake-up call" that could ultimately help the cutting-edge field of nanotechnology to advance.

Study co-author Jim Hutchinson of the University of Oregon's Department of Chemistry & Biochemistry says: "Years after showing that these materials were the most benign and among the least toxic materials that we've ever seen, we did these experiments with the surfactants and found that, in this case, they were toxic.

> "With an annual budget of $7.5 billion, the NSF supports around a quarter of all federally supported basic research conducted in America's colleges and universities."

"This isn't the first time that people have seen mixture toxicity, but it does remind us that two safe things mixed together doesn't mean the mixture is safe."

Elsewhere, CHE-backed researchers at New York University (NYU) recently discovered new molecular properties of water.

Liquid water is known as an excellent transporter of its own autoionisation products – the charged species when a water molecule (H20) is split into protons (H+) and hydroxide ions (OH-). Indeed, life itself would not be possible without this property.

For nearly a century, it was thought that the mechanisms by which water transports H+ and OH- ions were mirror images, except for the directions of the hydrogen bonds in the process.

However, state-of-the-art theoretical models predicted a

fundamental asymmetry in the mechanisms. If correct, this could allow systems to be tailored to favour one ion over another – but the experimental proof was hard to come by because of the difficulty in observing the two iconic species.

A team at NYU, led by Professor Alexei Jerschow successfully demonstrated the asymmetry with a novel experiment whereby water was cooled to its so-called temperature of maximum density - a point just above freezing at which asymmetry was expected to be strongest.

Using nuclear magnetic resonance methods, the researchers showed the difference in lifetimes of the two ions reaches a maximum value (the greater the lifetime, the slower the transport). By accentuating the difference in lifetimes, the asymmetry became clear.

"The study of water's molecular properties is of intense interest due to its central role in enabling physiological processes and its ubiquitous nature," says Professor Jerschow.

"The new finding is quite surprising and may enable deeper understanding of water's properties as well as its role as a fluid in many of nature's phenomena."

Other projects backed by CHE funding have ranged from ranged from the discovery of a previously unknown mechanism in DNA that governs whether viruses that infect the body will quickly kill their hosts or remain latent inside the cell to the synthesis of a new epilepsy medication that replaces the precious metals rhodium and dichloromethane with the much greener cobalt and methanol and the discovery of new fatty acids in vegetable oils - the first such discovery since the 1970s.

The CHE's work certainly supports the wider aims of the NSF, which was established in 1950 to "promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defence".

With an annual budget of $7.5 billion, the NSF supports around a quarter of all federally supported basic research conducted in America's colleges and universities. ■

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Chemistry: The growing body of work on signaling within bacterial communities

Emily Weinert, Assistant Professor of Chemistry at Emory University discusses an aspect of chemistry that concerns the growing body of work on the human microbiome

The varied nature of bacterial interactions with humans, playing essential roles in many aspects of human health, as evidenced by the growing body of work on the human microbiome,[1] causing millions of cases of antibiotic-resistant bacterial infections each year,[2] and the role of bacteria in crop and environmental health, has illuminated the need for an improved understanding of bacterial physiology. In particular, understanding the mechanisms by which bacteria sense their environment and alter cellular pathways to maximise survival has the potential to identify new chemical signals and macromolecular signalling cascades that can be targeted to modulate bacterial phenotypes, including growth and competition. However, our knowledge of the chemistry underlying many of these processes is still very minimal, despite the fact that understanding these pathways dictates our ability to rationally develop new methods to alter bacterial phenotypes.

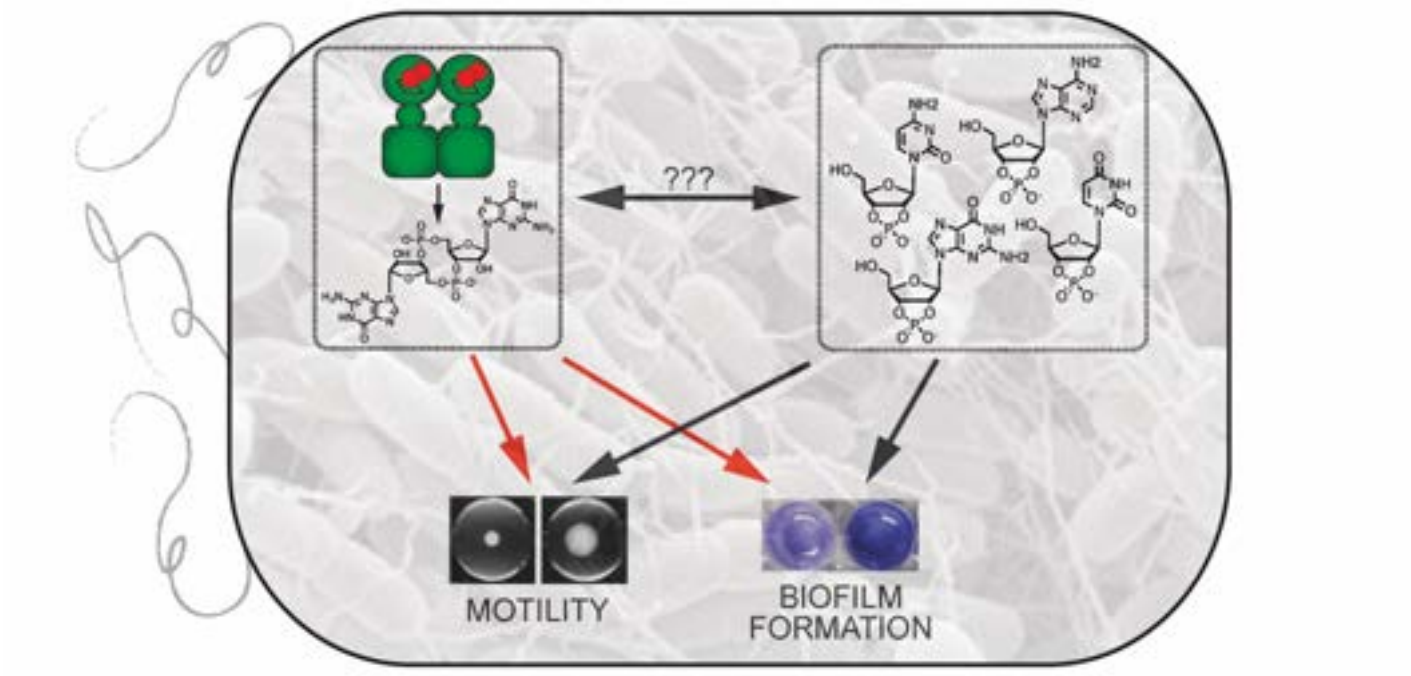
To advance our knowledge of bacterial chemical sensing and signalling networks, extensive studies are needed to identify small molecules and proteins that bacteria use to respond to their environment. In addition, identifying other proteins involved in the signalling pathway and mechanisms of intercommunication between different sensing/signalling pathways is necessary to generate a holistic view of bacterial cellular function. Without this fundamental knowledge, it is extremely challenging to predict how bacteria will respond to external stimuli, especially with regards to understanding what other pathways might interact, potentially muting or amplifying the phenotypic response. Generating this complex picture requires many types of experiments, from whole-cell methods that identify global effects, such as RNAseq and proteomics, to *in vitro* studies using purified components that allow for a molecular-level understanding of sensing mechanisms.

> "Besides the potential identification of targets for the development of new anti-bacterial treatments, these types of studies can also provide insights into previously unexplored mechanisms of signal transduction and bacterial signalling pathways, improving our fundamental understanding of bacterial signalling."

In my group, we are working to elucidate new bacterial signalling pathways using either a putative bacterial protein or small molecule as our starting point. To do so, my group has undertaken two interconnected projects involving previously understudied bacterial signalling pathways: 1) the mechanism and role of oxygen-sensing by diguanylate cyclase-containing globin coupled sensor (GCS) proteins and 2) the metabolism and cellular effects of 2',3'-cyclic nucleotide monophosphates (2',3'-cNMPs). By focusing on two different cyclic nucleotides found in bacteria, we can link results from our studies and provide insight into not only the individual pathways but the interlinked responses as well.

Towards this end, my group has focused on understanding signal transduction and downstream signalling for diguanylate cyclase-containing GCS proteins that serve as bacterial O_2 sensors, since diguanylate cyclase produce cyclic dimeric guanosine monophosphate (c-di-GMP), a bacterial second messenger that controls biofilm formation.[3] Working with a soft rot-causing plant pathogen, *Pectobacterium carotovorum*, we have demonstrated that the GCS protein controls O_2-dependent motility, virulence factor production and the rotting of a plant host, highlighting the importance of GCS signalling for controlling key bacterial phenotypes.[4] To understand how GCS proteins function, we have used a variety of biochemical, spectroscopic and microbiological techniques to shown that O_2 binding causes conformation changes that alter GCS oligomerization and diguanylate cyclase activity.[5]

Furthermore, we have identified interfaces and residues involved in transmitting the O_2 binding signal, which provides a starting point for developing tools to alter GCS activation. By providing key insights into signal transduction within GCS proteins, this work has improved our



understanding of heme-based sensors and ligand-dependent signal transduction and has highlighted GCSs as potential new targets for antibacterial therapies.

Building on our interest in bacterial nucleotide signalling pathways, another project is focused on 2′,3′-cNMPs in bacteria and has allowed us to begin to identify proteins involved in 2′,3′-cNMP metabolism and downstream effects. The presence of 2′,3′-cNMPs in cell extracts was reported in the 1960s,[6] but the results of those studies were discounted as artefacts of the extraction procedure shortly thereafter.

While quantifying 3′,5′-cNMP levels in various rat tissues, we discovered 2′,3′-cNMP isomers in rat organs, mammalian cells and *Escherichia coli*,[7] providing an intriguing starting point to delve into the cellular chemistry and signalling of these nucleotides. By identifying the enzyme responsible for producing 2′,3′-cNMPs in *E. coli* and developing (bio)chemical tools to regulate 2′,3′-cNMP levels, we have demonstrated that these rediscovered cyclic nucleotides are generated during cytoplasmic RNA degradation and regulate bacterial biofilm formation and motility,[8] suggesting potential interplay with c-di-GMP signalling pathways, which also regulate those phenotypes.

Our ongoing studies are focused on dissecting the cellular machinery related to 2′,3′-cNMPs, elucidating novel RNA decay pathways and highlighting novel stress-sensing pathways within prokaryotes, which may allow the 2′,3′-cNMP pathways to be engineered to control bacterial proliferation and virulence.

By identifying new molecules, proteins and pathways involved in bacterial signalling, the field can provide insights from the molecular to the organismal level, highlighting key bacterial phenotypes controlled by small molecules and the interplay between bacterial signalling pathways. Besides the potential identification of targets for the development of new anti-bacterial treatments, these types of studies can also provide insights into previously unexplored mechanisms of signal transduction and bacterial signalling pathways, improving our fundamental understanding of bacterial signalling.

References

1 Sommer, F., et al. Nat Rev. Microbiol. 2013, 11, 227.

2 Infectious Diseases Society of, A., et al. Clin. Infect. Dis. 2011, 52 Suppl 5, S397.

3 Walker, J. A., et al. Adv Microb Physiol 2017, 71, 133.

4 Burns, J. L., et al. ACS Chem. Biol. 2017, 12, 2070.

5 Burns, J. L., et al. Biochemistry 2016, 55, 6642.

6 Wade, H. Biochem. J 1961, 78, 457.

7 Jia, X., et al. Biomolecules 2014, 4, 1070.

8 Fontaine, B. M., et al. Biochem. J. 2018, 475, 1491.

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Advancing food and agricultural research in the U.S.

The USDA's Agricultural Research Services and National Institute of Food & Agriculture both play key roles in advancing food and agricultural research, effective resource management and economic opportunities for rural communities, as Open Access Government learns

The United States Department of Agriculture (USDA) was established in 1862 by President Abraham Lincoln at a time when around half of all Americans lived on farms.

Today, 156 years later, just 2% of Americans live on farms. Nevertheless, the modern USDA aims to stay true to President Lincoln's vision in its work on food, agriculture, rural development and conserving natural resources.

The Agricultural Research Services (ARS) is the USDA's chief in-house scientific research agency. It is charged with finding solutions to problems affecting Americans from the field to table, including food safety; assessing the nutritional needs of Americans; sustaining a competitive agricultural economy; and delivering economic opportunities for rural communities, as well as wider society.

> "This year, the NIFA has provided $2.4 million in funding to address shortages of veterinarians and ensure rural communities have sufficient access to livestock veterinary services."

The ARS runs 690 research projects within 15 National Programmes, employs 2,000 scientists and post-doctorate staff, as well as 6,000 other employees and runs more than 90 research locations both in the U.S. and overseas. The agency's annual budget tops $1.1 billion.

Recent ARS studies have looked at everything from developing a new way of estimating calories, which showed that not all calories in nuts such as pistachios and walnuts are used by the human body, to create a technology that streamlines the process of inserting multiple genes into crop plants. This could make it easier to breed varieties of potatoes, rice, citrus and other crops that are more tolerant to drought, resistant to diseases and produce higher yields.

Elsewhere, an ARS-led team has recently retooled tunicamycin, a compound secreted by a common soil bacterium that kills off encroaching bacteria by forming holes in their cell walls, so it poses little or no danger to human or animal cells but can still kill germs.

This could potentially be hugely beneficial in bolstering the effectiveness of penicillin, which ARS scientists originally helped to mass produce to treat troops during World War II.

Decades of widespread use has seen some germs develop resistance to penicillin. In lab trials, however, mixing the modified tunicamycin with oxacillin and other penicillin-based drugs made them 32 to 64 times more potent.

In addition, the compounds did not harm cultures of human and hamster cells when it was added to them in toxicity tests, the team reported in the Journal of Antibiotics.

The tunicamycin-producing Streptomyces bacteria were taken from the same repository where the first mass-produced strain of the penicillin mould is still kept – the ARS Microbial Culture Collection at the National Centre for Agricultural Utilisation Research in Peoria, Illinois, which in 2001 was designated as an International Historic Chemical Landmark.

The research was carried out by the ARS in cooperation with the University of Illinois College of Medicine and the Chinese Academy of Sciences.

Another key agency within the USDA is the National Institute of Food & Agriculture (NIFA), which administers federal investment in agricultural research and education to address national challenges and ensure ground-breaking scientific discoveries make it beyond the laboratory.

Its priority areas for investment include:

- **Food security:** Supporting science that boosts domestic agricultural production to meet global food demand and fight hunger.
- **Water:** Funding programmes that improve water quality and the efficient use of resources for sustainable agriculture, forest production and ecosystem services.
- **Human nutrition:** Supporting research, education and extension programmes that lead to a healthy population.
- **Agroclimate science:** NIFA-funded projects support adaptation to changing weather patterns, reducing greenhouse gas emissions and sequestering carbon.
- **Sustainable bioenergy:** Contributing to energy independence through investment in bioenergy production and bio-based commercial or industrial products.
- **Food safety:** Reducing food-borne illnesses by addressing the causes of microbial contamination and antimicrobial resistance, improving education for consumers and food safety professionals and developing enhanced food processing techniques.

This year, the NIFA has provided $2.4 million in funding to address shortages of veterinarians and ensure rural communities have sufficient access to livestock veterinary services.

It has also allocated $2.9 million for the 2018 fiscal year to the Rural Health & Safety Education Competitive Grant Programme, which provides funding for individual and family health education in rural communities. Initiatives focus on areas such as the value of good health at any age, providing information to increase people's motivation to take more responsibility for their own health and promoting access to health and educational activities.

Elsewhere, the NIFA has announced grants worth $2 million to support research looking at the implications of gene editing technologies in agriculture.

The University of Florida, Iowa State University of Science & Technology, Santa Fe Institute and Texas A&M University will lead projects that look at issues such as defining consumers' preferences for regulation and consumption of food derived from gene-edited crops; identifying inducements and impediments to the public trust of gene-edited foods; and evaluating the environment for public and stakeholder engagement around the potential research, development and use of gene drive technology in controlling pests.

At the larger end of the scale, the NIFA has committed $21 million to Supplemental Nutrition Assistance Programme (SNAP), which aims to encourage eligible low-income families to buy more fruits and vegetables by providing a range of incentives at the point of purchase.

Among the schemes receiving funding is an initiative to introduce an e-incentive benefits redemption system in Georgia – the first of its kind for nutrition incentives. The system will replace the use of wooden tokens that act as currency for SNAP-eligible foods. The scheme aims to eliminate the stigma attached to using tokens, while reducing the costs associated with the "analogue" system and encouraging repeat visits by being more user-friendly. Data on purchasing habits will also be used to shape marketing efforts.

Increasing low-income communities' ability to purchase fresh fruit and vegetables not only helps to improve the health of families but also expands economic opportunities for farmers. ■

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Agricultural Research: Plant cold hardiness in a changing climate

Michael Wisniewski and David Livingston III from the U.S. Department of Agriculture – Agricultural Research Service (USDA-ARS) share their expert thoughts on the topic of plant cold hardiness in today's changing climate

Since the late 1800's, scientists have sought to understand how plants adapt to freezing temperatures and can survive the formation of ice within their tissues. Unlike animals, plants cannot remove themselves from an unfavourable environment and so have evolved mechanisms that allow them to adapt to temperature stress. Plant responses to freezing temperatures have been divided into tolerance and avoidance mechanisms. As the names suggest, one set of responses allows plants to escape exposure to ice (avoidance) while the other represents changes in the biochemistry and physiology of plants that allow them to tolerate the presence of ice within their tissues (tolerance).

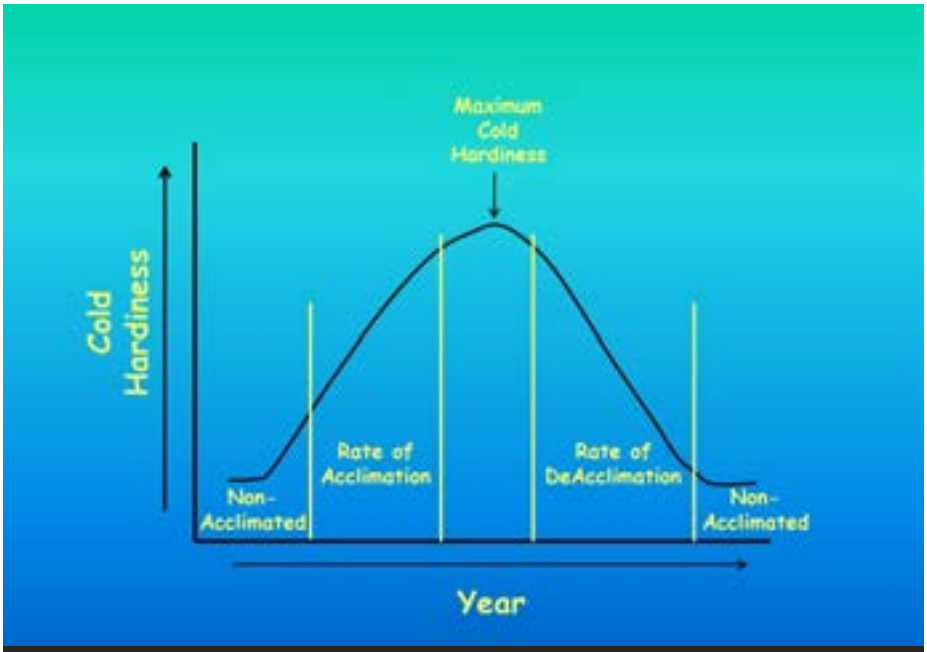

Figure 1: Diagram of the different phases of seasonal changes in cold hardiness, each of which can involve different mechanisms of adaptation and genetic regulation

> "During the past ten years, unseasonably mild winters and erratic spring weather conditions resulting from ongoing climate change have resulted in spring freezing events that have caused catastrophic economic losses to farmers and are inducing shifts in the community structure of the natural environment."

An annual life cycle (i.e. going from seed to seed) and the ability to supercool (i.e. the ability to prevent ice from forming at temperatures well below 0 °C) are examples of avoidance mechanisms, while the accumulation of sugars, cryoprotective proteins, reduction in cellular water and changes in membrane structure, are examples of biochemical changes associated with freezing tolerance.

Tremendous gains have been made over the past 30 years in understanding the molecular biology of cold acclimation, the process that plants undergo in response to exposure to shorter daylength and cool temperatures in the fall that results in increased freezing tolerance.

Key genes, called transcription factors, have been discovered that are induced by low temperature and that regulate the expression of entire sets of cold-responsive (COR) genes. The development of rapid, low-cost DNA sequencing technologies has also allowed researchers to compare the genomes of plant species and genotypes within a plant species that differ in freezing tolerance.

Despite these advances, our ability to improve and regulate plant cold hardiness in a reliable manner has been challenging. Our understanding of the molecular biology of cold hardiness has revealed an ever-increasing level of complexity and genome-wide association studies (GWAS) have made evident a large number of genetic loci that contribute to the polygenic trait of cold hardiness. The challenge in the coming years will be to understand

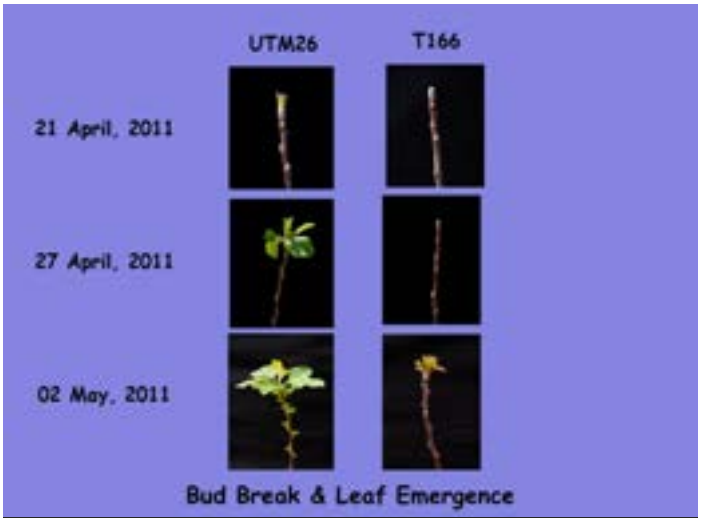

Figure 2: Photos of non-transgenic (UTM26) and transgenic (T166) shoots of apple. The transgenic apple has been engineered to overexpress a cold binding factor (CBF) transcription factor that improves cold hardiness and delays spring bud break

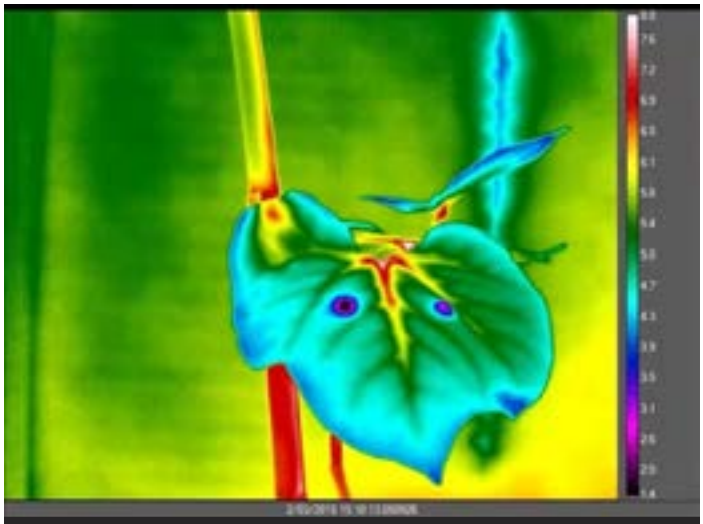

Figure 3: Image of a bean leaf in which the freezing of two drops of ice-nucleating bacteria is evident (purple and black drops) and initial freezing of the leaf is evident in the mid-rib (red/yellow) of the leaf. The image was obtained using high-resolution infrared thermography

how to utilise the explosion of information we have gained about plant cold hardiness to address the critical problems facing agriculture, forestry and the natural environment due to rapid climate change, the loss of high-quality arable land and a growing world population.

Seasonal changes in cold hardiness can be divided into several phases (Fig. 1), each of which can be under separate genetic control and involve different mechanisms of adaptation. Other seasonal aspects of plant development, such as dormancy, growth and flowering are also genetically linked to cold acclimation and need to be taken into account. Finally, tolerance to an acute freezing stress (single freezing episode) vs. a chronic freezing stress (sustained exposure to freezing temperatures for a week or more) must be considered. Only by recognising this complexity, can significant advances in improving plant cold hardiness be made.

During the past ten years, unseasonably mild winters and erratic spring weather conditions resulting from ongoing climate change have resulted in spring freezing events that have caused catastrophic economic losses to farmers and are inducing shifts in the community structure of the natural environment. These events have raised the importance of finding ways of preventing plants from deacclimating (losing cold hardiness), prematurely losing dormancy and avoiding freezing. In fact, genetic transformation has shown that it is possible to produce plants with delayed dormancy (Fig. 2) and high-resolution infrared thermography has been used to elucidate how plants freeze and how ice propagates throughout the plant (Fig. 3). The latter technique has been especially useful in evaluating frost-protection products and evaluating the freezing response of newly developed genotypes.

The increasing occurrence of extreme weather events due to climate change is inducing severe episodes of freezing injury on our modern cultivars of crop plants, exposing them to temperature events for which they have not been bred to cope with, or for which native plants have not had time to adapt to through selection pressures. Only by recognising the complexity of cold hardiness as a polygenic trait, defined by both biophysical and biochemical adaptations that impact survival, can progress be made in improving cold hardiness in a changing climate. This will necessitate a strong commitment to conduct cold hardiness research.

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Meeting the challenges of climate change for dryland cereal production

The effects of climate change threaten food security worldwide. What needs to be done to improve the resilience of vital dryland cereals to more extreme weather?

Image: © Bradley Stokes

Climate change, including warming, changes in precipitation patterns, and increases in extreme events, is continuing and accelerating, validating the model-based projections of climate scientists and the Intergovernmental Panel on Climate Change.

These changes threaten global food security through expected adverse effects on agriculture. Rain-fed cereals in semi-arid regions of the world are particularly vulnerable because often they are already functioning at the limits of sustainability set by annual precipitation and temperature regimes. Historical rates of increase in the yields of these commodities have already slowed in lower latitudes, with immediate implications for human well-being. Effects in higher latitudes may be delayed due to baseline conditions and the fertilising effect of elevated atmospheric CO_2 concentration, but eventually, these systems also will be at risk.

Building resilience of dryland cereals to the challenge of climate change must address entire cropping systems and their interdependent components. These components include crop varieties, methods of cultivation, nutrient management, rotational practices, pest, weed and disease management, crop harvesting, storage and transport.

Genetic improvement of the crops for yield, heat tolerance and water use efficiency must be accompanied by and compatible with improvements in all components of the cropping system. These improvements, include diversifying crops grown to reduce vulnerability associated with continuous cropping, preserving soil carbon, conserving soil moisture, protecting soil health and coping with climate-driven changes in pest, diseases and weeds.

For example, although water scarcity can be addressed by prudently implementing fallow periods, tillage and residue management, novel crop rotations and drought-resilient crop varieties, these will necessitate concomitant optimisation of nutrient, pest, weed and pathogen management. There is, therefore, an urgent need for coordinated efforts by scientists in many disciplines to address whole systems rather than isolated elements.

Further, although the technical advances needed seem achievable, they must be implemented in different social, economic and regulatory contexts. Success will require working closely with farmers and other stakeholders for innovation that can complement the science to ensure new approaches are adopted and supported effectively.

One of the most challenging effects of climate change on cereal systems will be those influencing pests, weeds and diseases. Crop protection is already difficult in most cereal systems and climate change is certain to complicate it. This is because climate change

can cause some pests, weeds and diseases to increase in severity while others may decrease.

Although models project that insect pest pressure in wheat, rice and soybean will uniformly increase with global warming, these have been developed with a focus on insect physiology and population dynamics.

Also important are shifts in pest geographic ranges, climate-driven changes in crop phenology or grower practices, and the effects of climate on natural enemies that provide biological control of pests. Indeed, likely due to these complexities, among the 12 species of wheat pests that have been studied for documented or anticipated responses to climate change, responses are mixed.

Variability in response to climate change is also likely for pathogens and weeds. Thus, against a general theoretical expectation of potential increases in pest, disease and weed pressure with climate change, specific studies are needed to delineate actual effects for individual species and systems and the prudent responses.

As another illustration of the complexity of agricultural system responses to climate change, crop production itself contributes to climate change. Agriculture is responsible for approximately 11% of total greenhouse gas emissions worldwide, with 65% of this due to nitrous oxide emissions from agricultural soils, which could be reduced through improved agricultural practices.

To address these complexities, coordinated efforts are needed that can support scientists and stakeholders in transdisciplinary efforts that consider entire production systems.

One such effort was the recently completed project, Regional Approaches to Climate Change for Pacific Northwest Agriculture (REACCH). The seven-year project, launched in 2011, involved a team of more than 100 faculty members, scientists, graduate students and others from the University of Idaho, Washington State University, Oregon State University and the USDA's Agricultural Research Service.

Participants represented the core agricultural disciplines, climate science, geography, sociology, economics, education and information sciences. The effort integrated research, education and extension. The outputs and impacts of REACCH can be viewed through the project website. Highlights include more than 100 scientific articles on aspects of these systems, a Special Research Topic in Frontiers, Building Resilience to Climate Change in Cereal Production Systems: Agroecosystem Components and Integrative Approaches, projections concerning wheat yields in the region under climate change and online tools for stakeholders to access these, surveys of producer attitudes and practices relating to sustainable wheat production, and a 640-page handbook for producers summarising information to help them succeed.

To share their findings with specialists working on cereal systems globally, the REACCH team also organised a conference, entitled Transitioning Cereal Systems to Adapt to Climate Change (TCSACC).

Experts from 17 countries attended the conference, with backgrounds as diverse as those within REACCH, shared insights and priorities for efforts going forward. One indirect outcome of this was the establishment of an Expert Working Group in Wheat Agronomy within the international Wheat Initiative, with an emphasis on the interdisciplinary integration highlighted through the TCSACC.

As summarised in a published synopsis of TCSACC, which also reflects the effort of REACCH, researchers around the world must:

1. Establish coordinated, large-scale, transdisciplinary efforts that are based on integration among knowledge communities.

2. Strengthen the comprehensiveness of cropping systems models.

3. Consider the global context of production systems by nurturing networks connecting these large-scale efforts. Achieving this will require continued support from national and international funding agencies.

The challenges expected from climate change across many sectors are numerous and some are already evident. Compounding these with decreased food security must be avoided.

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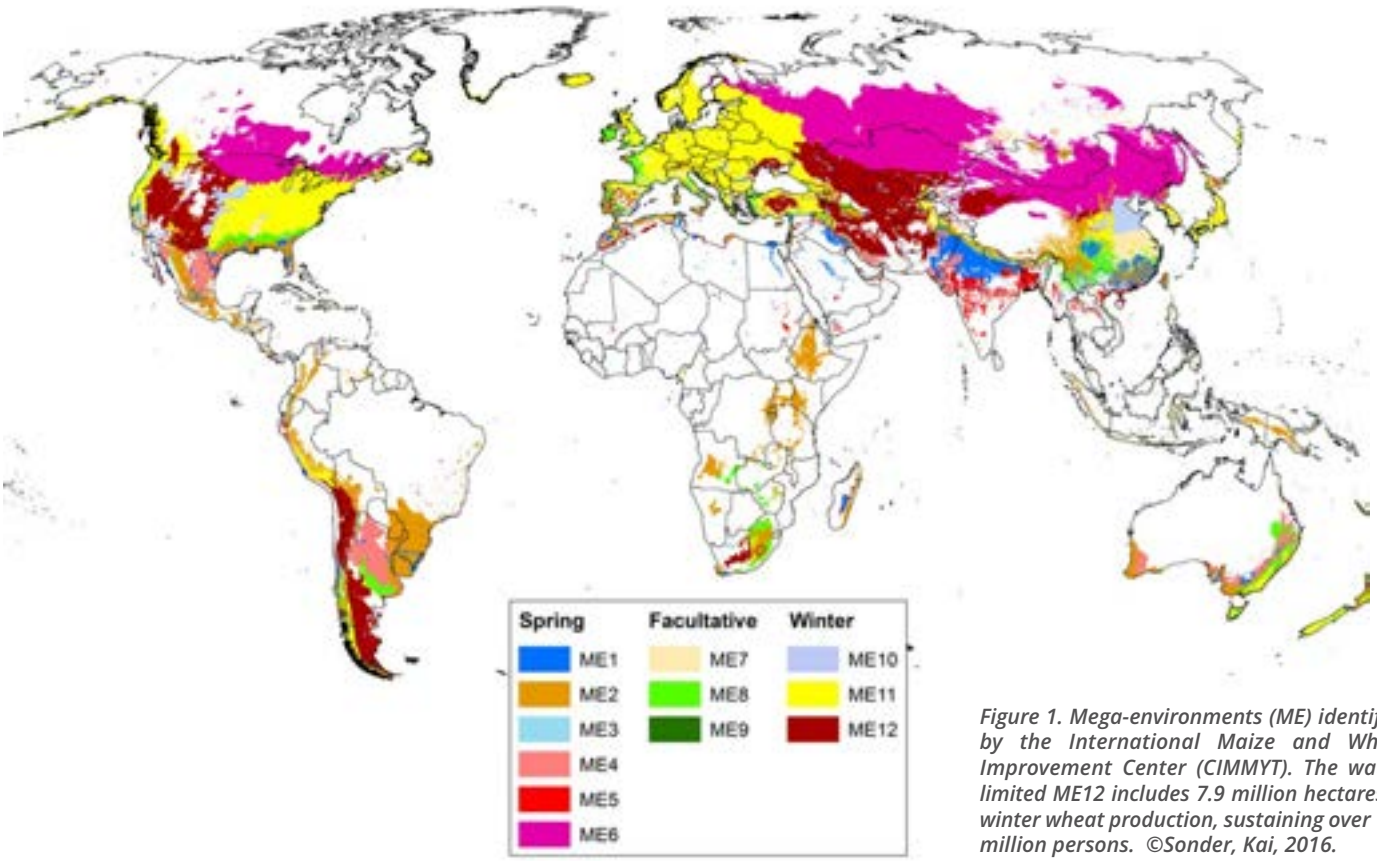

Figure 1. Mega-environments (ME) identified by the International Maize and Wheat Improvement Center (CIMMYT). The water-limited ME12 includes 7.9 million hectares of winter wheat production, sustaining over 140 million persons. ©Sonder, Kai, 2016.

Crop science: What's to be done about climate change?

Professor Robert Aiken, Research Crop Scientist at Northwest Research – Extension Center asks what is to be done about the creeping trends of climate change in terms of semi-arid cropping systems

Like the proverbial frog in the heating pot of water, we may not notice the creeping trends of climate change. The farmers I serve in the semi-arid U.S. Central High Plains encounter dramatic year-to-year fluctuations in weather patterns, which tend to overwhelm the long-term trends. We're just learning how to recognise and interpret long-term climate signals, such as the El Nino-Southern Oscillation[1]. What's to be done to ensure global food security in the face of climate change?

Semi-arid cropping systems, the focus of this series, include 7.9 million hectares of winter wheat production in western U.S., Argentina, western and central Asia (Figure 1); here the evaporative demand for water can exceed annual precipitation by factors of three to five. Is there an opportunity to increase crop productivity, given limited and untimely water supply? My thinking falls along two lines: improving crop water productivity and increased stress tolerance of critical processes such as ovule fertilisation by pollen.

The fundamentals of carbon-water exchange, which underlie crop water productivity, are 'managed' by leaf stomata – gateways permitting carbon dioxide (CO_2) entry to leaf biochemistry, as well as the exit route for water vapour diffusing into the atmosphere. This linked diffusion of CO_2 and water vapour supports the theory that the carbon-water exchange rate is closely regulated, affected by biochemistry and atmospheric humidity.

Greenhouse and field studies (Xin et al., 2009; Narayanan et al., 2013) indicate that sorghum cultivars do differ in carbon-water exchange rates (Figure 2) with parallel differences in radiation use efficiency (Figure 3). This evidence supports accelerated investigations

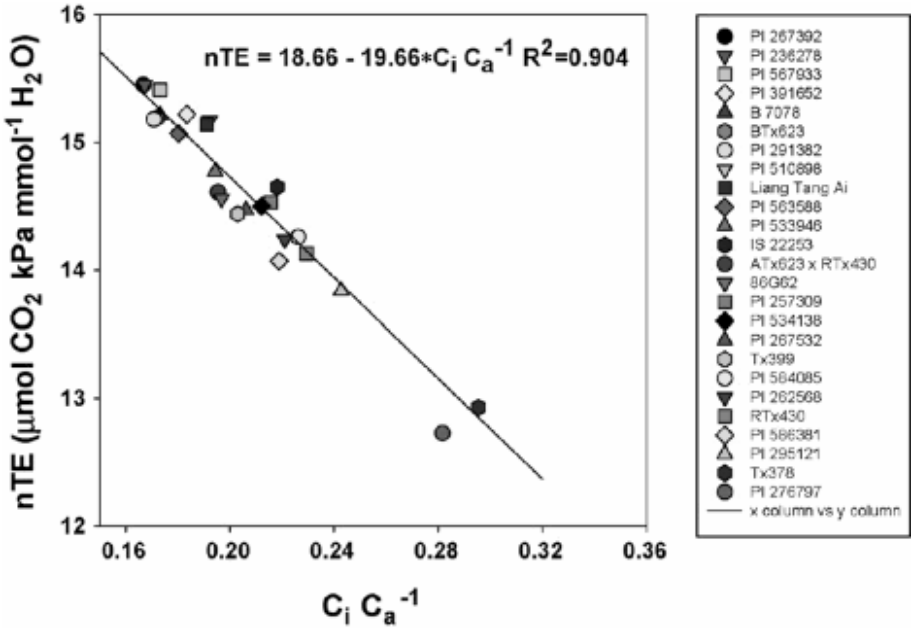

Figure 2. Evidence that sorghum cultivars can differ in the carbon-water exchange rate. Here, instantaneous transpiration efficiency (nTE), normalised by vapour pressure deficit (VPD)—a measure of atmospheric aridity, is shown in relation to the ratio of leaf internal CO2 concentration to air (Ci/Ca-1). ©Xin et al., 2009.

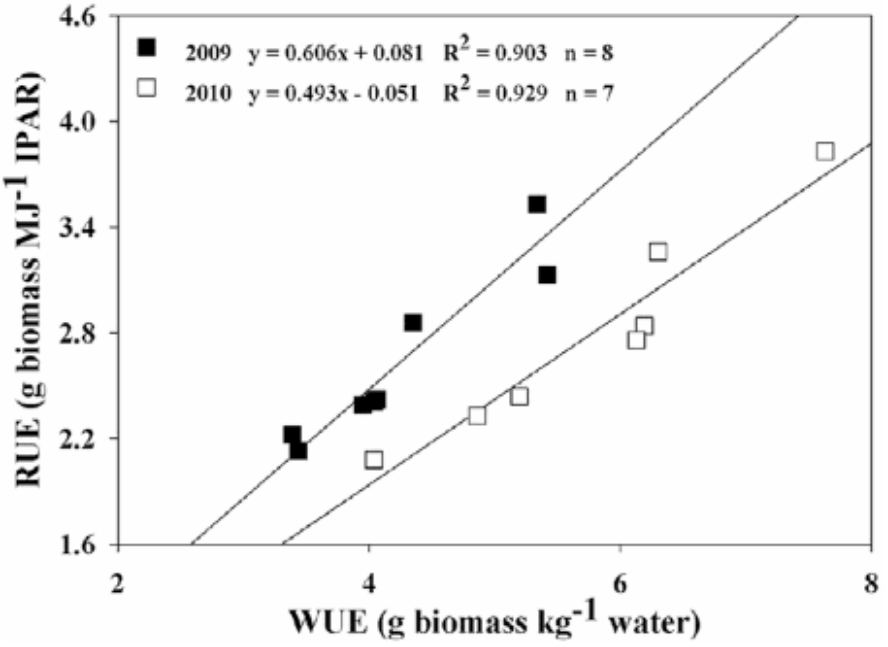

Figure 3. Field evidence that sorghum cultivars differ in biomass productivity in relation to use of water and radiation. Relationships are shown between water use efficiency (WUE) and radiation use efficiency (RUE) among sorghum genotypes; WUE was derived as the slope of the regression of above-ground biomass on cumulative water use, while RUE was derived as the slope of the regression of above-ground biomass on cumulative intercepted photosynthetically active radiation (IPAR). ©Narayanan et al., 2013.

into the mechanisms driving differences in plant carbon-water exchange rates as well as the development of high-throughput screening tools to identify desirable germplasm.

Heat stress and water deficits impair pollen development and fertilisation of ovules, resulting in the 'seed-set' required for grain production, according to careful studies conducted in the laboratories of Dr Vara Prasad[2]. Species of Aegilops, a relative of wheat, provide sources of genetic traits conveying heat and drought tolerance to pollen development and ovule fertilisation. Scientists in the Wheat Genetics Resource Center[3] are systematically integrating these traits with elite breeding lines, developing wheat varieties with increased stress tolerance.

Sustaining the increased crop productivity to provide global food security will require continued innovation, collaboration and vision.

References

1 ENSO, Fluctuations in the surface temperature of the equatorial Pacific Ocean

2 Director, Feed the Future Innovation Lab for Collaborative Research on Sustainable Intensification, www.k-state.edu/siil/

3 www.k-state.edu/wgrc/

Additional references

Narayanan, S., R.M. Aiken, P.V.V. Prasad, Z. Xin and J. Yu. 2013. Water and radiation use efficiencies in sorghum. Agron. J. 105:649-656. doi:10.2134/agronj2012.0377.

Pradhan, G. P., P. V. V. Prasad, A. K. Fritz, M. B. Kirkham, and B. S. Gill. 2012. High temperature tolerance in Aegilops species and its potential transfer to Wheat. Crop Science 52:292-304. doi:10.2135/cropsci2011.04.0186.

Sonder, Kai, 2016, "Global Map of Wheat Mega-Environments", hdl:11529/10625, CIMMYT Research Data & Software Repository Network, V4.

Xin, Z. R. Aiken and J. Burke. 2009. Genetic diversity of transpiration efficiency in sorghum. Field Crops Research 111:74-80. doi:10.1016/j.fcr.2008.10.010.

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Transformative research on Cowpea: *Innovative trap crop development and deployment*

Louis E. N Jackai and Beatrice N. Dingha from the Department of Natural Resources and Environmental Design at North Carolina A&T State University discuss their transformative research on Cowpea for increased and sustained production and use in the USA, with this first article focussing on innovative trap crop development and deployment

Cowpea, *Vigna unguiculata* Walp., is an important source of protein and vitamins. It is widely grown in the Southern USA and in most tropical and subtropical countries worldwide. Cowpea was historically used as a forage crop for horses and cattle (speculated source of the name cowpea), and is utilised primarily as a fresh market and frozen or canned vegetable in Southern USA but is consumed mostly as a dry pea (for example "blackeye pea") on a global basis.

In the Southwestern USA, especially in California and Texas, about 45,000 t of dry cowpea ("blackeye" and other types) is produced annually, on about 20,000 ha. Roughly a third of the production is exported to Europe, Middle East and elsewhere; North Carolina grows only about 2,000 acres, much below its actual potential.

Cowpea has other uses, including as cover crop (especially in organic systems) for soil health enhancement and as an animal feed supplement. Cowpea consumption by humans and livestock is known to have significant health attributes, some yet to be fully understood or exploited; for example, the potential for cowpea extract to reduce proliferation of triple negative breast cancer, a very aggressive form of cancer, as well as increasing immune system defense in ruminants against gastrointestinal parasites among other effects (Adjei-Fremah, 2017).

Cowpea is also attractive to pollinators, such as honey bees and other pollinating arthropods foraging for nectar as they carry out important ecological services that are critical for a productive and sustainable agroecosystem. Many varieties of cowpea have high-yield potential (>3,500 kg/ha), superior seed quality and various levels of resistance to insect pests and diseases.

Both small and commercial production can be profitable; fresh market production is primarily by small growers, while dry seed production is mainly a large commercial enterprise. However, the various benefits and uses of cowpea cannot be realised without adequate control of field and storage pests that can destroy an entire crop.

Production constraints

Pests on cowpea are indeed a bane worldwide. Realising the potential of cowpea as a crop, soil health enhancer, livestock feed or any other use will be difficult to achieve without our ability to minimise the damage and prevalence of insect pests and diseases. Entomologists, Drs Louis Jackai and Beatrice Dingha and their colleagues at North Carolina A&T State University in the USA have been working on the pest problems of small organic and conventional growers who produce 95% of the cowpeas in North Carolina.

The university is the only institution in the state that has a cowpea research programme focused exclusively on pest management. There is a good reason for this focus. Results from recent studies (funded by USDA-NIFA and USDA-ARS) to determine the factors that limit the expansion and use of cowpea indicate that insect pests, especially pentatomid pests, such as the brown marmorated stink bug (BMSB) and a weevil, the cowpea curculio (Cpc), may be among the most limiting challenges.

Cowpea as a trap crop for an emerging invasive pest

Research conducted at two locations, Greensboro, NC (in the Piedmont) and Goldsboro, NC (in the Coastal Plain) revealed that BMSB, a severe pest on fruit, ornamentals and vegetables and the Cpc present inverse population trends, with the former limiting production in the Piedmont zone and the latter in the Coastal Plain. This was most evident in 2014, when our research

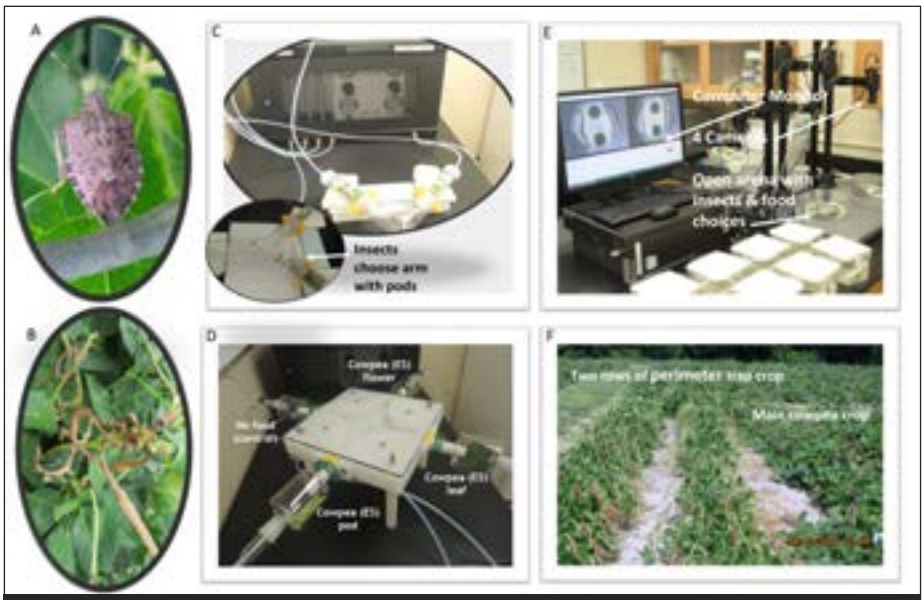

Figure 1: The brown marmorated stink bug (A) causes severe damage to cowpea (B). Several field and laboratory techniques are used in the discovery of a suitable trap crop for this insect including response to plant odors (Y-tube (C) and 4-arm (D) olfactometers and other behaviors related to attraction to a host plant source (using the Noldus Observer XT video system, E). One of the best cowpea trap crop varieties (ES) is shown in F as a 2-row peripheral trap.

showed a near crop failure from BMSB damage in the Piedmont and from the Cpc in the Coastal Plain region.

A broad range of laboratory and field experiments (Fig. 1) have since shown that a few cowpea varieties are particularly attractive to BMSBs and as such, can be used as decoys to attract and divert the pest away from a desired main cowpea crop, thus serving as a sink. This is the textbook definition of the trap crop concept (Hokkanen, 1991; Shelton and Badenes-Perez 2006; Parker et al., 2013), in this case an intra-specific trap crop that uses the same crop species both as trap and main crop.

This finding has many small vegetable growers excited about the long-term possibilities of minimising the use of high-risk pesticides leading to increased food safety and farm profits. In a spin-off from the initial grant, we started to examine the potential of using cowpea as a trap crop in other cropping systems to divert populations of BMSB from high-value crops (such as soybean, corn, sunflower and possibly peppers, tomato and fruit trees – the latter have not yet been tested) to a cowpea trap crop on which the pest can then be killed, with an appropriate insecticide or other method that would result in less environmental and human health risks, while obtaining reasonable crop yield.

The future of trap cropping and other pest management approaches for BMSB suppression

Crop protection using tactics such as trap cropping can take a long time to figure out *where* (field location; conventional wisdom of periphery trap placement may not always be optimal), *when* (time of trap crop introduction) and *how much/and for how long* (trap density/retention).

In some situations, multiple trap crops have produced better yields (Parker et al., 2016); using both perimeter and strip trap crops, our work and that of others, has produced great success in using a single trap crop variety. Traps work because of the olfactory responses that are triggered by semiochemicals (plant odours) that guide the insects to the trap crop.

The same compounds (single or mixtures) may also be present in the main crop, as in crucifer trap cropping, but their concentrations and gene expression may make all the difference. Ongoing work in our laboratories will try to understand these dynamics to make trap cropping more efficient and predictable. This approach is the nexus to sustainable pest management in organic systems and overall ecosystem sustainability; indeed, continued research funding from USDA and other sources as well as innovative ideas hold the key to future success of this and similar pest management tactics.

References

Adjei-Fremah, S. 2017. Molecular Effects of Cowpea Polyphenols on Mammalian Transcriptome, Proteome, and Microbiome. Doctoral Dissertation, North Carolina Agricultural and Technical State University. https://search.proquest.com/docview/1916583456?pq-origsite=gscholar.

Hokkanen, HMT. 1991. Trap cropping in pest management. Annual Review of Entomology 36: 119–138.

Parker, JE, C. Rodriguez-Saona, GC Hamilton &WE Snyder. (2013). Companion planting and insect pest control: INTECH Open Access Publisher.

Parker, JE, DW Crowder, SD Eigenbrode and WE Snyder. 2016. Trap crop diversity increases yield. Agriculture, Ecosystems and Environment 232: 254-262.

Shelton, AM., FR Badenes-Perez. 2006. Concepts and applications of trap cropping in pest management. Annual Review of Entomology 51: 285–308.

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Face to face vs. online training: What's your pick?

Kamy Anderson, an expert in learning management system and e-learning authoring tools, currently associated with ProProfs, explores the differences between face to face and online training

Online training has developed immensely compared to its humble beginnings. A long time ago, it was considered to have poor outcomes when it comes to acquiring knowledge and skills and the learning materials weren't actually embraced by participants. Luckily, the situation has now changed.

Nowadays, online training uses a set of carefully designed courses to cater to each learner's different learning styles and there are many software tools such as Learning Management System (LMS) software or e-learning software which contribute to the satisfaction of both learners and their trainers.

However, traditional face to face training shouldn't be overlooked just yet. Not all students are fans of the online learning environment and some subjects are just not so practical for self-guided learning. So, what to choose? Read on to discover the benefits of both of these approaches and determine what suits you most.

The benefits of online training

Great flexibility – Learners can choose the time and place where they want to take their lessons and are not strictly bound to a schedule. This type of training offers a number of various teaching methods which include audio, text-based or visual examples and explanations. Students can study and review their materials as many times as they wish, which is impossible in a regular face to face environment.

Affordability – Online courses are, in most cases, less expensive than face to face. Once the materials are paid for, they can be used over and over again without a requirement for paying a trainer. It is no longer needed to spend ridiculous amounts of time on organising classes or forcing employees to attend them at times inappropriate for them.

Platforms such as cloud-based LMS or e-learning software are completely automated and self-directed so that the time spent on administering learning activities can be decreased significantly.

Effectiveness – Large businesses can benefit from the scalability of online training to a large base of employees across multiple locations. This type of training is especially useful for compliance training as it reduces the time spent on identifying and addressing gaps as soon as they are detected.

Modular online courses allow your employees to access the materials quickly whenever they need to advance their skills in a certain area, which provides your company with more capacity to focus on new opportunities.

Consistency – Online learning ensures that all materials of a course have been covered by each and every learner. Traditional methods most often fail to do so since different trainers use different teaching styles which are not appropriate for everyone and that can lead to inconsistent outcomes.

Analytics – Exercises in online materials allow for a quick gathering of students' data so that trainers can use them effectively to track their progress and to make any changes in the design of the course, if necessary. Moreover, they allow for detailed feedback to be provided in order to reveal which areas need to be developed further.

Benefits of face to face training

Direct responsiveness – One of the greatest benefits of face to face training is that it enables the instructor to evaluate their students in real time. Instructors can see how attentive a student is, how engaged he or she

is with the studying materials and how well they understand it. With this in mind, teachers can easily adjust the pace of the lesson so as to help their students learn more effectively.

"Online learning is a great tool for someone who has a strong sense of self-discipline and is able to study without the assistance of others, but for someone without these skills, it is mostly useless as they might find it hard to motivate themselves to actually sit down and study."

Collaborative environment – Besides strengthening interpersonal relationships between individuals, team learning provides an engaging environment for people which provides a much wider studying outcome as team members can approach the material they are studying from different perspectives. This method of learning also gives way to discussion and debate among learners which promotes the effective acquisition of new skills and knowledge.

What's the ideal pick?

Clearly, both methods of teaching have their individual benefits and flaws and neither is perfect. When it comes to learning, a combination of different approaches and methods work best, but neither of these alone can promise to provide optimal results.

Online learning is a great tool for someone who has a strong sense of self-discipline and is able to study without the assistance of others, but for someone without these skills, it is mostly useless as they might find it hard to motivate themselves to actually sit down and study.

Other than being affected by the skills and preferences of learners, teaching methods also get affected by the area being studied. For example, certain soft-skills like business storytelling or conflict management would do much better in a collaborative environment since non-verbal communication can often be a very important element of the subject at hand.

The bottom line

As we have already stated above, a combination of both methods has the best chances of achieving good results, as both of these methods alone can perform poorly if utilised alone. As for how much of each should be used, that depends on the subject being studied and the comfort level of the people you need to be trained.

When it comes to policies, standards and any other form of regulatory compliance training, online teaching has shown to have great results while face to face teaching provides great results for studying abstract topics and soft skills. Because of this, the so-called "hybrid" teaching methods are considered to have the best results in universities, workplaces and schools alike.

All of this gave way to the development of platforms for learning management that take the best out of both methods to enable scheduling, administration and analysis of this hybrid learning campaigns' effectiveness. These platforms can help bridge the gap between face to face and online learning, which enables people to make better decisions about which and how much of each method they should utilise.

Kamy Anderson is an ed-tech enthusiast with a passion for writing on emerging technologies in the areas of corporate training and education. He is an expert in learning management system & e-learning authoring tools - currently associated with ProProfs. ■

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Blockchain: Benefits for the supply chain

Chris Burruss, the President of the Blockchain in Transport Alliance (BiTA), explains how blockchain can benefit the supply chain

Currently, moving goods from origin to destination is complex and lacks a single source to store and track all transactions and participants involved. That can potentially be solved with blockchain technology.

Blockchain can simplify the complex and fragmented processes commonly found within the supply chain. Blockchain can create smart contracts and transparency in documents and transactions, increasing supply chains' efficiency, agility and innovation. Smart contracts are computer code hosted on a blockchain that defines/executes the terms of an agreement between parties.

For every shipment, numerous parties are involved; transactions get executed (bills of lading, invoices, proofs of delivery, etc.). Blockchain records transactions, tracks assets and creates a transparent and efficient system for managing those documents. Each transaction becomes a permanent ledger record that is easily validated.

The Blockchain in Transport Alliance (BiTA) is a consortium of transportation and supply chain leaders developing industry standards for blockchain use. BiTA members share a common mission to develop a standards framework, educate the market on blockchain applications and encourage the use of those applications.

BiTA is investigating use cases and developing a common framework the industry can use to build blockchain applications. Through think-tank events, networking, meetings, webinars and online collaboration, members work with peers on common issues and share best practices.

The BiTA community's focus is on community aspects (networking, education, marketing and commercial outcomes). It is BiTA's voice to members, external organisations and stakeholders. The BiTA Standards Council provides a forum to develop industry standards and best practices. It focuses on data formats and the interoperability of blockchain platforms. It is a separate industry group governed by a standards board.

The Council is developing industry standards that: improve trust and enable transparency in the supply chain; and drive technological efficiency, ideally resulting in cost savings for those that adopt the standards. BiTA is not defining a single technology solution; it seeks interoperability and compatibility between solutions used across the supply chain. BiTA standards will be open source and royalty-free.

The key issues that concern leading companies in the freight technology industries that have a vested interest in the development of blockchain technology

While there are challenges that blockchain can solve, it will not solve every problem. Questions to consider about blockchain are: can traditional database technology meet needs; does more than one participant need to update data; does data need to be private; will the database be attacked or censored; do users need to trust each other; is a trusted third-party needed; do changes need to be controlled?

If there is a need for transparency, security and the elimination of intermediaries, blockchain is a solution that allows real-time visibility of freight assets across the supply chain.

Blockchain benefits

1. Monitors performance history

Allows parties to see evidence of participants' past performance, including on-time deliveries, on-time pickups, etc.

2. Maintains high-value assets history

A trusted/accurate record of asset history is imperative to ensure it complies with standards from the factory floor to delivery.

3. Improves quality assurance
Every authorised member of a transaction can access data to validate milestones and reduce unsubstantiated disputes.
4. Monitors real-time freight capacity
Available truck capacity changes constantly. Through blockchain transparency, capacity is visible.
5. Improves payments and pricing processes
Payment processing/settlement is secure in a blockchain and transaction information is accessible.
6. Deters fraud
Every transaction is visible to those on the network. Nothing can be removed without detection; transparency deters fraud. Through notarization/non-repudiation, shippers can securely track the creation and modification time of a document or transaction, thereby confirming authenticity.
7. Prevents theft
A blockchain can contain detailed information and rules, such as requiring photo IDs for freight pick-up/delivery. Added precautions improve security and reduce freight theft. A blockchain also enables the secure transfer of titles for smart properties.
8. Proves provenance
Blockchain ensures that every shipped good includes a digital "passport" proving its authenticity/provenance. Passports include data, such as where/when the product was manufactured and what steps it took throughout its journey.
9. Issuance of smart contracts
Smart contracts are considered by many to be the most important blockchain feature. Entrepreneur magazine states: "With smart contracts, agreements can be automatically validated, signed and enforced through a blockchain construct – eliminating the need for mediators and therefore saving the company time and money."

Barriers to widespread blockchain adoption (risks/difficulties)

Despite blockchain benefits, there are concerns which are slowing the technology's widespread adoption. Among them are:

Lack of standards: For blockchain to succeed, all constituents must agree to data characterisations (i.e., what details will every bill of lading carry, what will the proof of delivery or invoice contain? What actions should trigger if data is missing or not validated?).
Cost: Developing/maintaining the software/hardware required to run blockchain is expensive. Additionally, companies need qualified people to run blockchain, which can be expensive.
Legacy system integration: Companies must integrate blockchain into legacy systems. According to nasdaq.com, "Many organisations are reluctant to make a move to blockchain solutions because of the meticulous planning, time and money that would be required to achieve successful company-wide implementation."
Maturity: Blockchain is an emerging technology. While many anticipate its impact, blockchain is still uncertain. Also, blockchain has few standards or industry specifications for its adoption and use (which is the reason for BiTA's existence).

Why the industry needs common standards

When businesses cannot agree on a common framework, the government steps in and regulates the activity. This slows down processes and creates bureaucracy that increases cost. There is no example of government intervention in which costs were reduced. If the industry does not define the framework within which blockchain resides, the result may render blockchain moot.

The potential blockchain has in the logistics industry

Quite simply, it has the potential to revolutionise the $8 trillion global logistics/transportation/freight industry. Blockchain may be the solution to transparency, security and reducing or eliminating third parties. There are many use cases – payments, provenance and visibility of commercial assets, driver ID, smart contracts, instantaneous settlement of transactions – virtually every challenge with freight tracking and delivery may be solved with blockchain. ■

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eHarvestHub gives small farmers centre stage on the global market

Our global economy is leaving our small farmers behind, yet they produce more than 60% of the fresh food we consume. eHarvestHub gives farmers direct access to the global market making our food more affordable and accessible, as this analysis from Alvaro Ramirez at eHarvestHub reveals

We produce enough fresh food to feed the world, however, affordability and accessibility are a big problem. Fresh food is a global business, yet consumers pay high prices, while the farmers who feed us are financially being left behind. This can all be attributed to the complexity of our food chain. To make fresh food more affordable and accessible, we must radically change the food supply chain; from seed to the grocery store to the lending institutions who finance our small farmers each year.

To make this happen, "true decentralisation is needed and blockchain technology is perfect for it", notes Alvaro Ramirez, CEO and Founder of eHarvestHub. The company's approach to solving the affordability and accessibility of fresh food not only uses blockchain technology to achieve it, eHarvestHub's business model removes the layers of middlemen leaving only key market participants: the grower, the trucker, the grocer and the consumer. The company brings the small farmer to the global stage, giving grocers direct access to their inventories that today can only be accessed through the existing layers. Let's take a closer look.

According to World Bank agricultural data, more than 60% of our global fresh food production comes from the more than 480 million small farmers. The eHarvestHub marketplace gives these small farmers a global stage. Regardless of the geographical location, eHarvestHub has found that small farmers face the same core problems: 1) not enough volume; 2) dependent on middlemen to market their product and arrange transportation and; 3) high-interest loans.

Developed countries with high population and economic power drive food imports today. Twenty-five countries import more than $1 trillion of the world's food production and 66 countries also rely on imported food. For example, last year the United States imported more than $136 billion in fresh food, most of which came from the over 19 million farmers in Latin America. One of the main reasons why the United States imports fresh food from Latin America is because of food safety. Many farmers in Latin America follow Good Agricultural Practices (GAP) and similar food safety practices as American growers.

Small farmers don't produce enough volume to meet supermarkets' demand on their own, forcing them to sell to the multiple middlemen who clutter our food supply chain giving grocers little visibility to small farmers' available inventories. This leaves farmers making pennies on the dollar for their product, while consumers pay high prices and the middlemen profit the most in this ecosystem. The product

moves through the value chain – sometimes exchanging hands seven to 10 times – increasing the risk of contamination, food fraud, lowering shelf life and increasing costs each time a product exchanges hand.

Technology alone is not the answer. To solve the accessibility and affordability problem, eHarvestHub goes to the root of the problem: increase the farmer's margin using blockchain technology with its business model to give the small farmer a stage on the global market. eHarvestHub's CEO says that technology providers fall short because while they may have sound technology, they end up taking percentages from the farmers' profits, only becoming the new middleman. For technology to be effective, the business model must enable growers to have access to the technology without fear of losing their hard-earned money. With eHarvestHub's flat trans-

action fees and no middlemen, these two factors increase margins for the farmer and enable growers to gain the maximum use of the company's technology. This not only creates true transparency for grocers and consumers, but it gives farmers access to consumer-driven lending.

eHarvestHub's full enterprise technology solution provides its customers with traceability, a real-time inventory, order management, direct access to truckers a marketplace where grower, grocer and trucker can interact directly, and it is intuitive and built with not so tech-savvy customers in mind. eHarvestHub's use of blockchain, smart contracts and cryptocurrencies not only to help farmers give full transparency on their products, but to be paid soon after the product has been delivered. Farmers currently must wait up to 90 days after the product has been delivered to be paid. The marketplace smart contract places the funds for a transaction in an escrow account, which gives the buyer a peace of mind as funds only get released if the seller and carrier fulfil all their contracted obligations. Once all parties have fulfilled their obligations, the smart contract releases the funds to the seller and carrier.

Ed Treacy, Sr. Vice President of the Product Marketing Association, describes fresh produce logistics as a web because of the multiple times that fresh produce exchanges hands and locations. eHarvestHub simplifies that web by removing the middlemen. With the goal of making fresh food more affordable and accessible, lowering cost includes "not only removing the need for the supply chain middlemen but also the agricultural lender", explains Alvaro Ramirez. At the start of their planting season each year, farmers borrow from banks often paying up to 17% in interest.

Other financial institutions, unregulated in most countries, can charge up to 60% in interest. Since blockchain can truly connect farmer and consumer – regardless of their geolocation – consumers can see where the food they purchase comes from and where their money is going then they are most likely to support grocers who pay farmers higher. This transparency that eHarvestHub provides, coupled with its cryptocurrency, allows consumers to crowdfund loans for farmers at much lower interest rates than farmers currently pay. This truly gives the power back to consumers and putting the value where it belongs, with our farmers.

eHarvestHub's approach to solving fresh food affordability and accessibility through blockchain technology and its social-economic business model truly disrupt and rewrite how our food reaches consumers. Helping farmers make more money will allow farmers to become more sustainable, as they will possess the funds to do so. Food waste can dramatically be decreased as farmers could plant fresh food based on market needs. The company's approach to consumer lending for farmers has the potential to uplift many farmers from poverty while helping consumers make an extra income.

For more information on how to get involved with eHarvestHub, you can contact Alvaro Ramirez at Alvaro@eHarvestHub.com or visit their website at www.eHarvestHub.com

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A balanced approach to the global challenge of dementia

Dr Yves Joanette, Scientific Director at the CIHR Institute of Aging argues for a balanced approach when it comes to their collaboration-based approach to face the challenge of dementia

Thanks to advances in health care and public health programmes throughout the life trajectory, the world's population are getting older as both the number of older individuals and life expectancy itself are increasing.

Canada follows this trend, as it will reach in some decades the club of super-aged countries, led by Japan, where more than 30% of the population is age 60 or more.

One of the most impacting health challenges in older age – and the incidence increases dramatically as one gets older – is dementia. This condition is the expression of numerous neurodegenerative diseases that are typical of ageing, with the most common being Alzheimer's disease.

Dementia is characterised by a slow and progressive impairment of memory and other cognitive functions, as well as changes in personality and mood. While the disease process is extremely complex and intermingled, it is known that some of the underlying mechanisms causing dementia began over 25 years before the first clinical signs appear.

More than 400,000 Canadians age 65 or older are among the 50 million people estimated to be living with dementia worldwide. The number affected by dementia are at least double when the impact on caregivers is considered.

The challenge is particularly acute for women. Two-thirds of people living with dementia are women. Women are often the primary caregiver for family members with

dementia. In addition, some women must cope with caring for a parent or partner and caring for children at the same time.

Because of the complexity of the challenge and because answers are needed both for those living with dementia and for those who would not want to live with dementia in their future, CIHR has adopted a balanced approach under its Dementia Research Strategy (DRS). The Strategy takes advantages of Canada's existing strengths in the neurosciences, clinical research and the social sciences, while establishing a platform for coordinating research activities and facilitating international collaboration.

The Canadian Consortium on Neurodegeneration in Aging (CCNA) is the flagship initiative of the DRS in Canada. The CCNA supports the collaboration of leading researchers from universities and research centres across the country. It is funded through a partnership between CIHR and a group of charities, industry partners, provincial research funding agencies and philanthropic organisations.

The CCNA addresses the challenge of dementia in a balanced way by focusing on preventing, treatment and quality of life issues.

Since it was launched in 2014, the CCNA has made significant progress. They have assembled teams to focus work on the themes and specific topics. They established the infrastructure to standardise and share data and results. Their work has so far resulted in 100 health oriented peer-reviewed publications. Most importantly, they have established new inter-disciplinary and inter-sectorial research collaboration which takes advantage of the Canadian strengths across universities and provinces.

To tackle the complexity of the diseases causing dementia, CCNA has created a unique clinical research platform involving more than 1,600 Canadians with dementia, mild cognitive impairment and self-report memory problems. The data collected from participants will help identify the mechanisms underlying the development and progression of dementia.

Notably, the CCNA is the only national dementia research platform in the world that includes a cross-cutting sex and gender component, allowing for comparisons of women and men and male and female animal models. This focus will help researchers better understand the sex and gender differences in dementia.

The CCNA is also the main Canadian hub for international collaborative efforts as the global challenge of dementia requires a global answer.

Most recently, the Canadian Academy of Health Sciences asked the CCNA to draft a consensus statement on dementia. The draft statement was the basis for a global statement released by the InterAcademy Partnership (IAP), which includes a World-Academy supported call to action that aims to develop an evidence-based and public health-oriented approach to tackling the challenge of dementia. The IAP joins other global bodies, including the World Health Organization and the World Dementia Council, which are urging coordinated global action on dementia.

Under the DRS, CIHR is contributing to the global efforts and supporting the participation of Canadian researchers in international research programmes. For example, Canada was the first non-European Union member of the Joint Programme for Neurodegenerative Disease Research, the largest international collaborative initiative in the area of dementia.

CIHR is also supporting the participation of Canadian researchers in established collaborative research programmes, such as the U.S. National Institutes of Health's Alzheimer's Disease Neuroimaging Initiative.

Dementia is one of the world's most pressing health challenges. Canada has heard the call. Together with its partners, CIHR is working hard to respond to this challenge and improve the health and wellness of people living with dementia and their families, for today and for tomorrow. ■

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Infections may be the new paradigm explaining the pathogenesis of Alzheimer's disease

Tamas Fulop from Université de Sherbrooke's Research Center on Aging, explains precisely why infections may be the new paradigm explaining the pathogenesis of Alzheimer's disease (AD)

Alzheimer's disease (AD) is one of the most deleterious neurodegenerative diseases. Starting with memory problems, it progresses unstoppably towards the total loss of the patient's identity.

In our ageing society, it has become one of the most disastrous plagues of humanity. AD and dementia are expected to almost triple during the next 30 years. Today, we do not know the exact cause and therefore, no real cure exists. Due to the failure of the present approaches, new and bold avenues of research need to be pursued to unravel new pathomechanisms leading to successful prevention and/or treatment of AD.

Alzheimer's disease (AD) as described by Alois Alzheimer has been known for more than 100 years. The prevailing hypothesis for AD, termed the amyloid cascade hypothesis, states that local production and deposition of amyloid beta peptide (Aβ) is the cause of the disease. This protein forms fibrillar structures in the brain resulting in extracellular amyloid plaques which lead to inflammation and neuronal synapse destruction. Neurodegeneration in AD is also related to intracellular hyperphosphorylation of Tau (ptau) and the formation of neurofibrillary tangles. The failure of more than 400 clinical trials targeting Aβ and especially the deleterious results observed when Aβ levels decrease in the brain indicate that we have not completely grasped this hypothesis. Furthermore, we need a radically new approach to discover new treatments.

There is growing evidence that AD is a syndrome and may have multiple causes. Notably, the vascular hypothesis and the infection hypothesis are very strong candidate explanations for the pathogenesis of AD.

Even if the vascular hypothesis could not be a stand-alone cause, it has been integrated as a risk factor for the development of AD and led to clinical trials for AD prevention. Under the leadership of Professor Cunnane, we have performed interventional trials including the use of exercise[1] but above all ketogenic interventions[2].

We pioneered the use of a brain ketone PET imaging. We have also tested a dietary ketogenic supplement for the prevention/treatment of AD at various stages. Ketones are an important fuel for neurons. They also inhibit the inflammasome and consequently decrease inflammation. We have shown that brain uptake of ketones is not altered in patients suffering from mild cognitive impairment (MCI) or AD and that supplementation with ketones improves several domains of cognitive function in MCI and AD.

The recognition of the role of neuroinflammation is important to understand AD pathology. The destruction of the synapses is the first direct consequence of neuroinflammation and leads to neuron death. Since neuroinflammation starts many decades before the appearance of clinical symptoms, we ask ourselves how exactly the immune system is involved and what is causing neuroinflammation.

Prof Fulop is leading the work on the elucidation of the involvement of the peripheral immune system in AD. We have made considerable progress in mapping the role of each element of the peripheral immune system in the early stages of AD pathogenesis. Recognition that the blood-brain barrier becomes more permeable during the development of AD supports a role for the peripheral immune response in this disease. The previous paradigm that the brain is an immune-privileged organ has now been superseded by general acceptance that peripheral immune cells may be found in the brain. We have shown that peripheral monocytes, NK cells, neutrophils and lymphocytes are differentially activated at various stages of AD, likely by a stimulus other than Aβ[3].

These observations provide a new trigger for the study of neuro- and

systemic inflammation in AD. Many years ago, several groups evoked the infection hypothesis of AD. They discovered remnants of various microorganisms (viruses, bacteria and fungi) in the AD and pre-AD brain. These findings led to intense investigations; however, progress has been very modest because it is difficult to prove a causative versus innocent bystander role.

Recently, the infection hypothesis was reinforced by the discovery that Aβ is an antimicrobial peptide (AMP). This peptide inhibits the growth of bacteria and fungi as well as viruses. We contributed importantly to the understanding of this mechanism, especially the role of Aβ as an antiviral peptide[4,5]. There is still a missing link, however, relating infection to development and progression of AD: how do microorganisms provide a long-term stimulus to Aβ synthesis? We made progress in this area by showing that microorganisms may survive over a substantial time in microglia and in circulating monocytes where they may become reactivable under certain circumstances.

Together, these findings lend support to the infection hypothesis, suggesting that latent and chronic infections stimulate a pro-inflammatory response. The stimulation of the central nervous immune system by infective agents may pass either directly through the olfactory bulb or by mouth, or indirectly by innate immune cells. Once exposed to infective agents, neurons secrete Aβ as a means to protect neighbouring neurons. Aβ and pathogens are then taken up by functioning microglia and the infection and inflammation are halted. However, when the infection becomes chronic, the microglia are no longer able to neutralise all the Aβ produced and amyloid plaques convert into biofilms enclosing the microorganisms, neuroinflammation further proceeds and neurons are destroyed[6].

Recognition of this infection-induced vicious circle between the periphery and the central nervous system is the strategy we propose for research for the future treatment of AD. The following approaches should be explored in the near future: 1. the use of effective antibiotics to destroy microorganisms which can be detected in a personalised manner using peripheral biomarkers (since different individuals will have different chronic infections) at very early stages in cognitive decline and; 2. the use of polyvalent vaccines.

Alzheimer's disease treatment research: ketones and antimicrobial interventions

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1 Castellano CA, et al. J Alzheimers Dis. 2017;56(4):1459-1468.
2 Croteau E, et al. J Alzheimers Dis. 2018;64(2):551-561.
3 Le Page A, et al. Exp Gerontol. 2018;107:59-66.
4 Bourgade K, et al. Biogerontology. 2015;16(1):85-98.
5 Bourgade K, et al. J Alzheimers Dis. 2016;50(4):1227-41.
6 Fulop T, et al. Front Aging Neurosci. 2018;10:224.

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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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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

www.brocku.ca