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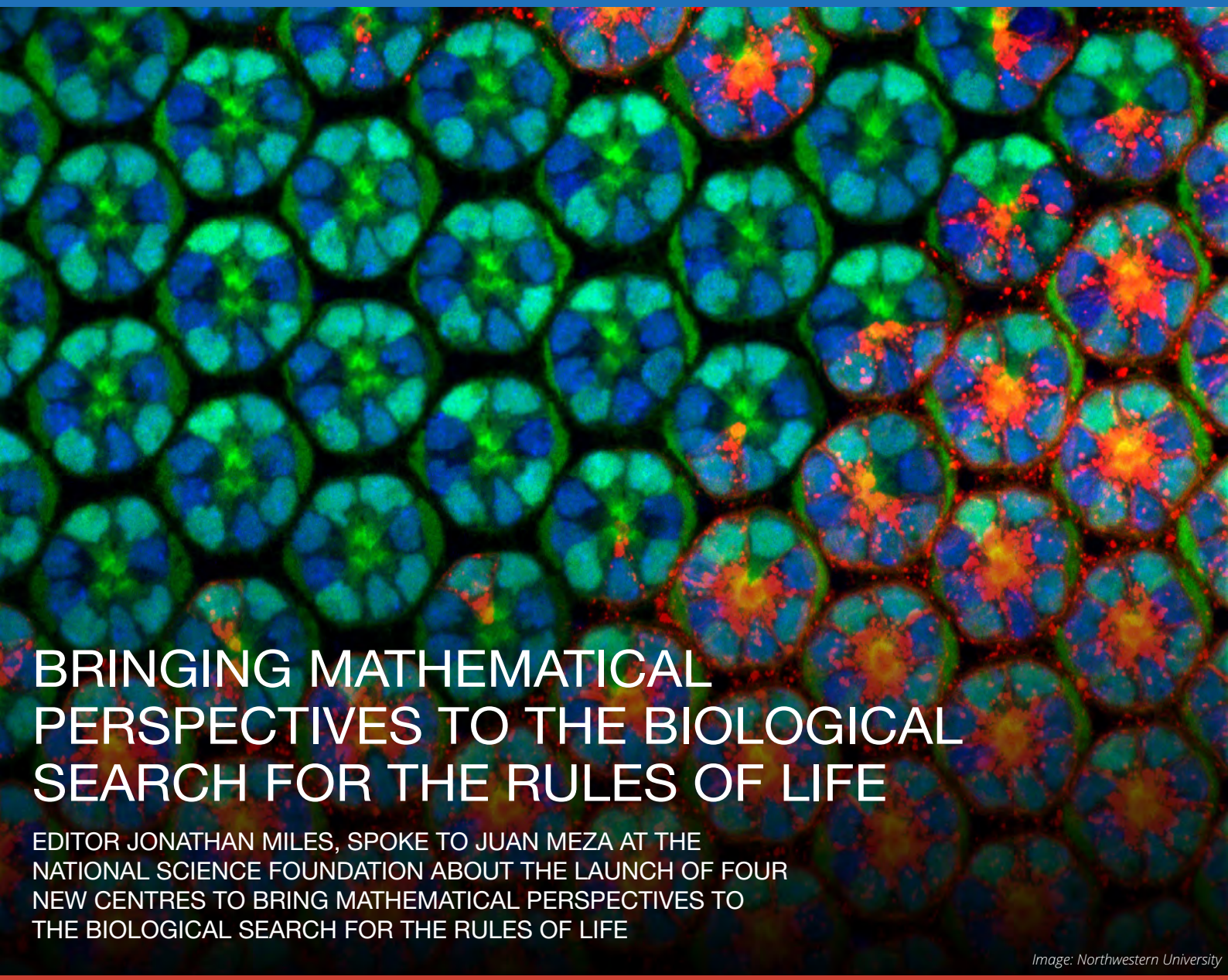
NORTH AMERICA ANALYSIS



BRINGING MATHEMATICAL PERSPECTIVES TO THE BIOLOGICAL SEARCH FOR THE RULES OF LIFE

EDITOR JONATHAN MILES, SPOKE TO JUAN MEZA AT THE NATIONAL SCIENCE FOUNDATION ABOUT THE LAUNCH OF FOUR NEW CENTRES TO BRING MATHEMATICAL PERSPECTIVES TO THE BIOLOGICAL SEARCH FOR THE RULES OF LIFE

Image: Northwestern University

IN THIS ISSUE

Jim Siegrist, of the U.S. Department of Energy details how the organisation is building for discovery, using the excellent example of their High Energy Physics program

Dr Diana W. Bianchi, of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), details the critical need for research to address maternal mortality

Greg Rosenthal of the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service details the importance of the multiple safeguards in systems approaches

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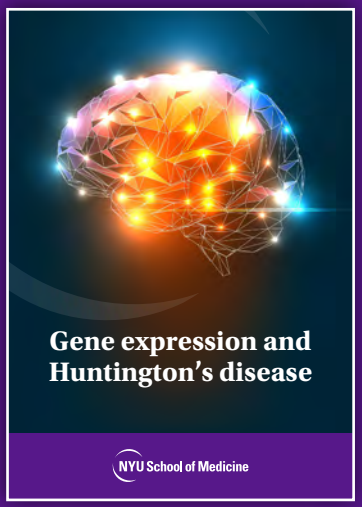
Gene expression and Huntington's disease

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 the July 2019 edition of North America Analysis, which features a wide range of insightful content on policy issues, including health & social care, research & innovation, environment, maritime affairs, agriculture, energy and education.

A special focus in this publication is biology, the highlight which is my interview with Juan Meza at the National Science Foundation about the launch of four new centres to bring mathematical perspectives to the biological search for the Rules of Life. We find out that collectively, the centres will produce a new generation of scientists equipped to tackle questions that cannot be answered today.

Another fantastic article comes from Jim Siegrist, Associate Director for High Energy Physics in the Office of Science, U.S. Department of Energy. In his absorbing piece, he details how the organisation is building for discovery, using the excellent example of their High Energy Physics program. We learn that the organisation works with partners around the world: "to create truly world-leading instruments to tackle some of the biggest questions in science."

So, we've had some brilliant biology and physics content but we also include compelling analysis on chemistry here. We are very honoured to include insight from Carol Bessel and Melissa Olson from National Science Foundation's Division of Chemistry (CHE), who reveal the organisation's goal of advancing basic chemical research while also developing a globally competitive workforce.

I hope you enjoy reading the main high-profile pieces in July 2019's North America Analysis. Please contact me if you have any ideas for future articles, or perhaps you'd like to provide feedback on this edition. ■

Jonathan Miles
Editor

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Supporting the addition of asthma medications to the exemption list in the UK

Dr Fred A. Wagshul, Pulmonologist and Medical Director at the Lung Center of America, explains why he supports the addition of asthma medications to the exemption list in the UK

I read with great interest the article on the Open Access Government website from Asthma UK about How Unfair Prescription Charges are Putting People with Asthma at Risk. It is true that in the UK, the U.S. and elsewhere throughout the world, the cost of treating chronic asthma is astronomical and can be virtually unsustainable for many with limited financial resources who struggle to breathe every day. So let me say at the outset that I support the addition of asthma medications to the exemption list in the UK.

But as I read the following in the Open Access Government post, "People with asthma have to take their medication every day…They need…a 'preventer' inhaler…and a 'reliever' inhaler…and many…need allergy medication… or antibiotics", I felt compelled to offer some information that will be surprising to most, and it is this: These patients don't have to live that way.

There is sound, medically scientific proof that the symptoms of asthma can be eradicated. The treatment protocols that can accomplish this should be adopted not only to bring down the costs associated with the treatment of asthma but more importantly, to bring these people who struggle to breathe daily the ability to breathe easily for life.

For many people dealing with the scourge of chronic asthma, the notion of living symptom-free of asthma for life borders on the absurd. That's because the 'band-aid' drugs commonly prescribed for asthma – inhalers, relievers, allergy meds and more – cause patients to become dependent upon those drugs for life. But medical studies published in some of the world's most highly respected medical journals clearly show that by identifying the root cause of a patient's asthma and treating that, the symptoms can be

altogether obliterated. This would obviate the need for long-term medications, rescue inhalers (many of which contain dire black box warnings), emergency room visits and hospitalisations.

Studies have demonstrated that certain bacteria (i.e. Mycoplasma pneumoniae and Chlamydia pneumoniae) are associated with pulmonary disorders, including asthma. Therefore, the specific bacteria identified in a patient's system can be targeted through the development of an individually prescribed antibiotic protocol that has proven to be tremendously successful.

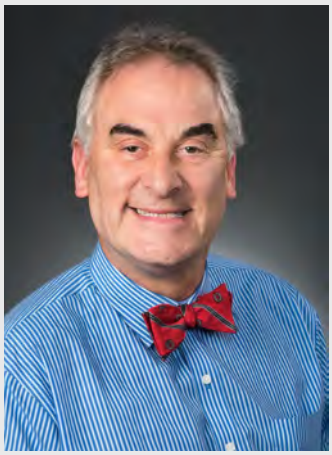
> "There is sound, medically scientific proof that the symptoms of asthma can be eradicated. The treatment protocols that can accomplish this should be adopted not only to bring down the costs associated with the treatment of asthma but more importantly, to bring these people who struggle to breathe daily the ability to breathe easily for life."

What this means is that people with asthma, COPD, chronic bronchitis and even emphysema do not have to live with life-limiting breathing difficulties. They can live symptom-free and even find total remission from their debilitating symptoms. Many of our patients, who had experienced significant declines in the quality of their lives have returned to their normal, active lives. Many of our patients' experiences can be found here: https://www.lungcenterofamerica.org/stories

It is heartbreaking to learn from the Open Access Government post that, "The number of adults with a lifetime diagnosis of asthma in the UK is increasing and the UK death rate from asthma is among the worst in Europe." These statistics are unacceptable – since we know what works to prevent the suffering of this magnitude. I have been asked by so many of my patients why, if I can put their asthma into remission, other doctors aren't doing the same thing. Here's why.

Firstly, I know for certain that the use of long-term antibiotics is essential in treating the cause of asthma, rather than just the symptoms. This protocol is not popularly accepted by mainstream medicine, despite documented excellent outcome data as published repeatedly in prestigious medical journals. (See study links at https://www.lungcenterofamerica.org/.

Secondly, $80 billion is spent annually in the U.S. just



Dr Fred A. Wagshul
Pulmonologist

on the treatment of asthma alone. Approximately 70% of the costs of asthma care are generated through emergency room visits and subsequent hospitalisations. Over 98% of all physicians/physician groups nationwide are tied to hospital reimbursement systems that help subsidise physician salaries. If that 70% was left unspent, most of these physician groups would collapse. Additionally, the out-of-pocket costs incurred by patients in the U.S. is on average, $3,000. This is in addition to the premiums they pay for health insurance. It's a financial house of cards.

All of this is in stark contrast to our office patients who are treated for the root cause of their breathing difficulties, (over 20,000 and climbing). They rarely go to the emergency room or are ever hospitalised, so that is why Lung Center of America has one of the lowest hospitalisation rates for pulmonary patients in the nation.

It is my fervent hope that this information will be shared with those empowered to review and approve asthma medications for the exemption list in the UK. Even more importantly, it is imperative that patients who struggle to breathe understand that they most certainly do not have to live that way. ■

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Integrated *in vivo* imaging and mathematical modeling to investigate nanoparticle pharmacokinetics

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Nanocarrier-based therapeutics and diagnostics hold the promise for generating advances in drug delivery and diagnostic imaging, respectively, given their ability to carry out targeted delivery of the cargo using passive or active targeting strategies. Nevertheless, according to a review of the literature from the past 10 years, the *in vivo* nanoparticle (NP)-based delivery efficiency to tumors has averaged only around 0.7% of the injected dose[1]. Additionally, the clinical translation of NPs has been hindered by insufficient understanding of their *in vivo* structure activity relationships (SAR).

To establish an understanding of the SAR quantitatively, we used an integrated *in vivo* imaging and mathematical modeling approach to obtain correlations between NP physicochemical properties and their *in vivo* biodistribution and clearance kinetics[2]. Healthy female rats were injected with radiolabeled mesoporous silica nanoparticles (MSNs) and imaged over time using the single photon emission computational tomography/computational tomography (SPECT/CT) imaging modality. The serial images were computationally quantified to obtain radioactivity concentration (surrogate for NP concentration) in various regions of interest (ROIs) across the body of the animal (Figure 1a). The kinetics data were used to develop a semi-mechanistic mathematical model (Figure 1b) and non-linear regression was performed to estimate important model parameters.

MSNs were selected for this study due to their high *in vivo* stability, ability to undergo surface functionalization, and precise synthesis control that allows for selection of particle size, shape, and pore size. In our investigation, MSNs were systematically varied in size, charge, and surface chemistry, in addition to their route of administration (intravenous or intraperitoneal). Three different surface chemistries for the indium (^{111}In)-labeled MSNs were tested, (1) PEG-polyethylenimine (PEG-PEI), (2) PEG-quaternary amine (PEG-QA), and (3) PEG-trimethylsilane (PEG-TMS). All three configurations presented nominal diameters of 50 nm, and average pore diameters of 3.5-3.8nm. Further, PEG-TMS was also tested for nominal diameters of 25, 90, and 150 nm to investigate the role of particle size in disposition kinetics. Zeta potential measurements showed that PEG-TMS MSNs were neutral, while PEG-PEI and PEG-QA were strongly positively charged.

As seen in Figure 1c, the radioactivity observed in the SPECT/CT images is produced collectively by NPs circulating through the vasculature of a ROI, and by NPs sequestered in the extravascular space of the ROI. The first group of NPs are still bioavailable for delivery to the target site, while the second group is trapped at non-target sites, unless already at the target. To mechanistically describe the generalized biodistribution of MSNs, the ROIs were classified into 'sink-like' and 'source-like' based on the high or low density of physiological *traps* present in the organ, respectively, where *traps* refer to the physiological and anatomical components found in the microvasculature of the organs, e.g., vessel wall fenestrations, interendothelial gaps, or resident macrophages[3-4]. The classification of the organs was validated by the behavior obtained from the quantification of the SPECT/CT images. The sink-like organs, such as the liver and spleen, showed NP accumulation over time due to the activity of the traps causing NP retention in the extravascular space and thus loss of bioavailability. In contrast, in the source-like organs, such as the lungs, abdominal aorta, muscles, heart, and brain, the NP concentration declined with time showing an analogy to blood concen-

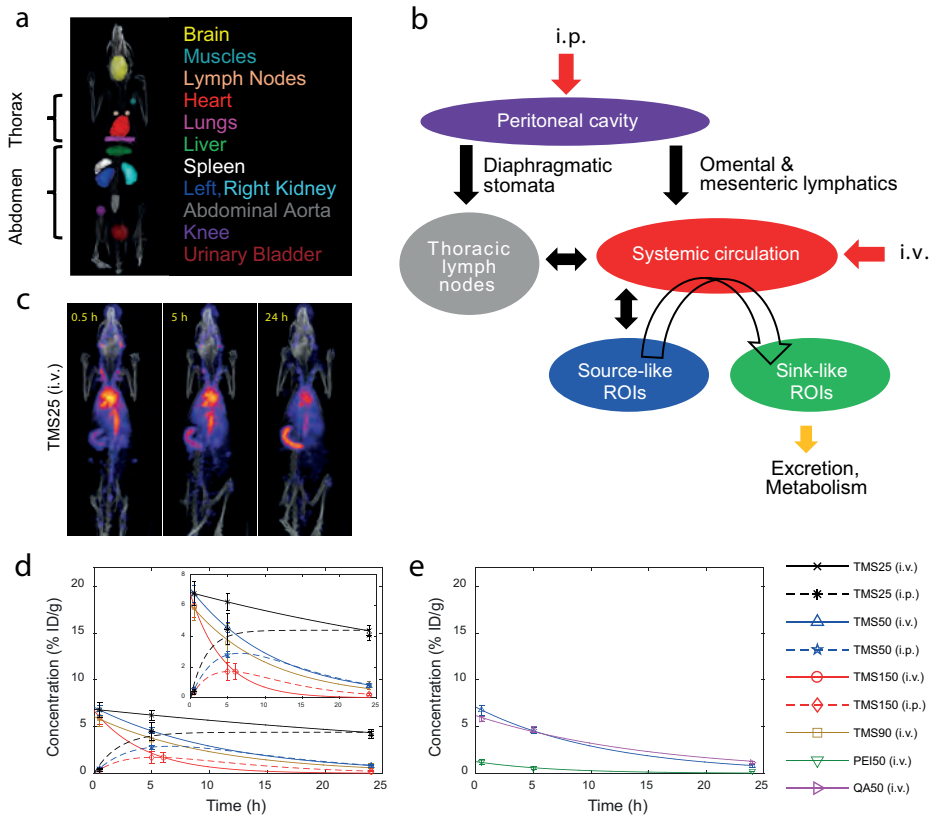

Figure 1 | Integrated in vivo imaging and mathematical modeling. a) Regions of interest for investigation of MSN disposition kinetics. b) Schematic of organ classification in the context of whole-body disposition of MSNs. c) Representative SPECT/CT longitudinal images of an animal injected with 25 nm sized TMS-coated MSNs. d,e) One-compartment PK analysis of MSNs in the heart.

tration kinetics, indicating that NPs in source-like organs traverse through the vasculature without getting trapped. The MSN concentration kinetics in various ROIs was modeled with the following double exponential function and its variants:

$Ci\,(t) = A \bullet (e^{-k_{out,i} \bullet t} - e^{-k_{in,i} \bullet t})$ (1) where Ci is the NP concentration in organ i, A is the back extrapolated concentration of the decline phase at time $t = 0$, and $k_{in,i}$ and $k_{out,i}$ represent the uptake and elimination rate constant of NPs, respectively.

Further, to estimate pharmacokinetic parameters, a one compartment PK model was applied to the heart concentration kinetics data (surrogate for systemic blood kinetics) (Figure 1d,e). The fitted concentration-time curves demonstrate the effect of MSN size, surface chemistry, zeta potential, and route of administration on their systemic kinetics. For both routes of administration, the area under the curve of heart concentration-time curve showed a strong negative linear dependence on particle size, suggesting that smaller size correlates with greater systemic bioavailability of MSNs. Furthermore, the trend in uptake rate constants suggested that the peritoneal cavity absorption of NPs following i.p. injection is independent of particle size, and the systemic bioavailability is primarily a function of the elimination rate parameter. The half-life ($t_{1/2}$) results indicated that smaller size correlates with a longer $t_{1/2}$, and upon entering the blood stream, MSN kinetics is independent of the route of administration. This result emphasizes the in vivo stability of MSNs which is required for clinical translation. With respect to excretion, the TMS-coated MSNs of different sizes, regardless of the administration route, were excreted to comparable amounts. Finally, positively charged particles tended to be excreted out faster.

Through this study, we thus demonstrated the non-invasive imaging-based pharmacokinetic analysis of MSNs and established their SARs necessary for preclinical development and clinical translation.

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The role of TXNIP in mitochondrial-lysosomal axis dysregulation in diabetic retinopathy

Lalit P. Singh, Associate Professor (Department of Ophthalmology, Visual and Anatomical Sciences (OVAS) at Wayne State University School of Medicine, explains the role of TXNIP in mitochondrial-lysosomal axis dysregulation in diabetic retinopathy

Diabetic retinopathy (DR) is a devastating disease affecting millions of people around the world, leading to blindness. Yet, there is no known cure till today. Diabetes is mainly of two types – Type 1 diabetes (insulin deficiency to due pancreatic beta cell death, an autoimmune disease, T1D) and Type 2 diabetes (insulin resistance, T2D) often associated with obesity. Whether it is T1D or T2D, sustained hyperglycaemia prevails in the blood and causes tissue injury.

Currently, the mechanism(s) for the initiation and progression of DR is not fully understood. One gene that is strongly induced by diabetes and high glucose in tissues, including pancreatic beta, renal and retinal cells, is the thioredoxin interacting protein (TXNIP). TXNIP causes cellular oxidative stress, low-grade inflammation, cell death in DR.

TXNIP binds to thiroredoxin (Trx), inhibiting its anti-oxidant and thiol-reducing capacity. Trx1 is present in the cytosol/nucleus while Trx2 is in mitochondria (Fig. 1-I). Another cellular anti-oxidant system is the glutathione/glutathione peroxidase (GSH/GPX). However, under chronic hyperglycaemia, TXNIP continues to inhibit Trx1 and Trx2 causing cytosolic and MT reactive oxygen species (ROS) generation. Stressed mitochondria are inefficient in ATP synthesis while generating ROS. Therefore, removal of the damaged mitochondria is critical for cellular and MT health. For this, the damaged part of the mitochondrion is first separated by fission involving dynamin-related protein, DRP1 and fission protein, Fis1. Then, isolated mitochondria are removed by mitophagy (a specific process of autophagy) via lysosomal degradation.

The retina being a part of the central nervous system consumes large amounts of glucose and oxygen for its bioenergetics and visual function via the MT inner membrane electron transport chain (ETC). During ATP production, electrons leak, which are captured by O_2-generating ROS. Although there are anti-oxidants in both the cytosol and the mitochondrion, they are overwhelmed by sustained blockade of the Trx-TrxR system by TXNIP. This leads to overutilisation of GSH.

Ultimately, MT damage occurs, which needs to be cleared by mitophagy, a complex process yet to be fully understood. Briefly, upon MT damage, PTEN-induced kinase 1 (Pink1) accumulates on the outer membrane and phosphorylates membrane proteins, which attract Parkin (an E3 ubiquitin ligase) marking for degradation (Fig. 1-II). TXNIP also interacts with REDD1 (regulated in development and DNA damage 1) and inhibits mTORC1 (mechanistic target of rapamycin complex 1), which phosphorylates ATG1 (ULK1) and ATG13 to block autophagy/mitophagy. Furthermore, TXNIP/REDD1 inhibit ATG4B, which delipidates LC3B-II in autophagophore; thereby increasing double membrane autophagophore formation. Then, mitophagy receptors, optineurin and p62/sequestosome 1, are phosphorylated by TANK-binding kinase 1 (TBK1) enhancing their interaction with MT cargo and LC3B-II and mitophagophore formation.

The mitophagophore then fuses with lysosomes to form the autolysosome, which degrades the MT cargo. Disturbance of the lysosomal membrane by autophagy/mitophagy causes translocation of transcription factor EB (TFEB) to the nucleus and enhanced transcription of lysosomal and ATG genes and PGC1α, an MT biogenesis factor (Fig. 1-III). Although new mitochondria are generated, fusion with existing mitochondria to form functional MT network may be blunted due to MT stress.

Accumulation of fragmented mitochondria leads to bioenergetics deficiency. One aspect of TFEB regulation under mitophagy is that TFEB is phosphorylated by mTORC1 including at Serine 211 and sequesters in the cytosol via interaction with 14-3-3 scaffold protein while calcineurin-mediated dephosphorylation of TFEB leads to nuclear translocation and expression of CLEAR (Coordinated Lysosomal Expression and Regulation) genes. Which of the two proteins – mTOR or

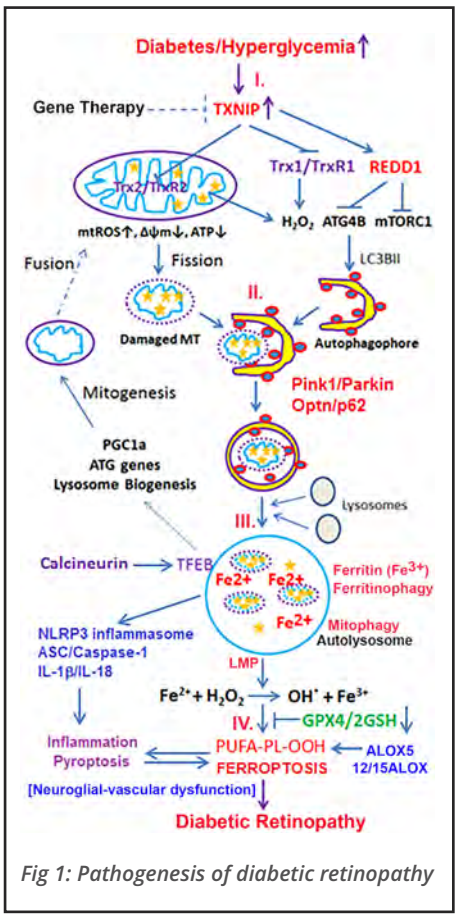

Fig 1: Pathogenesis of diabetic retinopathy

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calcineurin – dominates the TFEB regulation in DR is yet to be defined?

Another consequence of sustained oxidative stress and mitophagic flux in cells is the accumulation of damaged mitochondria, membrane lipids, oxidised proteins, free iron and H_2O_2 causing lysosomal enlargement, destabilisation and membrane permeabilisation (LMP) (Fig. 1-IV).

Mitochondria are major sites of iron metabolism including iron-sulphur cluster/complex biosynthesis, heme synthesis and storage in MT ferritin. MT TCA cycle enzyme (m-aconitase/ ACO2), Complexes I and III all contain 4Fe-4S clusters. In the cytosol, c-actonitase (ACO1) also contain 4Fe-4S cluster and serves as a dual function protein – (i) conversion of citrate to isocitrate and (ii) as an iron regulatory protein 1 (IRP1) in the absence of iron-sulphur. Under oxidative stress or hypoxia, 4Fe-4S complex in ACO1 is degraded and IRP1 binds to iron regulatory elements (IRE) in the 3'-UTR of transferrin receptor 1 (TfR1) mRNA and stabilises to increase TfR1 translation and iron uptake. Cytosolic iron is stored in ferritin (ferric iron, Fe^{3+}) and iron utilisation requires autophagy of ferritin (ferritinophagy) to generate free/labile ferrous Fe^{2+}, which is highly reactive with H_2O_2 (Fenton reaction) to generate reactive hydroxyl radicals ($^{\cdot}OH$) and ions (OH^{-}).

Subsequently, oxidative stress ($^{\cdot}OH$) and iron overload cause plasma membrane phospholipid peroxidation (PL-OOH), mainly polyunsaturated fatty acids (PUFA) and ferroptosis, a non-apoptotic cell death mechanism by iron overloading and lipid peroxidation due to a decrease in the GPX4 activity. GPX4 is the sole enzyme that detoxifies PL-OOH using two GSH.

In addition, arachidonate 5-lipoxygenase (ALOX5) and 12/15ALOX, which are regulated by iron and oxidative stress, may also be activated and mediate PL-OOH.

Ferroptosis, being a non-apoptotic cell death, releases cellular DAMPs (damage-associated molecular patterns) including oxidised mtDNA and nuclear HMGB1 (high mobility group box 1), which further evoke innate immune responses.

Further, LMP activates NLRP3 inflammasome. ALOX5 generates leukotriene B4 (LTB4), which attracts immune cells such as microglia/macrophage mediating neuroinflammation and neurodegeneration in DR. Therefore, we propose that gene therapy for TXNIP knockdown and/or administration of mitochondria-targeted antioxidants (mito-Tempo, SS31), iron chelating agents (deferasirox, deferiprone) and ALOX inhibitor (Zileuton) may serve as potential combination therapies to prevent/slow down the progression of DR.

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Hearing speech in noisy environments

PhD students Courtney Coburn Glavin, Kailyn A. McFarlane, and Assistant Professor Jason Tait Sanchez discuss the mechanisms, barriers, and future progress for hearing speech in noisy environments

When you find yourself struggling to hear in a noisy restaurant, chances are you aren't alone. Difficulty understanding speech-in-noise (SIN) is one of the most common hearing-related complaints[1]. This problem is not unique to individuals with clinically defined hearing loss; estimates suggest that as many as 26 million people complain of hearing difficulties in noisy situations despite having clinically "normal" hearing[2]. Even with renewed attention to this problem in the fields of audiology and hearing science, its etiology, and thus, diagnosis and treatment in humans remains elusive.

In this research profile we: 1) explore potential mechanisms underlying this phenomenon, 2) consider barriers to validating and identifying this problem, and 3) discuss our lab's novel approach to this problem.

Potential mechanisms

Cochlear synaptopathy – a term used to describe synapse damage and loss between inner hair cells of the cochlea and auditory nerve fibers – has been demonstrated to occur after noise exposure in animal models[3,4,5]. This form of hearing impairment is termed "hidden" hearing loss because traditional tests of hearing integrity are not sensitive enough to detect this synaptic disruption. Some theorize that synaptopathy could explain SIN deficits in humans, given that it occurs after auditory insult and is a deficit "hidden" from traditional hearing tests. However, the presence of synaptopathy following noise insult is not ubiquitous, even in animal models[6]. Results in humans are further complicated by the fact that synaptic damage cannot be directly verified because of the invasive nature of doing so. Many studies, using proxy measures of synaptopathy, have failed to find systematic evidence of this pathology in humans[7,8]. This could be due to the inability to directly measure the phenomenon, the lack of experimental control in exposing humans to environmental insults, or the true absence of synaptopathy in humans. Based on existing evidence, synaptopathy is likely not the sole explanation for SIN deficits in humans.

Hearing loss in frequency regions not typically evaluated with traditional hearing tests has also been suggested as a reason for SIN difficulty. Though the range of human hearing extends up to 20,000 Hz, traditional hearing tests evaluate frequency sensitivity only to 8,000 Hz. Testing higher frequencies is time-consuming and there are equipment limitations in presenting high frequency stimuli. Both of these factors have resulted in a significant portion of the human hearing range left unevaluated.

This dilemma is important because the cochlea of the inner ear is frequency-tuned (i.e., tonotopic); specific regions are most sensitive to high frequency sounds, while other regions are most sensitive to low frequency sounds. The region sensitive to higher frequencies is also believed to be most susceptible to environmental insult, making the relationship between high frequency hearing loss above 8,000 Hz and SIN difficulties conceivable. More research in this area is needed to better understand this potential relationship.

Limitations to validation and identification

A major barrier to identifying SIN difficulties in humans is the shortage of diagnostic tests that are sensitive enough to evaluate the integrity of specific anatomical locations within the complex auditory pathway. This prevents us from obtaining a clear picture of functional and structural changes that occur with age or environmental insult. The traditional test of hearing is the behavioural audiogram. Though it is the current gold standard for assessing auditory function, it is a gross measure of hearing.

While the health of some anatomical sites of the auditory pathway can be reliably assessed through existing diagnostic tools (e.g., integrity of outer hair cells is thought to be captured by measures of otoacoustic emissions), others, such as inner hair cells, cochlear synapses, and more central structures cannot be assessed and interpreted in a straightforward manner in humans.

For example, Wave I of the auditory brainstem response (ABR) is thought to reflect the integrity of the synaptic connection between inner hair cells and auditory nerve fibers. However,

studies investigating the use of Wave I as a biomarker for functional SIN deficits have yielded mixed results in humans[9,10,11].

The clinical use of diagnostic measures beyond the audiogram is another problem in characterising SIN deficits in humans. Fewer than 15% of audiologists report routinely assessing SIN performance in their patients[2]. Even when used clinically, existing SIN tests are highly variable and may not assess the same constructs.

For example, some SIN tests use speech babble as background noise, whereas others use steady-state noise; some use an adaptive procedure that changes based on performance, whereas others use a fixed procedure. Thus, some SIN procedures may not accurately reflect real-world listening situations, and their variability limits cross-study comparisons of patient performance. This limits reliable identification of SIN problems and their relationship to other measures of hearing.

Future progress

Ultimately, the largest barrier to identifying the etiology of SIN deficits lies in the complexity of the human experience. Over the course of a lifetime, a person is exposed to an amalgamation of environmental insults, each of which interact with the person's genetic makeup. Mechanisms underlying problems with SIN are multifaceted in nature and are likely more complex in humans than other animals.

"Sound conditioning" and "toughening", for example, are ideas that previous noise exposure leads to reduced susceptibility of the auditory system to noise[12,13]. Individuals who have a history of noise exposure may then be less vulnerable to future auditory insults. Sound conditioning has been proposed as one explanation for the mixed evidence of SIN etiology and difficulties in humans.

The research conducted in the Sanchez Laboratory at Northwestern University takes a unique approach to examining SIN deficits in humans. Specifically, we compare individuals with self-reported SIN deficits to those with no reported SIN issues on an extensive battery of auditory diagnostic tests. In this way, we do not rely solely on objective measures of SIN ability, which are highly variable and may not reflect real-world experiences.

From our extensive test battery and large pool of participants, we hope to identify clinically viable measures that validate patient complaints and are sensitive to the underlying mechanisms behind SIN deficits. Given the number of individuals who experience SIN-related problems, there is a tremendous need to improve their communication abilities. Treatment options, however, cannot fully be explored until we understand the etiology of this issue and can reliably validate and identify it in humans.

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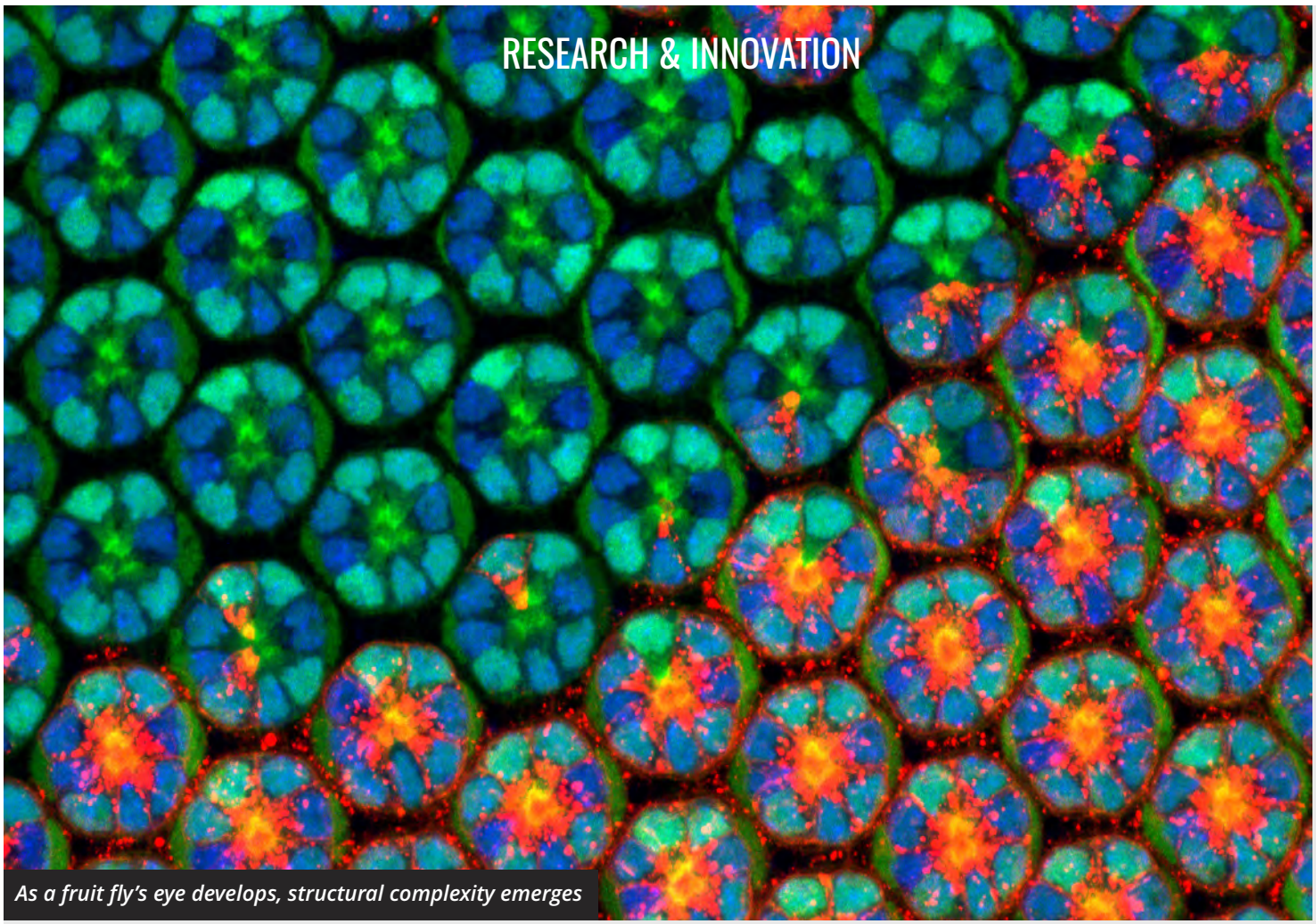

As a fruit fly's eye develops, structural complexity emerges

Image: Northwestern University

Bringing mathematical perspectives to the biological search for the Rules of Life

Editor of Open Access Government, Jonathan Miles, spoke to Juan Meza at the National Science Foundation about the launch of four new centres to bring mathematical perspectives to the biological search for the Rules of Life

The National Science Foundation (NSF), in partnership with the Simons Foundation, in May 2018, launched four new centres to bring mathematical perspectives to the biological search for the Rules of Life. Collectively, the centres will produce a new generation of scientists equipped to tackle questions that cannot be answered today.

The NSF-Simons Research Centers for Mathematics of Complex Biological Systems aim to explore how information encoded in DNA results in complex organisms with diverse forms, functions and behaviours when it is manipulated by changing environments across multiple time scales.

The NSF-Simons Centers will enable scientists to understand, with unprecedented clarity, how genes translate into so many diverse phenotypes. This endeavour will help the NSF address one of its 10 Big Ideas, Understanding the Rules of Life: Predicting Phenotype, which explains how the Rules of Life are expressed across many scales of structure and time.

In this question and answer interview with Juan Meza at the National Science Foundation (NSF), we learn that such knowledge may lead to a predictive framework for understanding the pathways that lead from the DNA within a cell to the myriad expressions of an organism in its environment. We also discover that

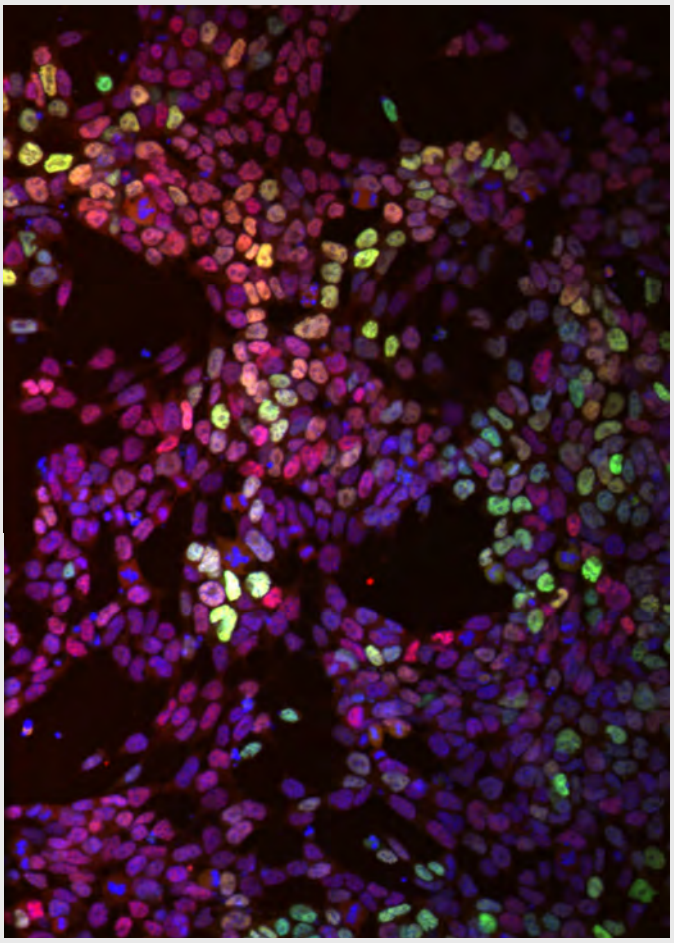

Image: Georgia Tech/Melissa Kemp

Gene expression and cell decisions guide stem cells (green) into differentiated cells (red). Researchers at Georgia Tech are studying how basic stem cells become specific cells in the body based on which genes are expressed and other cellular decisions

maths is more than just proofs or calculations but is a really powerful tool that helps us study nature.

Thank you for taking the time to speak to me today. First, tell us how the National Science Foundation (NSF), in a partnership, has launched four new centres to bring mathematical perspectives to the biological search for the Rules of Life?

The partnership came about through a lot of discussions, both internally and externally. We had a workshop here at the NSF and we followed that up with discussions with other parts of the organisation. Throughout these discussions, we realised that we had reached a tipping point at which the combination of mathematics, data and biology could have a big impact on our understanding of biological processes. Thus, we came up with a couple of goals, the first of which was to enable innovative and collaborative research at the intersection of mathematics and three different areas of biology: molecular, cellular and organismal.

A secondary goal was to establish new connections between the two disciplines and to promote the interdisciplinary education and workforce training that we felt was needed to proceed in the field.

Thank you for that very interesting answer. What kind of knowledge will the centres explore and what could this lead to, for example, a predictive framework for understanding the pathways that lead from the DNA within a cell?

The main focus is to explore the interface between mathematics and biology. All the centres are going to be involved in trying to develop a better understanding of these thought processes because they are very complex and involve the entire spectrum going from the genotype to the phenotype. But each centre is going to have a goal or a specific set of goals that are all slightly different.

For example, The NSF-Simons Center for Multiscale Cell Fate Research at the University of California, Irvine, will look at what determines cell fate – the differentiation of cells into specific biological cell types. The best way to describe it is to say, "well, how do individual cells develop into specific types of tissue?" So you start with a single cell and then after a while, you have a liver cell, a heart cell or a muscle cell - how does that happen? We know that these cells receive signals from other cells and that will tip them off and let them know that they should be doing certain things. But how, when and where these signals occur is still something of a mystery.

Many thanks for this insight. Now, I am very intrigued by your comment that "many people think of math as proofs or calculations, but it's so much more" and wondered if you could develop this thought when it comes to applying mathematics to the complex processes that underlie biology?

I sometimes get a laugh out of this because I think that many of us develop a maths phobia and what we remember is that in this subject you need proofs. For

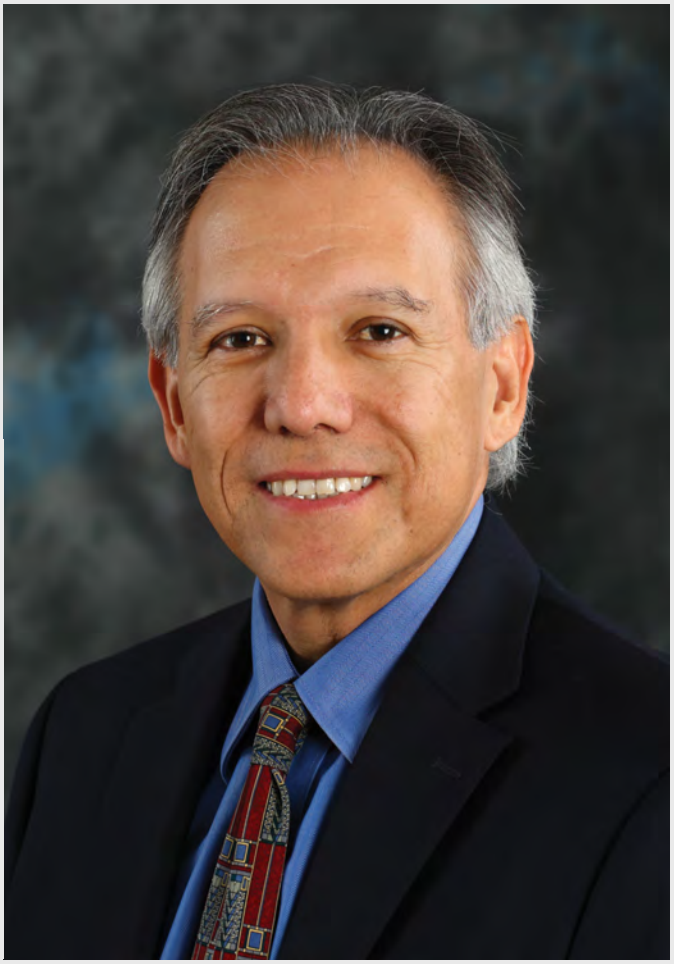

Image: Trevor Hirst, UC Merced School of Natural Sciences

Juan Meza, Director, Division of Mathematical Sciences

example, think back to when you took Geometry and wanted to show that one triangle was the same as another one. That was a sort of proof that we had to come up with. Or sometimes we think in terms of algebra, so, many of us dreaded the old question of, "how do you solve this quadratic equation?" We're given these formulas and calculations – that's what we think of when we think of maths. But I like to think of it as something completely different in that maths' power really comes in because we can develop models and use them for both describing and predicting things. What that does, is that it allows us to really understand complex processes.

We state the problem in terms of mathematics – that's the first step but then that allows you to bring in literally hundreds or maybe even thousands of years of knowledge to bear on the problem. And it allows us today to provide accurate weather forecasts. It allows us to provide links between environmental and genetic factors and certain diseases. Each of us uses maths every day whenever we make a phone call or make a purchase online – using number theory to encrypt your messages back and forth.

Now in biology, it's slightly different in the sense that there are a lot of processes and mechanisms that are very complex, but they lend themselves easily to mathematical modelling. In the example I just gave with the cell fate, you could model how a signal is sent from one cell to another. And then you want to see how these signals are interconnected with a network of cells. You might think of it in the same way you might model electricity by moving it through the power grid. Essentially, it is the same kind of mechanism.

Here, the applications are really quite different. But the mathematics is quite similar so that that gives us the power of the maths to be able to apply it to many different applications, some of which are very complex.

Tell us how the centres will build research capacity at the interface between mathematics and biology through cross-disciplinary training of students and postdoctoral associates, for example.

I'm really excited about the training of a new generation of researchers and the young folks who could come in and work well in both worlds – in biology and mathematics. I think it's too easy to spend all of our time in one small part of our research but I predict the future major advances are going to occur at the interface of the scientific disciplines, for example, in maths and biology. That's why I think it's important to train the next generation of researchers because we want them to be able to work in multiple disciplines and to be able to talk across these different disciplines. That's where the core of the new ideas will be coming from.

As an example of the four centres, tell us about the aims of the NSF-Simons Southeast Center for Mathematics and Biology and how they will address how genetic information impacts phenotypic traits.

We want to develop an interdisciplinary collaborative

team to model these complex biosystems. This centre is actually a little different than the other ones. What they propose is to have seven different projects and each of them will have a pairing so there will be one biosystem experimentalist working side by side with one mathematician. And each team will look at a particular problem in the genotype to phenotype landscape. Just to give you one example, one of the things we're going to look at is why that phenotype is consistent despite variations in both genotype and the environment. In other words, why is biology so robust? But we have a genotype, and depending on the environment, it will do a certain thing.

> "I'm really excited about the training of a new generation of researchers and the young folks who could come in and work well in both worlds – in biology and mathematics. I think it's too easy to spend all of our time in one small part of our research but I predict the future major advances are going to occur at the interface of the scientific disciplines, for example, in maths and biology."

You can look at the example of the development of a stem cell to a muscle cell – the environment is not the same each time this happens yet we always get the same result at the end. Somehow biology and life have managed to develop a system that despite many differences in the environment, we still end up with a fairly robust system that tends to give you the same result after many instances.

How will the NSF-Simons Centers enable scientists to understand, in unprecedented clarity, how genes translate into so many diverse phenotypes?

I'd like to point out that there have been some incredible advances in technology during the last 10 or so years. And it has completely changed how we address biology problems. If you take a look at, for example, gene sequencing or new imaging technologies that led to having access to unprecedented amounts of data, much of which is very high-quality data. We're able to get sequencing on single cells at this point and we have incredible detail on imaging. So that sort of points out and there is a lot of information here but how do we take advantage of this wealth of data?

What we believe is that by combining the data with the mathematical models, such as the ones that I mentioned earlier, it's going to allow us to develop predictive models. These models will have been validated with real data, so what that allows us to do is to then be able to predict certain things and then we can go back and check them. The models will help us understand where we might look for more detail. That will allow us to go back and do more experiments and fill in the gaps and that means a more accurate and more predictive model. It is a cycle, in fact, that gives us more and better models and higher-quality predictive models.

Is there anything you would like to add?

Well, first of all, thank you for the opportunity to talk with you. I think it is wonderful to share our exciting results but I would like to add that we're only at the beginning of an incredible and really important journey. Nobody knows how this is going to play out but I think the potential for revolutionary advances in biology is tremendous, especially when it's coupled with mathematics and all of the data that we have. ■

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Chasing the e-commerce market: The Omni-channel revolution

Experts from the Indian Institute of Management Ahmedabad, and the University of Michigan share their thoughts on the Omni-channel revolution

To quote the State of Retail Supply Chain Report (SRSCR) 2018: "This is the most dynamic era in retailing and the only constant is change." There is no doubt that e-commerce will continue to shape retailers' strategic and tactical decisions in the coming years. In 2018, U.S. e-commerce sales hit more than $500 billion – an increase of about 15% from the previous year – and accounted for about 14% of the total U.S. retail sales. These strong indicators have not been confined to the US only. The global e-commerce sales in 2018 were almost $3 trillion – an increase of about 18% from the prior year – and accounted for about 15% of the total global retail sales. It is projected that e-commerce sales will continue to grow and reach a 17% share of total retail sales within the next few years (in contrast, U.S. e-commerce sales a decade ago was only 6% of the total U.S. retail sales).

The message is clear: E-commerce growth is real, not just a passing fad. Since a significant portion of the growth in retail sales is expected to come from e-commerce purchases, retailers need to master a sound e-commerce strategy to remain competitive in the market. The execution, however, is not easy. Thanks to the so-called Amazon effect, consumers nowadays are used to an easy online shopping experience and a quick delivery. Alas, providing such a high level of shopping experience is extremely costly! This has motivated retailers to experiment with new approaches, collectively dubbed as the omni-channel strategies. Some failed, some survived and those who survived continued to improve and innovate.

Classic omni-channel: Strategies and challenges

Consider, for example, the challenge of satisfying consumer expectation of quick delivery. Unless you are a giant e-commerce retailer, such as Amazon, you most likely do not have either the right scale or infrastructure to operate as cost-efficiently as Amazon in the quick-delivery space. If your customer is located far from your nearest warehouse, it could take a few days for his or her package to be delivered. What's the alternative? One way is to fulfil e-commerce orders directly from a brick-and-mortar store near to the customer, which can cut down the delivery time to at most two days.

Another option is the so-called Buy-Online-Pickup-In-Store (BOPIS, or click-and-collect), which was first introduced by John Lewis, a UK-based chain of a high-end department store, in 2007. BOPIS has since been widely adopted by many retailers worldwide and is nowadays considered a standard strategy of omni-channel fulfilment.

In addition to ship-from-store and BOPIS, there are plenty other omni-channel strategies that focus on improving the customer shopping experience such as Buy-Online-Return-In-Store (BORIS), ship from one store to another store, locker pick-up, curbside pick-up, etc.

While the idea behind many omni-channel strategies is intuitive, their implementation can be quite challenging. Consider again the ship-from-store fulfilment strategy. To implement this, retailers need to first have real-time inventory visibility across all stores. Sadly, some retailers still work with a legacy system that does not provide them with the necessary visibility. Secondly, since store inventories are now used to fulfil both in-store and online demands, retailers need to improve their forecast accuracy. The inaccurate forecast may lead to unfavourable business scenarios: either too much inventory in stock, resulting in high in-store carrying cost or too little inventory causing high stock-out rates. In the word of one of the respondents of SRSCR 2018, "You need the right balance of inventory to support both the omni-channel experience and the in-store experience. To succeed, it would take a different way of thinking about demand forecasting than how we've viewed it in the past." But, forecasting is not easy either. Some retailers need to come up with forecasts of not only a single product but at least a few hundred thousands of products and sales data is not always abundant. Finally, retailers also need to optimise their fulfilment decisions. Although fulfilment from the closest store seems intuitive, it is not always optimal because it ignores future demand forecasts and inventory distribution across all stores.

Looking into the future: The challenge of urban logistics

At the time when Amazon was born in 1994, little did the rest of the world know that retailing as we knew it will forever be changed. Today, some of the most sophisticated quantitative methods are being developed and applied to solve retail problems on a daily basis, all in the name of meeting consumer expectations. While the last decade has witnessed the transformation of many retailers into so-called omni-channel retailers, the next decade is likely to see a more intense transformation and competition closer to home.

> "The message is clear: E-commerce growth is real, not just a passing fad. Since a significant portion of the growth in retail sales is expected to come from e-commerce purchases, retailers need to master a sound e-commerce strategy to remain competitive in the market."

As reported in[1], in New York City alone, there are 10 million people within a 20-mile radius of the Empire State building who spend a total of about $20 billion every year on e-commerce purchases. It is also reported that 64% of online consumers expect orders placed by 5 pm to qualify for same-day delivery. Imagine the possibilities if retailers could tap into this consumer segment. But, implementing urban fulfilment is not easy. While labour availability and last-mile delivery costs are no longer issues in a big city, stores in a highly populated city have a much smaller storage space, which requires more careful inventory planning. In addition, there are many limiting city infrastructures such as limited parking area and stop times, restrictions on vehicle sizes and traffic congestion that will affect order delivery. Indeed, increasing activities in urban fulfilment could result in worse traffic congestion, which will affect city life.

So, what is the best urban fulfilment strategy to deliver a high customer shopping experience?

How can retailers work together with city officials to create as minimal disruptions to city life as possible?

These are but some of the questions that retailers and policymakers alike need to grapple with within the next decade.

1 Urban fulfilment centers: Helping to deliver on the expectation of same-day delivery. Deloitte, 2019.

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Physics: Building for discovery in the global context

Jim Siegrist, Associate Director for High Energy Physics at the Office of Science, U.S. Department of Energy details how the organisation is building for discovery, using the excellent example of their High Energy Physics program

The pursuit of science drives innovation. Big questions attract bright minds and these dedicated scientists and engineers solve big problems. Discovering the nature of our universe, for instance, demands experiments that operate in the extremes, from ultra-sensitive deep underground detectors to space-based experiments and the largest machine ever constructed, the Large Hadron Collider.

Delivering scientific discoveries that advance human knowledge requires pushing the frontiers of technology. The new tools that are developed, in turn, impact energy, the economy and national security. This engine of innovation is the core mission of the U.S. Department of Energy's (DOE) Office of Science. As the largest federal sponsor of basic research in the physical sciences in the United States, the DOE Office of Science supports scientists and engineers at hundreds of institutions across the country and stewards ten national laboratories that host tens of thousands of users each year across their facilities.

DOE user facilities provide some of the most advanced tools of modern science, including the world's fastest supercomputer, facilities for studying the nanoworld, the environment and the atmosphere, as well as world-class light sources, neutron sources, particle accelerators and colliders. These facilities are available to all users, without regard to nationality or institution, based on the scientific merit of the proposed work. Use of the facilities is also free for research intended to be published in the open literature. This strategy aims to enable scientists to use the best possible resources in their pursuit of discovery. To keep advancing our science program, the Office of Science is continually investing in this infrastructure and building for discovery.

For example, the High Energy Physics program, which seeks to understand how the universe works at its most fundamental level, is bringing together scientists from around the globe to create a U.S.-hosted world-class facility to study the science of neutrinos. There are three known types of neutrino but these ghostly neutral particles, a million times lighter than an electron, change their type as they travel from one point to another. The first clue to this puzzling behaviour was observed fifty years ago by Ray Davis, Jr., whose Nobel Prize- winning work found fewer neutrinos than expected from the sun in a detector in the Homestake Mine, a mile underground in the Black Hills of South Dakota.

> "The DOE Office of Science invests in the future. The technology our scientists and engineers develop not only enables advances in science but impacts medicine, industry and national security. Our user facilities provide advanced tools that enable scientific discovery. We work with partners around the globe to create truly world-leading instruments to tackle some of the biggest questions in science."

Now we are returning to the same mine to host the international Deep Underground Neutrino Experiment, which will precisely measure this oscillation of neutrino types while aiming to measure any difference between the matter and antimatter versions of neutrinos. Over a thousand scientists from around the world are collaborating to build this experiment and their work may help us understand why the universe today is made of matter instead of antimatter. Eight hundred miles away, the Long-Baseline Neutrino Facility under construction at Fermi National Accelerator Laboratory will support this experiment by sending the world's

most intense neutrino beam directly through the earth between Illinois and South Dakota. We're also working with international partners on a new linear accelerator that will power the Fermilab Accelerator Complex, serving this and future world-leading experiments.

Our scientists and engineers also apply their expertise to international experiments and facilities hosted elsewhere. Our long and successful partnership with CERN began with agreements signed in 1997, enabling U.S. scientists to provide important accelerator and particle detector components to the Large Hadron Collider programme. The Large Hadron Collider provides the only way for particle physicists to create and study the Higgs boson, which was discovered in 2012 and led to the 2013 Nobel Prize in Physics for its role in revealing the origin of mass of subatomic particles. The new bilateral U.S.-CERN agreement signed in 2015 enables over a thousand U.S. scientists to continue their collaborative research at the world's highest energy particle collider, while developing and building accelerator and detector components for the future High-Luminosity Large Hadron Collider programme.

In Chile, the construction of the Large Synoptic Survey Telescope is underway in order to perform a ten-year optical imaging sky survey of nearly forty billion stars and galaxies in the southern hemisphere. The unprecedented amount of data it will provide will enable scientists to probe the nature of dark energy, which is accelerating the expansion of the universe. The National Science Foundation (NSF) leads LSST and the DOE Office of Science is contributing the largest digital camera ever constructed, with over three billion pixels, to record high- quality images with minimal downtime. In parallel, DOE is building the Dark Energy Spectroscopic Instrument, which DOE will operate on NSF's Mayall Telescope in Arizona. It will provide complementary optical spectra of tens of millions of galaxies, enabling scientists to build a three-dimensional map of the nearby universe to shed light on dark energy. LSST and DESI will make their data publicly available after a proprietary period.

A suite of experiments are exploring the nature of dark matter, which accounts for five times as much of the universe as all ordinary matter combined. Dark matter could be created and detected using beams of particles from accelerators, such as the Large Hadron Collider or a number of DOE national laboratory facilities. Ultra-sensitive detectors deep underground are searching for signs of galactic dark matter as it passes through the earth. Our investments in technology development are also creating new types of detectors based on quantum sensors, which may find an early application in searches for ultralight dark matter particles that were previously thought inaccessible to experiment.

The DOE Office of Science invests in the future. The technology our scientists and engineers develop not only enables advances in science but impacts medicine, industry and national security. Our user facilities provide advanced tools that enable scientific discovery. We work with partners around the globe to create truly world-leading instruments to tackle some of the biggest questions in science. By providing enticing scientific challenges and offering world-class facilities that can help meet those challenges, the U.S. Department of Energy attracts the next generation of innovators to our programs and trains them to be the leaders of tomorrow. ■

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Physics: Negative ion formation in complex heavy systems

Dr Alfred Msezane from Clark Atlanta University's Department of Physics lavishes us with his knowledge about an intriguing aspect of physics, which focusses on his research on negative ion formation in complex heavy systems

The investigation of negative ion formation in low-energy electron elastic collisions with complex heavy systems through the total cross sections (TCSs) calculation provides a novel and robust approach to producing unambiguous and definitive relevant atomic and molecular data for the first time. The novelty and generality of the Regge-pole approach is in the extraction of the anionic binding energies (BEs) from the calculated TCSs for the complex heavy systems; for ground state collisions these BEs yield the definitive theoretically challenging to calculate electron affinities (EAs). Much has been reported and discussed in the published literature about negative ions in general from various perspectives, including their nature and applications. The major objective here is the production of reliable data for complex heavy systems, such as the lanthanide and actinide atoms and fullerene molecules through low-energy electron elastic scattering TCSs calculations. This presentation toward quality data production is organised for convenience in the following four inter-connected subtopics: I. Overview and novel robust theoretical approach; II. Ground state negative ion formation in complex heavy systems: electron affinity extraction; III. Metastable and excited states negative ion formation in fullerene molecules: new insights; and IV. Negative ion formation in the lanthanide and actinide atoms: determination of reliable EAs.

I.1 Overview

One of the most challenging and lingering problems in atomic and molecular physics and still continues to plague both experiments and theory alike when exploring negative ion formation in complex heavy atoms and fullerene molecules is the determination of the unambiguous and reliable electron affinities (EAs) of the atoms and molecules involved. Indeed, the published literature abounds in ambiguous and unreliable EAs for the lanthanide and actinide atoms. Also calculating the EAs of complex heavy systems is a formidable task for conventional theoretical methods due to the presence of the large and diverse intricate electron configurations. The use of theoretical methods that account correctly for the important physics, viz. electron-electron correlation effects and core-polarization interaction is fundamental to the reliable investigation and understanding of negative ion formation in complex heavy systems. This is the adopted approach in the investigation here.

Essentially, many existing experimental measurements and sophisticated theoretical calculations have considered the anionic BEs of the electron attachment to metastable and/or excited anionic states leading to stable negative ion formation to correspond to the EAs of the considered complex heavy atoms, such as the lanthanide and actinide atoms. Indeed, this is contrary to the usual meaning of the EAs found in the standard measurement of the EAs of such complex systems as atomic Au and Pt as well as of the fullerene molecules from C_{20} through C_{92}. In these systems, the EAs correspond to the anionic binding energies for electron attachment to the ground state of the formed negative ions. Therefore, there must be a consistent and definitive meaning of the EA to avoid the proliferation of ambiguous and confusing meaning of the EAs of these complex heavy systems.

Unfortunately, progress toward a theoretical understanding of the fundamental mechanism underlying low-energy electron scattering from complex heavy atoms, including fullerene molecules, leading to stable negative ion formation has been very slow. In the lanthanide and actinide atoms, the presence of many intricate and diverse electron configurations that characterise low-energy electron interactions in these systems leads to computational complexity. This renders very difficult to obtain unambiguous and reliable electron affinities (EAs) for complex heavy systems using conventional theoretical methods consisting of large notoriously slow converging expansions. In particular, electron affinities calculated using structure-based theoretical methods tend to be riddled with uncertainties.

I.2 Novel and robust theoretical method

In recent years, the Regge-pole methodology has proved to be essential to the determination of reliable negative ion formation in low-energy electron collisions with complex heavy systems through the TCSs calculation. Regge-poles, singularities of the S-matrix, are generalised bound states within the complex angular momentum (CAM) description of scattering; they are, therefore, appropriate for the present investigations. The great advantage of the Regge-pole calculated electron elastic total cross sections (TCSs) is the extraction from them of the energy positions of the characteristic Ramsauer-Townsend (R-T) minima, shape resonances and the dramatically sharp resonances manifesting ground, metastable and excited states negative ion formation. The novelty and generality of the Regge-pole approach used here is in the extraction of the binding energies (BEs) of the anionic ground states from the calculated elastic TCSs of the complex heavy systems; these BEs have been identified with the measured EAs.

Within the CAM theory, the calculation of the TCS embeds fully the essential electron-electron correlation effects. Its calculation uses the Avdonina-Belov-Felfli (ABF) potential which accounts for the vital core-polarization interaction. The ABF potential has the appropriate asymptotic behaviour and accounts properly at low electron impact energy for the polarization interaction (both ground and excited states). It has five turning points and four poles connected by four cuts in the complex plane. The presence of powers of the charge Z as coefficients of the r and r^2 (r is the radial distance) in the ABF potential ensures that spherical and non-spherical atoms and fullerenes are correctly treated. Also appropriately treated are small and large systems.

I.3 Accomplishments

The EAs provide a stringent test of theoretical methods when the calculated EAs are compared with those from reliable measurements. Accurate and reliable atomic and molecular EAs are essential for understanding chemical reactions, whose importance and vast utility in terrestrial and stellar atmospheres as well as in device fabrication, catalysis, organic solar cells and drug delivery are well-documented.

Unfortunately, the published literature abounds in ambiguous and difficult to interpret EA values for complex heavy systems, particularly for the experimentally difficult to handle radioactive actinide atoms. Entirely new in the field of electron-cluster/fullerene collisions, the Regge-pole method has been benchmarked on the measured EAs of atomic Au and Pt as well as of C_{60} and C_{70} fullerene molecules yielding an outstanding agreement. The method requires no assistance whatsoever from either experiment or other theory to accomplish the remarkable feat. Indeed, very recently, it has been demonstrated for the first time that the ground state anionic BEs extracted from our Regge-pole calculated elastic scattering TCSs for C_{20} through C_{92} fullerenes matched excellently the measured EAs for these fullerene molecules. This is an unprecedented theoretical achievement; existing theoretical calculations are still struggling to go beyond the C_{60} fullerene because the EAs are at the heart of the fullerene shell model potentials.

In our research, the characteristic R-T minima, shape resonances and the ground, metastable and excited anionic BEs are extracted from the calculated TCSs for complex heavy systems, focusing mainly on the ground state anionic BEs. In the process, the following have been exposed and elucidated: 1) Novel mechanism for creating long-lived metastable atomic negative ions by exploiting the orbital collapse mechanism in the lanthanide and actinide atoms, impacting significantly the polarization interaction; 2) Manifestation of polarization-induced fullerene-like behaviour in the TCSs for the large actinide atoms Pu and Lr due to the size effects; 3) Multiple functionalisation of large fullerene molecules through the rich negative ion resonances in their TCSs; and 4) Effective use of Regge Trajectories to probe electron attachment at the fundamental level in multi-electron systems. They are also used to delineate and identify ground, metastable and excited states negative ion formation through the anionic BEs. And importantly, these Trajectories are essential in assessing the role of relativity in the TCSs calculation.

Recently, the conundrum in the measured EAs of the complex heavy atoms Eu, Tb, Tm, Nd and Nb has been clarified and resolved through the scrutiny of the calculated electron scattering TCSs using our robust Regge pole methodology. It has been concluded that the measured and previously calculated EAs for the investigated atoms, including the most recent measurements of the EAs of Eu and Nb correspond to the BEs of excited anions of these atoms. This demonstrates the importance of our research.

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Peptides: Why advancing peptide science and technology should be a priority

Paula Gomes, Associate Professor of Chemistry and Senior Researcher in Bioorganic and Peptide Chemistry at the University of Porto, Portugal, explains why peptides are amongst the most promising molecules for the future

Research on peptides and their prospective applications has been regaining momentum, as we are running out of options to tackle life-threatening conditions, mainly due to drug safety and resistance issues. Due to their potent and selective action, a broad range of biological targets and effects and generally low toxicity and immunogenicity, bioactive peptides are currently the most appealing alternatives to the so-called "conventional drugs", to fight neurodegenerative diseases, drug-resistant cancers and, especially, antibiotic-resistant infections in humans. Antimicrobial peptides (AMP) are being actively pursued as the antibiotics of the future, for use not only in humans but also in livestock and food plants, as there is an urgent need to find sustainable alternatives to either drugs or pesticides that are unsafe and/or no longer efficient.

The extraordinary value of peptides is not exhausted in their antimicrobial properties, as bioactive peptides are proven to be highly efficient for non-infectious diseases, as well as nutraceuticals or cosmeceuticals. For example, anti-hypertensive, antioxidant, antidiabetic, neuroactive and immuno-modulatory peptides are formed when milk is processed to produce yoghurt. Likewise, collagen-boosting peptides present in commercially available cosmetics have been under the spotlight not only for their known anti-ageing effects but also for their wound-healing properties that could be of use in skin and soft tissue infection (SSTI) management. As life expectancy grows, active research on peptides as effective and biocompatible options to deal with hypertension, diabetes, ageing and health complications thereof, such as chronic wounds (venous/pressure/diabetic foot ulcers), is an urgent need and not merely an academic exercise.

> "Gomes hopes that positive signs in this same direction will come up soon in more peripheral regions, as Peptide Science is crucial within strategies for smart specialisation."

At the forefront of materials science and engineering, we can also find peptides, although they do not necessarily exhibit intrinsic bioactivity. In this setting, self-assembling peptides (SAP) have gained relevance for their potential use as biomimetic structures, such as collagen-like materials or components of synthetic extracellular matrices built to promote tissue regeneration. SAP have been also explored as biocompatible vehicles for intracellular delivery of drugs or biosignaling molecules like, for example, nitric oxide, a potent vasodilator relevant in many physiological processes.

Having early perceived peptides as one of the most promising types of molecules for the future, Paula Gomes pursued her PhD in Peptide Chemistry (1997-2000), to work on peptide-based vaccines mentored by Professor David Andreu, in Barcelona. Returning to her Alma Mater, the University of Porto, she gathered a bioorganic & medicinal chemistry research team now integrated into the Molecular Synthesis group of the largest Chemistry-based Research Unit in Portugal, LAQV-REQUIMTE. Research at Gomes's lab builds on peptide chemistry principles to develop new therapeutic strategies, in close collaboration with experts from complementary areas, such as biomedical engineering, pharmaceutical sciences, biotechnology and agricultural and food sciences. The main lines of research at Gomes's lab focus on: (i) New antimicrobial and wound-healing peptides to tackle SSTI; (ii) Peptide-modified materials for diverse biomedical applications, including osteogenic growth promoters, antibacterial surfaces and nitrogen oxide releasing hydrogels; (iii) Cell-penetrating peptides as drug and nucleic acid carriers; (iv) Identification and potential applications of AMP derived from animal toxins, like snake venoms or amphibian secretions and more recently; (iv) AMP-based strategies to combat plant diseases or prevent food spoilage.

The previous are only a few of the applications that can be envisaged for peptides, explaining why interest in these biomolecules and added-value products thereof is rapidly growing in

Figure 1: It took 15 years for Paula Gomes to gather the necessary means to set up and consolidate a peptide synthesis lab that evolved from exclusively manual methods (top left) to fully automated synthesis using state-of-the-art multiple-channel instrumentation (right) and purification by preparative high-performance liquid chromatography (bottom left). Setting up a large-scale peptide synthesis and purification unit able to meet the requirements of industrial partners is Gomes's next goal.

diverse sectors, including the pharmaceutical industry. The latter is a relevant sign that times are finally changing, as the Big Pharma has for many years relegated peptides as prospective drugs. This has been mainly due to peptides' low oral bioavailability, extensive metabolic degradation and rapid excretion and high production costs either by biotechnological or chemical routes; however, the multiple advantages of peptides as therapeutic agents, along with latest developments in both large-scale production methods and metabolically-stable peptide analogues underpin the ongoing paradigm shift, which peptide scientists have been longing for.

The rising awareness on the scientific, technological and economic worth of peptides is starting to energise investment on peptide research and peptide production facilities. One example is the Peptide Synthesis Facility of the Faculty of Sciences of the University of Porto, which Gomes coordinates. This facility, yet unmatched in Portugal, was open to provide peptide synthesis services in 2016, thanks to Portuguese/European Union co-funding to acquire a state-of-the-art multiple synthesizer (Figure 1) the only one in the country. According to Gomes, the next step to make Portugal truly competitive in Peptide Science, by attracting industrial partners working on or with peptides, is a large-scale production unit. Other European facilities are on this track, like, e.g., PeptLab, where a large scale peptide synthesizer has been instated on the past 12th of June. Gomes hopes that positive signs in this same direction will come up soon in more peripheral regions, as Peptide Science is crucial within strategies for smart specialisation.

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Advancing basic chemical research while developing a globally competitive workforce

Carol Bessel and Melissa Olson from National Science Foundation's Division of Chemistry (CHE) reveal the organisation's goal of advancing basic chemical research while also developing a globally competitive workforce

The Division of Chemistry (CHE) at the National Science Foundation is committed to the goal of advancing basic chemical research while also developing a globally competitive workforce. The pursuit of fundamental chemical science, however, is not just bound to the lab. Rather, it serves to address and solve some of the most pressing societal challenges.

CHE actively solicits and funds projects that design and develop sustainable chemistry pathways from synthesis to recycling; advance algorithms and novel qubit structures for quantum computing; accelerate and complement chemical discovery with data mining and artificial intelligence (AI); and seek to understand and engineer the biochemistry governing life processes such as in synthetic biology, epigenetics and studies of the microbiome. Because each of these grand challenges straddles disciplinary lines and national borders, CHE also promotes interdisciplinary and international teams. Any real solution to these grand challenges also requires public support, calling chemists out of the lab to communicate, interact and broaden participation.

Chemistry forms the basis of nearly all consumer products, from the long, messy chains of carbon atoms in plastics, to the atomically precise molecules in pharmaceuticals with chiral structures. While these products prove incredibly useful and sometimes lifesaving, their entire 'life cycle', from cradle to grave to cradle, must be considered. The desirable durability of plastics leads to their problematic persistence in the environment, as witnessed in plastic 'islands' in the oceans. Aiming to reduce plastics in the environment, CHE funds projects exploring catalysis for novel polymers designed to be chemically or mechanically degraded, biodegraded and/or upcycled into new consumer goods. The atom-level precision required in fine chemicals often leads to many-step reactions and purification processes, each consuming energy or generating solvent waste. Creating sustainable synthetic methods, real-time characterisation and facile separations are priorities for CHE. Organic electrosynthesis is an especially opportune area for collaboration, especially with engineering partners such as the Division of Chemical, Bioengineering, Environmental and Transport Systems (CBET) Division at NSF. CHE also hopes to strengthen this field through international partnerships in the future.

> "One of the first, large-scale projects to develop and adopt big data concepts was the Human Genome Project. Sequencing the human genome was a momentous achievement, but it also raised a myriad of additional, interesting scientific questions."

While developing sustainable chemistry is imperative, fundamental research underpins all advances. This includes the particle-to-particle and atom-to-atom interactions defined by quantum mechanics. Through Quantum Leap, one of NSF's Big Ideas to guide the next decade of research, CHE supports research addressing and exploiting a wide variety of quantum phenomena, from spectroscopy with entangled light to controlling electronic spin for molecular qubit design. This work blurs interdisciplinary lines and requires a new approach to workforce development, so CHE partners with eight other NSF divisions for projects such as QISE-NET, which builds 'Triplets' between students, academic mentors and industrial mentors and Quantum Leap Challenge Institutes, large-scale interdisciplinary research projects that seek to advance the frontiers of quantum computation, communication, simulation and/or sensing.

Image: © National Science Foundation

While the development of quantum computing harnesses the smallest of phenomena, chemists are also turning to big data. With the generation and assemblage of mass amounts of computational and experimental data, exploration of new chemistries can be guided and accelerated with tools such as data mining, machine learning and cheminformatics. CHE supports the development and application of these tools through the Data-Driven Discovery in Chemistry program and through the Harnessing the Data Revolution Big Idea. These projects touch all fields in chemistry, from the optimization of chemical reactions in microdroplets to the search for protein folding guidelines. These techniques can require programming and statistical analysis that go beyond the bounds of traditional chemistry. To foster new collaborations between mathematicians and chemists, CHE has worked with the Division of Mathematical Sciences to sponsor an Innovation Lab bringing together investigators from both disciplines to innovate and generate new ideas and project proposals.

One of the first, large-scale projects to develop and adopt big data concepts was the Human Genome Project. Sequencing the human genome was a momentous achievement, but it also raised a myriad of additional, interesting scientific questions. Another NSF Big Idea, Understanding the Rules of Life, aims to tackle one of these questions – how to predict phenotype (observable characteristics) from genetic information. CHE plays a significant role in answering this question, especially as it is reduced to molecular interactions and chemical responses. These projects include designing platforms for the study of macromolecules that reproduce the crowded conditions in cells and synthesizing artificial organelles, both of which are co-funded with CBET or the Directorate for Biological Sciences.

While poised to address the scientific aspects of these challenges, chemistry needs an informed and active public to help fund or implement any solution. Every award that CHE makes requires investigators to consider the broader impacts of their work, which includes the impacts on the public. Chemistry encourages investigator efforts aimed at education, for example, Energy and U, a collaboration between the chemistry and theatre departments at the University of Minnesota that teaches students about the laws of thermodynamics. Other investigators develop entirely new media for education, such as 3D printed protein structures to help teach blind students about protein dynamics. CHE also encourages chemists to engage in efforts outside academe, offering support for graduate students to pursue internships in industry or government laboratories.

Though CHE strategically supports the programs and initiatives mentioned above, it continues to support basic chemical research of all kinds. Chemistry remains a powerful tool, both inside of the lab when exploring fundamental phenomena and beyond the lab, improving the world around us. ■

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Chemistry and biochemistry: Sugar conformational equilibria and dynamics

Ian Carmichael[a], Robert J. Woods[b] and Anthony S. Serianni[c] share their expertise on an aspect of chemistry and biochemistry that concerns circular statistics and NMR which reveal sugar conformational equilibria and dynamics

Carbohydrates are talented actors on the biological stage. In addition to their roles in metabolic energy production, they are found on cell surfaces, conjugated to membrane-associated proteins and lipids and as such serve as ligands of extracellular receptors that mediate cellular processes such as cell-cell recognition, bacterial and viral infection, immunity and intracellular trafficking.[1] Sugar conformational equilibria and dynamics can be complex in that saccharides contain multiple, flexible elements that collectively determine their overall shapes in solution. The properties of these flexible elements are often correlated and include pyranosyl ring pseudorotation, exocyclic hydroxyl and hydroxymethyl side-chain rotation, *N*- and *O*-acetyl side-chain motions and motions about *O*-glycosidic linkages in oligosaccharides (Figure 1).

For decades, NMR spectroscopy has been used to characterise these solution behaviours by measuring, for example, nuclear Overhauser effects (NOEs), scalar couplings, residual dipolar couplings and nuclear spin relaxation.[2] These parameters yield valuable insights into saccharide behaviours but cannot provide, independently, continuous conformational models; their interpretations rely on input from computed energies and/or molecular dynamics (MD) simulations. This dependence is troublesome because (a) saccharide computed energies are error-prone due to the influences of hydroxyl group conformation and/or solvation and (b) saccharide MD simulation models are very difficult to validate experimentally. Current research relies on MD to provide information on saccharide conformation and dynamics in the absence of definitive experimental evidence that MD models provide accurate pictures of solution behaviour.

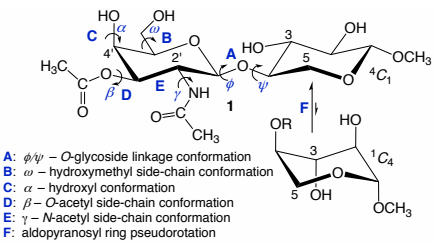


*Figure 1. Some common conformational elements in saccharides, illustrated in the disaccharide, methyl 2-acetamido-2-deoxy-3-O-acetyl-β-D-galactopyranosyl-(1→4)-β-D-xylopyranoside (**1**).* ***[click image to view full size]***

A new development in the analysis of NMR scalar couplings promises to break the circular arguments and provide independent experiment-based models of saccharide solution behaviour. The technique, known as *MA'AT* analysis,[3–6] yields outputs very similar to those provided by MD, allowing direct superimposition of *MA'AT*-derived models on those obtained by MD simulations.

MA'AT analysis involves six steps (Figure 2), illustrated in the modelling

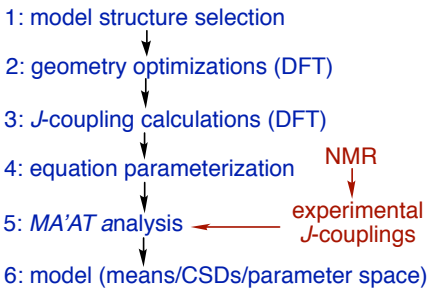


Figure 2. Flow chart for MA'AT analysis. After model selection (1), DFT is used to conduct geometry optimizations (2) and to calculate J-couplings (3). Parameterized J-coupling equations (4) are used along with experimental J-couplings as input to the MA'AT program (5). Conformational models are obtained as output (6).

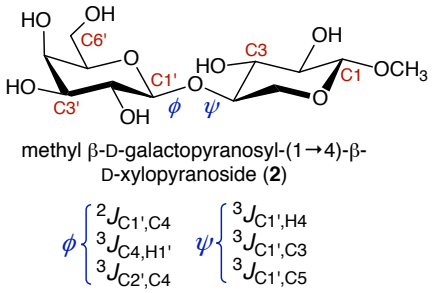


*Figure 3. Definitions of φ and ψ in disaccharide **2** and redundant NMR spin-couplings sensitive to these torsion angles.*

of the *phi* (ϕ) and *psi* (ψ) *O*-glycosidic torsion angles of disaccharide **2** (Figure 3). The structure of **2** is encoded in the *z*-matrix input to *Gaussian*.[7] Ensembles of redundant *J*-couplings sensitive to ϕ and ψ are required and in this case, three *J*-values are sensitive to each angle (Figure 3). Rotating ϕ and ψ in the *in silico* model of **2** through 360° in 15° increments produces 576 conformers and each is geometry optimised using density functional theory (DFT) (Step 2). The six *J*-couplings are calculated in

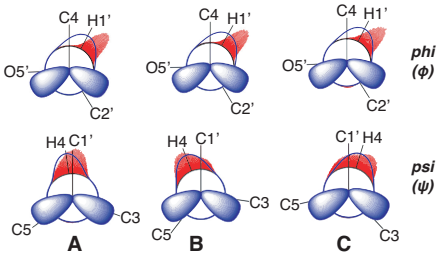


*Figure 4. MA'AT and MD analysis of ϕ and ψ in (A) βGal-(1→4)-βGlcOCH$_3$ (**3**), (B) βGal-(1→4)-βAllOCH$_3$ (**4**) and (C) βGal-(1→4)-βXylOCH$_3$ (**2**), shown as Newman projections down each C–O bond. Histograms (red) were obtained from 1-μs aqueous MD simulations on which are superimposed distributions (blue) determined from MA'AT analysis. Data were taken from ref. 4.*
[click image to view full size]

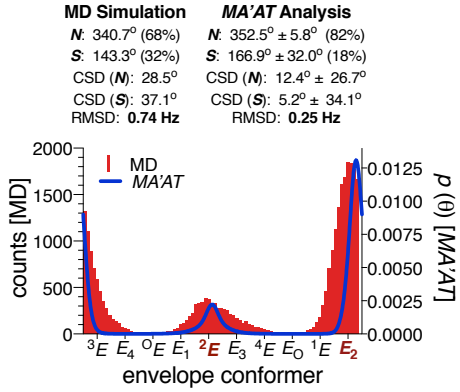


*Figure 5. MA'AT analysis of methyl β-D-ribofuranoside (**5**), yielding a two-state E$_2$/^{2}E model (blue curve) superimposed on the model predicted by a 1-μs aqueous MD simulation (red histogram). Fitting statistics for both models are shown above the plot. [unpublished]*
[click image to view full size]

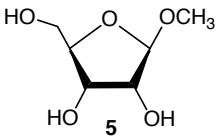
the 576 conformers (Step 3) and the dependencies are encoded into parameterised equations that generally take the form, J_{exp} = A + B cos θ + C cos 2θ + D sin θ + E sin 2θ (Step 4). The experimental *J*-couplings are measured in **2** and the experimental values and parameterised equations are used by the *MA'AT* program (Step 5), which applies a Monte Carlo search and circular statistics to fit the experimental *J*-values to conformational models of ϕ and ψ (Step 6). In this case, only single-state models of ϕ and ψ pertain due to the small number of observables, but multi-state models can be tested if the number of experimental *J*-couplings is sufficient (see below).

MA'AT outputs include the mean values of ϕ and ψ and circular standard deviations (CSDs) of these mean values, the latter providing information on the librational character of each torsion angle.

The application of *MA'AT* to ϕ and ψ in **2** gives the single-state models shown in Figure 4(C), superimposed on those determined by aqueous MD simulation. The models are in good agreement for ψ, but differ for ϕ. The sensitivity of the method can be demonstrated by examining βGal-(1→4)-βGlcOCH$_3$ (**3**) and βGal-(1→4)-βAllOCH$_3$ (**4**) in a similar manner (Figure 4A and B). *MA'AT* models of ψ in **3** and **4** recapitulate the MD models well, but discrepancies in ϕ are observed similar to that found for **2**.[4]

MA'AT analysis can be applied, in principle, to any conformational element in any molecule if multiple, redundant *J*-values exist, can be measured reliably and can be parameterised. For example, the conformational behaviour of the furanose ring in methyl β-D-ribofuranoside (**5**) was investigated using nine intra-ring J_{HH}, J_{CH} and J_{CC} values to give a two-state E$_2$/^{2}E pseudorotational model that recapitulates, although not exactly, that obtained by MD simulation (Figure 5).

MA'AT analysis was first described in 2017,[3-4] and its power and applicability have yet to be fully illuminated. It is expected that the method will lead to improved MD force-fields, especially in cases where solvent effects play key roles in determining conformational preference in solution. In addition, while current applications have been limited to saccharides, studies of oligopeptides and oligonucleotides and perhaps larger molecules, are anticipated.



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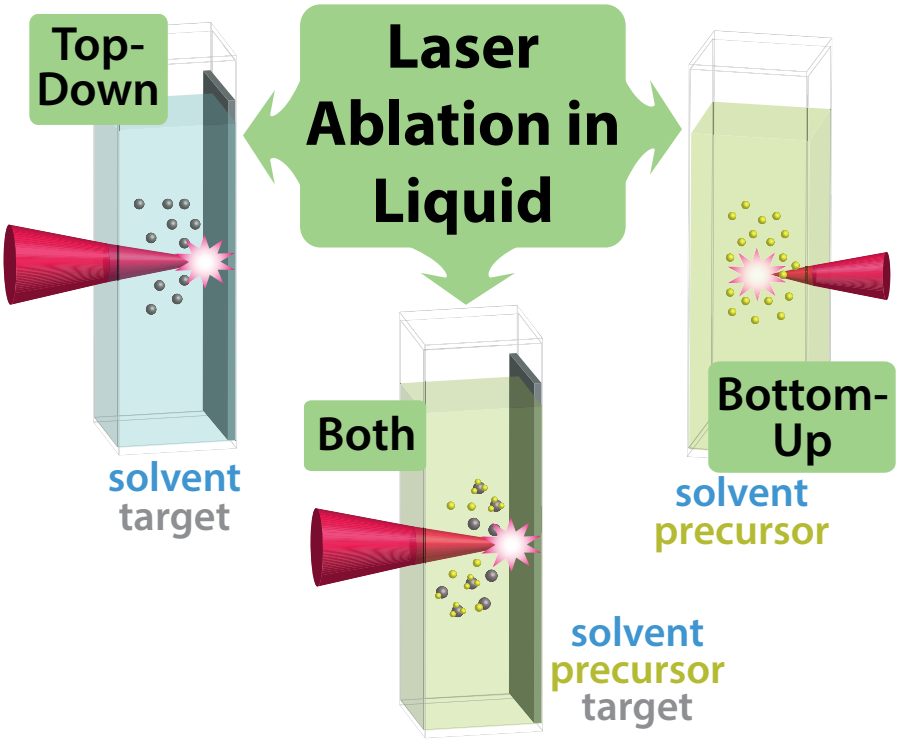
Chemistry focus: Advances in engineering functional nanomaterials research

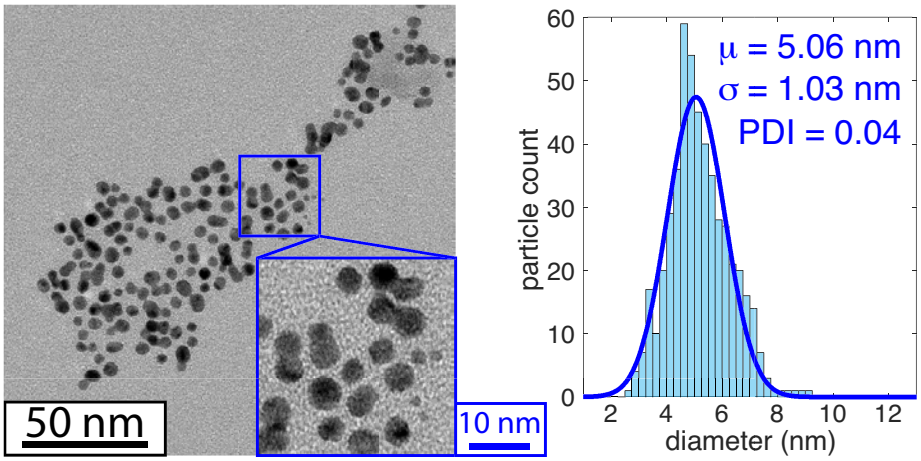
Katharine Moore Tibbetts, Assistant Professor at Virginia Commonwealth University, shares with us her expertise on advances in engineering functional nanomaterials, an area of chemistry research that has benefitted society in various ways

Nanomaterials have well-defined structures on length scales smaller than 100 nm (1,000,000,000 nm = 1 m), close to the size of individual atoms and molecules. These small sizes impart unique optical, electronic and catalytic properties that cannot be obtained in bulk materials. In recent years, advances in engineering functional nanomaterials have revolutionised applications from cancer therapy and drug delivery to industrial catalysis and solar fuel generation. Nanomaterials are, therefore, enabling 21st century technologies to meet major challenges to society such as sustainable energy development.



While immense progress in synthetic methods over the past three decades has made it possible to create tailored nanomaterials with well-defined sizes and compositions, the most commonly used wet-chemical synthetic methods suffer from two major drawbacks. First, they typically require excessive quantities of toxic chemicals that generate large amounts of waste. For instance, the standard procedure for making ultrasmall <2 nm gold nanoparticles requires a 10-fold excess of reducing agent and at least 3-fold excess of capping ligand. Second, the capping ligands that are needed to control nanoparticle sizes can hinder the use of these nanoparticles in applications. For instance, cytotoxic ligands must be removed from metal nanoparticles prior to use in biomedical applications and organic ligands can block access to catalytically active surface sites in metal nanoparticle catalysts. As a result, "naked" nanoparticles with no capping ligands are highly desirable for these and other applications.

Laser ablation in liquid (LAL) has recently emerged as a versatile synthetic route to a variety of nanomaterials that overcomes the major drawbacks of wet-chemical synthesis. Instead of requiring a complex mixture of toxic chemicals, LAL can produce nanomaterials using only water and solid or powdered target material. The lack of toxic chemical use and waste generation means that LAL methods satisfy the major principles of "green chemistry" and can become a platform for environmentally sustainable nanotechnology development. Moreover, nanoparticles synthesised by LAL often do not require capping ligands because they emerge electrostatically stabilised. As a result, LAL is a powerful method for producing naked nanoparticles uniquely suited to biomedical and catalysis applications.



These advantages of LAL coupled to advances in commercial pulsed laser technology have generated surging interest in LAL for nanomaterial synthesis. This interest is captured by the 30-fold increase in citations from an ISI Web of Knowledge search of "laser synthesis nanoparticles" from 563 in 2003 to 16,925 in 2018. LAL-synthesised nanomaterials show promise in applications such as electrochemical water-splitting, photocatalytic hydrogen generation and photothermal cancer therapy. While LAL manufacturing of nanomaterials at industrial scales is likely years away, grammes per hour production rates are now attainable with advanced high-repetition-rate lasers.

In LAL, a high-power pulsed laser is focused into a liquid medium or onto a solid-liquid interface (Figure 1). LAL encompasses both "top-down" and "bottom-up", as well as combined approaches to nanomaterial synthesis. In top-down methods, an immersed solid or powder of the target material produces nanomaterials in the surrounding solution as atoms and clusters are blasted off of the surface or powder particles are fragmented in the laser focus. In bottom-up methods, a precursor such as a metal salt dissolved in solution produces nanomaterials through photochemical reactions of the precursor and solvent initiated by laser irradiation. Combined approaches involve immersion of a solid or powder in a precursor solution to produce composite nanomaterials from ablated material reacting with the precursor and solvent.

The top-down approach is by far the most widely used in the LAL community due to the low cost of solid materials relative to molecular precursors, simplicity of performing synthesis reactions and ability to manufacture large quantities of nanomaterial products. However, a significant drawback of top-down approaches is the often limited control over the size distributions of the resulting nanoparticles. For instance, gold nanoparticles have been synthesised by top-down ablation of gold foil for at least two decades, but even recent studies typically report asymmetric size distributions containing large >20 nm particles despite a mean particle size of 5 nm.

For applications where tight particle size distributions are needed, bottom-up LAL synthesis represents a promising alternative. For instance, our laboratory recently reported uniform 5-nm gold nanoparticles using bottom-up photoreduction of the tetrachloroaurate salt in water using a commercial 532 nm Nd:YAG laser (Figure 2) [1]. While bottom-up LAL synthesis has received less attention than the common top-down methods, it represents a potential platform for tailoring photochemical reactions to attain exquisite control over the sizes and compositions of nanomaterials produced with LAL. Achieving this potential will require advances in understanding the photochemical reaction pathways that convert precursors in solution to nanomaterials, which is a primary goal of our laboratory's research.

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Microfluidic devices: The future is here

Dr Stefan H. Bossmann and Dr Christopher T. Culbertson, Professors of Chemistry at Kansas State University, explain why microfluidic devices are in their view, the future

Microfluidics is all about controlling the flow of liquids on the micro-scale. In microfluidics, tiny channels are etched onto circuit boards, smaller than a human fingernail, through which minuscule volumes of chemicals and other liquids can flow. One use of this technology is for everyday inkjet printers, where the channels help carefully control where the ink is sprayed in the printing process. These channels can also be merged, allowing two separate chemicals to mix and react, which is why some of these microfluidic devices are sometimes known as the 'lab-on-a-chip'.

This team of investigators is led by Dr Christopher T. Culbertson and Dr Stefan H. Bossmann at Kansas State University. We are very excited by some of the possibilities that microfluidics and the lab-on-a-chip offer. In our highly interdisciplinary and collaborative project, our teams are working together to develop this technology into a miniature analysis lab. Our technology will, for the first time, offer profiling in a timely manner so that it could be used for "point-of-care-devices" (POC) capable of:

- Detecting the onset of a disease (e.g. cancer in a group of risk patients (BRCA1,2 or other mutations) or asthma/chronic obstructive pulmonary disease (COPD));
- Detecting the progress versus regress of a disease during treatment (e.g. chemotherapy);
- Detecting the recurrence of a disease (e.g. solid tumours versus other inflammatory diseases) and;
- Precision pain management.

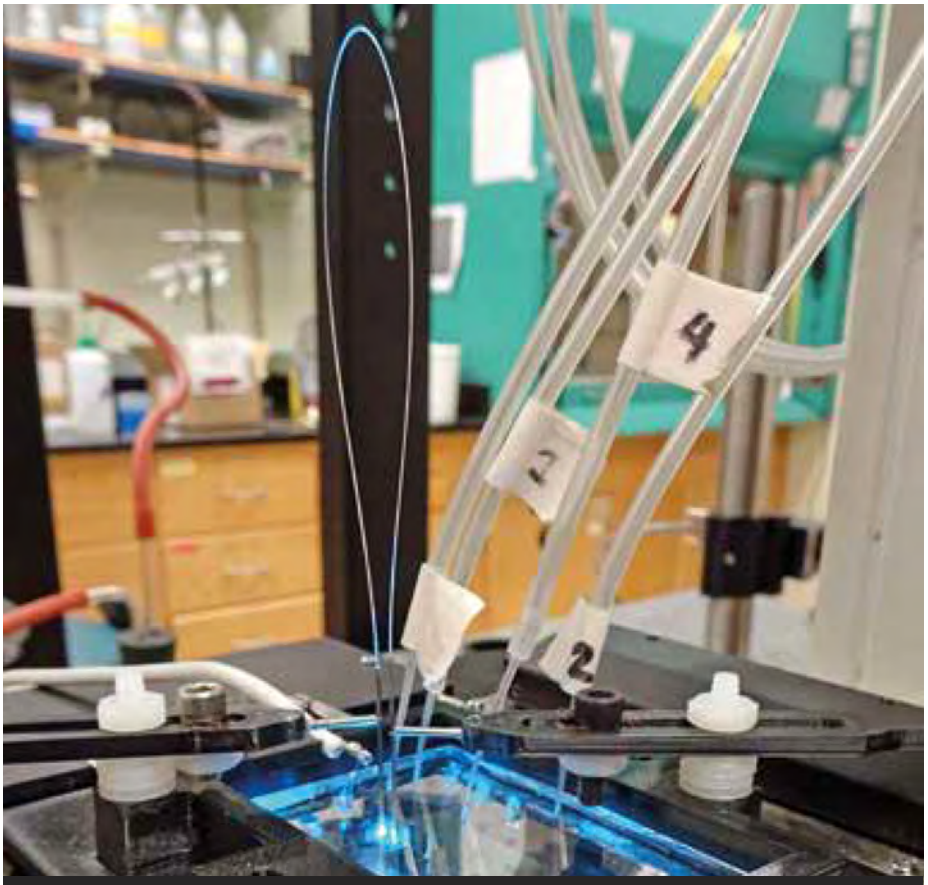

Figure 1: Prototype microfluidic device in a printed 3D cartridge integrated with electric and pneumatic connectors for single cell analyses via cell lysis and electrophoretic separation

Our team is constantly designing new markers for reporting cell activities, such as key metabolic enzymes, proteolytic profiles, kinase network analysis and epigenetic reporting. Many of these markers are either designer peptides or contain designer peptides as functional elements.

Seeing cells

Microfluidic devices are inherently well-suited to looking at biological processes, as the micrometre channel size conveniently corresponds to the size of cells. Most cells are between 1 – 100 micrometres, with a human hair being approximately 60 micrometres thick. This means that the channels can not only be used to provide a highly controlled environment for cell

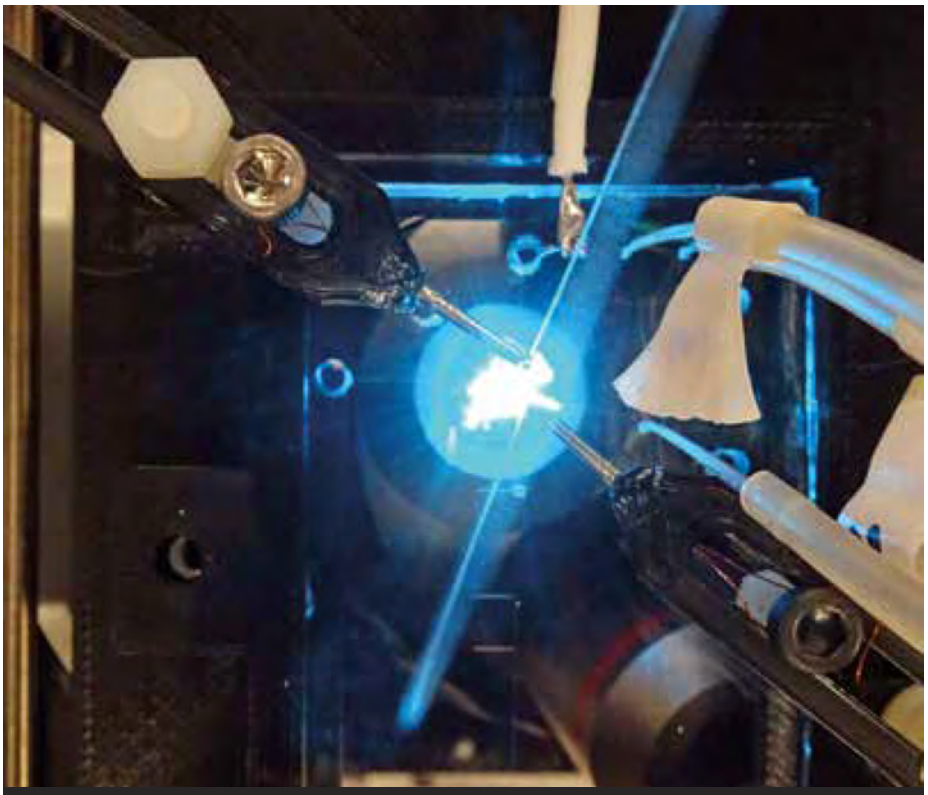

Figure 2: Two 3-D printed micromanipulators are used to align the fibre with the microfluidic channels and the laser light emitted from a microscope objective

growth, that is often more effective than a human-scale lab, but also to separate out different cells of different sizes.

We have already succeeded at using optical fibres to integrate this light detection technology onto a lab-on-a-chip. What is unique about our design and project is the off-chip placement of the optical fibre bridge: this means the chip design is not further complicated by the inclusion of the fibre. One of the big challenges with microfluidic devices is in their design; making components on such a small scale is difficult to do reliably and inexpensively, so this is a key advantage of our design.

Another unique feature of our project is creating a microfluidic device with multiple detection and excitation spots to detect the sample of interest, while still using only one laser and detector. The motivation behind this is to increase the versatility and capabilities of the device. Now with the integration of the optical fibres, they can detect the intact cell before the breakdown of the cell membrane, as well as the components from the cell after it is lysed. Each of the excitation spots on the microchip is like a viewing window for the cell's activities, so the greater the number of spots you have, the greater the amount of information you can obtain. With more information, it becomes possible to better understand exactly how diseases lead to deformation and destruction of the cell.

Counting lines

We want to go beyond just being able to image and identify cells. This work involves designing very bright markers, so when the cells bind a chemical marker that glows after it absorbs light from a laser, this emitted light from the cell is sufficiently intense that a single molecule in a single cell can be detected. These markers also have to be rapidly taken up by the cell so that the detection can be done in 'real time'. This is important if this device will be used to reduce patient diagnosis times. This will be achieved by combining ultrabright fluorescent dyes or quantum dots with state-of-the-art peptide design, which enables the uptake and transport of markers to cellular targets (e.g. mitochondria or nucleus) within minutes. A large number of enzyme markers that can be monitored will allow for the detection of many possible diseases.

The work combining optical fibres with microfluidic devices will open up many new possibilities in understanding diseases at the cellular level and more tools for cell imaging and diagnosis. All of this is an important part in the development of lab-on-a-chip technology for making rapid, handheld diagnostic devices a routine part of healthcare.

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Climate toxicology: The impact on human health

Eduardo A. González, B.S. and Pamela J. Lein, Ph.D., University of California, Davis discuss how global climate change is increasing toxicological impacts on human health

The global climate is changing at an unprecedented pace, driven largely by increased carbon dioxide emissions that are steadily warming the Earth. Worldwide warming trends are contributing to melting of the polar ice caps, rising sea levels, worsening global air pollution, deteriorating watershed conditions, drought, and increased frequency and severity of extreme weather events. As documented in the 2018 World Health Organization (WHO) COP24 Special Report entitled "Health & Climate Change", these destabilising climate changes are already exerting significant negative impacts on human health.

Direct effects of climate change on human health include the physiological effects of extreme heat (heatstroke and increased incidence of heart attacks, stroke and respiratory distress), as well injuries and death caused by extreme weather events, such as drought, floods, heatwaves, storms and wildfires. Climate change also affects human health indirectly, largely via ecological changes that compromise food and water security, promote the spread of infectious disease, and/or force the displacement of populations. Emerging scientific evidence suggests that global climate change also impacts human health by increasing human exposure to toxic chemicals and/or increasing chemical toxicity.

A number of persistent organic pollutants have historically been sequestered in polar regions due to the phenomenon of global distillation. Temperature and wind patterns carry volatile chemicals towards the poles, depositing them in frozen water and soils for decades.

However, melting of the polar ice caps is releasing these pollutants back into the environment. Multiple studies have documented increasing levels of bisphenol A, polychlorinated biphenyls, and DDT, being released from polar regions. Increasing temperatures allow these chemicals to more readily transition into the gaseous phase, which facilitates their global redistribution.

Current climate prediction models estimate significantly altered patterns of precipitation, and significantly increased incidence of extreme weather events. Increased rainfall will increase chemical deposition into soils and runoff into water sources. Increased nutrient runoff due to flooding or increased irrigation in areas of drought coupled with warming of surface waters will increase the incidence, geographic distribution and duration of harmful algal blooms. Human exposure to algal toxins via ingestion of contaminated seafood, skin contact with affected waters, or inhalation of toxins that have become airborne is linked to nausea, vomiting, diarrhoea, paralysis, slurred speech, and other neurological symptoms.

Conversely, in areas experiencing decreased rainfall, air pollutants will persist longer in the atmosphere.

Drought will increase the likelihood and magnitude of dust storms. Both of these scenarios can increase human exposure to pollutants via inhalation. Decreased rainfall is also linked to a predicted tripling in the incidence of wildfires by 2050.

"Global climate change is the greatest health challenge of the 21st century. The health impacts of climate change are predicted to force 100 million people into poverty by 2030, with significant impacts on mortality and morbidity."

Exposure to the smoke generated by wildfires, as well as the toxic chemicals generated by pyrolysis that remain in the debris, pose significant risks for human health. The most toxic components of wildfire smoke include carbon monoxide and particulate matter, which exacerbate cardiorespiratory disease and adversely impact brain function, whereas wildfire debris often contains elevated levels of toxic metals and persistent organic pollutants.

Climate change is predicted to increase human exposures to pesticides. For example, warming temperatures will likely shift agricultural zones towards higher latitudes. This change will be accompanied by increased application of pesticides in areas where pesticide usage has traditionally not been heavy. A warming climate is also expected to expand the geographic range of mosquitos and other disease-carrying insects over the next 30 years.

Many nations are facing or will be faced with the challenge of managing malaria or other infectious diseases carried by mosquitos, which likely result in expanded use of dichlorodiphenyltrichloroethane (DDT). DDT, a persistent organochlorine insecticide, has been linked to increased risk of obesity and metabolic disorders, cardiovascular disease, and cancer. In addition to increasing human exposure to toxic chemicals, global climate change is predicted to exacerbate human response to toxic chemicals.

For example, warmer temperatures have been shown to increase the toxicity of some metals, including lead and cadmium, on wildlife health, and data suggests that this may the case for humans as well. A similar relationship is reported for pesticides and air pollution: the negative effects of these toxic chemicals on the heart, lungs, and brain are exacerbated by increasing temperature.

The biological basis for this relationship is unknown, but a leading hypothesis is that increasing body temperature increases the activity of enzymes involved in the metabolism of toxic chemicals, some of which detoxify the chemical, but many of which increase chemical toxicity. An alternative explanation derives from experimental and epidemiological studies indicating that chronic stress exacerbates the effect of toxic chemicals. There is abundant evidence indicating that global climate change increases stress, particularly in those populations facing food or water insecurity or who have been displaced by climate-driven events.

Another mechanism by which global climate change increases chemical toxicity is the depletion of the ozone layer, which filters out harmful ultraviolet (UV) radiation. Increased UV levels at the Earth's surface increases the toxicity of phototoxic chemicals, defined as chemicals that have increased toxicity with exposure to UV radiation. Phototoxic chemicals include titanium dioxide nanoparticles, a common ingredient in sunscreen, medicine, and toothpaste.

Global climate change is the greatest health challenge of the 21st century. The health impacts of climate change are predicted to force 100 million people into poverty by 2030, with significant impacts on mortality and morbidity. A highly conservative estimate of 250,000 additional deaths each year due to climate change has been projected between 2030 and 2050. These estimates did not take into account the impacts of climate change on the toxicological impacts on human health, so the true impacts could be even greater. Collectively, these data underscore the significance of the conclusion reached by WHO that the global costs of mitigating climate change would be more than offset by the savings in human healthcare costs.

UCDAVIS VETERINARY MEDICINE

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Reading the warning signs: Research needed to address the crisis of maternal mortality

Dr Diana W. Bianchi, Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), part of the U.S. National Institutes of Health, details the critical need for research to address maternal mortality

Mavis Stephens, a mother and U.S. Army veteran, recounted her near-death experience giving birth. She shared her story at a recent maternal health forum sponsored by my institute, reminding the audience of how precarious pregnancy can be for women and their offspring.

"Pregnancy can be a rollercoaster ride," Stephens said. "Before you get on a rollercoaster, there are signs that say, 'You need to be this tall to ride. If you're not, don't ride.' We need those signs for pregnancy."

I agree.

Stephens, who is African American, was in her 20th week of pregnancy when she started to see signs of trouble. She mentioned to her doctor that she was having headaches and feeling dizzy. He suggested she stay off her feet and cut back on dietary salt. At 27 weeks, she had blurred vision and unbearable headaches and dizziness. Her doctor took her blood pressure and immediately sent her to the nearest hospital emergency room. Tests showed she was struggling with preeclampsia, a pregnancy-related high-blood pressure disorder. Within a day, she was fighting to stay alive. She had an emergency C-section, but her baby boy died within two days. Her story was a wake-up call that we all should heed.

The United States has one of the worst maternal death rates in the developed world. The U.S. Centers for Disease Control and Prevention (CDC) estimates that 700 women die each year as a result of pregnancy or delivery complications. Death rates are higher among women of colour. Even celebrity status and wealth aren't enough to insulate women from these pregnancy-related health threats, as tennis champion Serena Williams and singer/songwriter Beyoncé have recently shared. According to the CDC, black and American Indian/Alaska Native women are about three times more likely to die from a pregnancy-related cause than white women.

In addition, serious and life-threatening complications following pregnancy, called severe maternal morbidity, have been steadily increasing. CDC estimates that since 2014, more than 50,000 U.S. women have been affected by severe, unexpected complications from labour and delivery.

My institute, NICHD, was founded more than 50 years ago specifically to understand and improve maternal health and pregnancy outcomes. Our research led to the development of the first home pregnancy test in the 1970s and has made several contributions to reducing maternal morbidity and mortality, but much more needs to be done.

Maternal deaths can result from a variety of causes: a pregnancy complication, a chain of medical events started by the pregnancy, worsening of an unrelated condition because of the pregnancy and other factors. Death may occur during pregnancy, childbirth, in the 48 hours immediately following childbirth or up to one year after the pregnancy ends. Complications that do not result in death may cause short- or long-term health problems or disability, which can deeply affect a woman's quality of life. A full spectrum of research is


Dr Diana W. Bianchi

needed to better understand the causes of these deaths and how to prevent them in the United States and around the world.

Some of NICHD's recent research has found that taking low-dose aspirin may prevent the onset of preeclampsia in high-risk women. NICHD-funded researchers have also found that vaginal birth after a prior C-section – commonly called VBAC – is safe under certain situations and leads to lower infection risk and faster recovery. An NICHD-supported network helped determine that a low-cost drug, called misoprostol, prevents maternal haemorrhage (extreme bleeding) after delivery. This treatment has saved many lives in the developing world.

However, there is still much to be accomplished not only to understand the biomedical causes of maternal mortality, but also to understand the full social and behavioural factors that contribute to these deaths. Recent NICHD workshops highlighted the need to identify research gaps in data collection, clinical obstetrical factors and health disparities, specifically racial and ethnic inequalities, in the care of women before, during and after pregnancy. Our Community Engagement Forum on Improving Maternal Health in early April 2019 was an opportunity for women, such as Mavis Stephens, to share experiences with health care providers and advocates.

> "The United States has one of the worst maternal death rates in the developed world. The U.S. Centers for Disease Control and Prevention (CDC) estimates that 700 women die each year as a result of pregnancy or delivery complications. Death rates are higher among women of colour."

In the biomedical realm, an ongoing NICHD research project called PregSource® allows women to track their pregnancy experiences. This crowdsourcing project uses confidential questionnaires to gather data directly from pregnant women in hopes of informing future studies aimed at improving maternal and obstetric care. In addition, NICHD has invested more than $60 million to develop novel technologies that help us better monitor the development of the placenta throughout pregnancy. Among other accomplishments, the Human Placenta Project has supported the design of a handheld device that monitors the flow of blood and oxygen between mother and fetus. This small device may one day be used by expectant women to detect early warning signs of complications and to seek care accordingly.

Any maternal death is one too many. It shouldn't happen in the United States or anywhere else. We know there are warning signs, like the ones Stephens experienced. Let's work together to figure out how to read those signs, intervene and make a difference for every expectant woman and her family. ■

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Vitamin D and preeclampsia research: Improving maternal and foetal health

Yuping Wang and David F. Lewis, from Louisiana State University Health Sciences Center – Shreveport, share with us their fascinating research on vitamin D and preeclampsia research, including a promising option in this vein to improve maternal and foetal health

Vitamin D deficiency is a newly recognised risk factor for preeclampsia. Drs Yuping Wang and David F. Lewis at Louisiana State University Health Sciences Center in Shreveport (LSUHSC-Shreveport) are exploring ways of vitamin D to protect placental cells by targeting vitamin D receptor (VDR), a promising option to improve maternal and foetal health.

Preeclampsia, characterised with increased maternal blood pressure and the presence of proteinuria after 20 weeks of gestation, is a serious complication in human pregnancy. This pregnancy disorder is one of the leading causes of maternal and foetal morbidity and mortality worldwide. Although the cause of preeclampsia is not clear, recent studies have shown that low maternal vitamin D levels are associated with a higher incidence of preeclampsia. Therefore, it is considered that vitamin D deficiency is a risk factor for this pregnancy disorder. Since placental cell dysfunction plays significant roles in preeclampsia development, the research at LSUHSC-Shreveport aims to address the roles of vitamin D in placental cells (trophoblasts, foetal vessel smooth muscle cells (VSMCs) and endothelial cells) and to better understand how vitamin D, a pleiotropic hormone, could ameliorate or rescue placental cell dysfunction in preeclampsia.

Vitamin D metabolic system in placental cells

The key molecules that engage in synthesis and degradation of vitamin D include vitamin D binding protein (VDBP, that carries and delivers 25(OH)D and $1,25(OH)_2D_3$ to target cells and tissues), *25-hydroxylase* (converts cholecalciferol to calcidiol, 25(OH)D), *1α-hydroxylase* (converts calcidiol to calcitriol, $1,25(OH)_2D_3$), *24-hydroxylase* (degradates both 25(OH)D and $1,25(OH)_2D_3$) *and vitamin D receptor* (VDR). $1,25(OH)_2D_3$ is the bioactive form of vitamin D. After binding to its receptor VDR and forming heterodimer with other nuclear hormone receptors, the complex then binds to vitamin D response elements (VDRE) in the promoter of genes, in which it regulates and subsequently elicits downstream vitamin D biological actions. Therefore, VDR is an absolute determinant of vitamin D bioactivity.

To study vitamin D metabolism in the human placenta, Drs Wang and Lewis team demonstrated that placental cells are enriched with all the elements that are involved in the synthesis and catabolism of vitamin D. Their results showed:

1) VDBP and VDR are strongly expressed in placental trophoblasts throughout pregnancy;

2) Vitamin D synthases (*25-hydroxylase* and *1α-hydroxylase*) are not only in trophoblasts and VSMCs but also present in foetal vessel endothelial cells, especially in the third trimester/term placentas, while vitamin D catabolic enzyme (*24-hydroxylase*) is weakly expressed in placental cells throughout pregnancy and;

3) VDR expression is inducible by $1,25(OH)_2D_3$ in trophoblasts, VSMCs and foetal vessel endothelial cells. These findings indicate that placental cells could produce and store vitamin D to maintain its homeostasis within the placental microenvironment and to provide and transfer prehormone (25(OH)D) from the maternal circulation to the foetus to support the growing foetus' requirements.

Their works further demonstrated that in preeclamptic placentas, trophoblasts had altered levels of vitamin D synthesis and catabolic enzymes, along with a reduced amount of VDR. Their studies also demonstrated these changes seen in

trophoblasts could be induced by mimicking preeclamptic condition induced by oxidative stress in the laboratory.

Could vitamin D improve placental cell function in preeclampsia?

It is known that not having enough vitamin D during pregnancy increases the risk of preeclampsia, but how vitamin D is able to affect placental cell function and whether vitamin D could reverse any of the alterations associated with placental cell dysfunction in preeclampsia are less clear. To answer the questions, the team took the approach to look into the most relevant adverse events that occur in placental trophoblasts in preeclampsia: increased oxidative stress and superoxide generation, increased vasoconstrictor thromboxane and inflammatory cytokine production and increased microparticle release.

Using primary trophoblasts from the human placenta, they demonstrated that bioactive vitamin D, $1,25(OH)_2D_3$ could suppress oxidative stress-induced increase in thromboxane production and superoxide generation, which is due to the ability of vitamin D to inhibit cyclooxygenase-2 (COX-2) upregulation since both thromboxane and superoxide are metabolites of cyclooxygenase pathway. They also demonstrated that $1,25(OH)_2D_3$ could suppress oxidative stress-induced microparticle release by placental trophoblasts via preservation of eNOS expression and inhibition of caspase-3 cleavage and ROCK1 activation in trophoblasts. These findings are important because thromboxane is a potent vasoconstrictor and suppression of thromboxane production could reduce vascular contractility and improve placental blood perfusion.

Moreover, suppression of microparticle release would diminish maternal vascular inflammatory response induced by trophoblasts-derived harmful stimuli. In addition, their data also show that $1,25(OH)_2D_3$ could inhibit inflammatory cytokine TNFα, IL-6 and IL-8 production. Their work, combined with others of suppression of sFlt-1 production by vitamin D, holds a promise that vitamin D has the ability to improve and restore trophoblast function in preeclampsia.

In addition to trophoblasts, they also proved favourable effects of $1,25(OH)_2D_3$ on foetal vessel endothelial cells and found that bioactive vitamin D could promote superoxide dismutase (CuZn-SOD) expression, an essential antioxidant to dismutate superoxide radicals. Their recent study also revealed that $1,25(OH)_2D_3$ could stimulate endothelial cells to produce more miRNA-126, an endothelial specific miRNA that exerts anti-inflammatory activities to govern vascular integrity.

The team also studied vitamin D effects on placental VSMCs and found that $1,25(OH)_2D_3$ could inhibit angiotensin II-induced placental VSMC contraction. Similar to that of losartan, an angiotensin II receptor – 1 (AT-1) blocker, by inducing a signalling mechanism called phosphorylation of the myosin phosphatase target subunit 1 (MYPT1) pathway molecule. This is a key player involved in myosin light chain phosphatase (MLCP) activation that is essential for VSMC relaxation.

Could VDR hold a key to improve trophoblast function in preeclampsia?

The actions of bioactive vitamin D are mediated by VDR, a ligand-activated transcriptional factor that functions to control target gene expression. VDR expression is inducible in placental cells. Therefore, the amount and the activity of VDR present in placenta cells, especially in trophoblasts, are critical to determining the biological effects of $1,25(OH)_2D_3$ derived from the maternal circulation, as well as produced by trophoblasts. However, the amount of VDR on trophoblasts is reduced in preeclampsia. Lack of VDR expression causes trophoblasts unable to respond to $1,25(OH)_2D_3$ properly. Hence, one of the goals of the research projects of Drs Wang and Lewis research is to find a way to promote VDR production/expression and increase VDR activity in trophoblasts to correct and restore trophoblast function and subsequently, to reduce the incidence or severity of this pregnancy disorder.

LSU Health SHREVEPORT

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Oxytocin, vasopressin and mother nature

Dr Sue Carter, The Kinsey Institute, discusses the critical role of oxytocin in birth, lactation and maternal behaviour and in tuning the baby's developing endocrine and nervous system

Like little scuba divers, most mammals begin their lives swimming in an intrauterine pool of amniotic fluid. Through a two-way tether, the umbilical cord, babies receive oxygen, nourishment and hormones, and transmit chemical signals to their mother. The mammalian infant also is being pre-programmed during pregnancy and by birth for life on "dry land." After birth, this programming continues in the form of hormones in milk and styles of parenting.

We now understand that one neuropeptide oxytocin, plays a critical role not only in birth, lactation and maternal behaviour – but also in tuning the baby's developing endocrine and nervous system. Oxytocin works in conjunction with an even more ancient chemical, known as vasopressin. Together these molecules are essential elements in adaptations to perinatal life and in the events surrounding birth.

Birth and birth interventions

Birth presents one of life's most important challenges. Embedded in the perinatal period and birth experiences are biochemical messages that can help the infant feel safe, or alternatively prepare it for life in a threatening world. Yet, remarkably, the specific consequences of the birth experience itself for either mother or child's physiology and behaviour have received little attention.

Although a basic biological process, the birth transition is often subject to medical and cultural modification. Hormonal treatments, including synthetic oxytocin (also known as Syntocinon or Pitocin) are widely used to induce or augment labour and protect against postpartum bleeding. Initially it was assumed that oxytocin produced by or given to a mother did not reach the infant in amounts sufficient to affect the child. The effects of oxytocin were believed to be transient, disappearing as soon as the hormone was cleared from the system.

However, studies in animals and humans indicate that oxytocin can cross the placenta around the time of birth and may be transmitted in mother's milk. We also now understand that endogenous oxytocin is an important factor in normal development, with long-term effects on brain maturation as well as in the capacity to manage stress, the autonomic nervous system and immune system.

In a search to better understand the developmental role of oxytocin, we have experimentally administered extra hormone, or in some cases injected agents that block the oxytocin receptors. Treatments were given just before birth via the mother or directly to the infant just after birth. These studies were conducted in the highly social prairie vole, a rodent species that shares with humans, "social monogamy " – a lifestyle characterised by a high level of sociality and the tendency to form families constructed around a mother, father and sometimes several generations of offspring. In prairie voles, and likely in humans, patterns of parenting play a role in sculpting expression of later behaviours, including later tendencies to form social attachments or care for infants.

Oxytocin plays a central role in many features of maternity, including synchronising social interactions and

attachment between mothers and infants. Oxytocin has a wide breadth of functions including effects on social behaviour, metabolism, cardiovascular function, immunity, and the autonomic nervous stress. Oxytocin through its effects on birth and lactation, allowed the development of large primate brains and eventually supported human evolution and cognition.

Vasopressin is a more primitive hormone, related to oxytocin and like oxytocin, is designed for change. Our work in prairie voles revealed that a single exposure to oxytocin on the first day of life could down-regulate the vasopressin receptor in brain regions involved in aggression. The one brain area in which oxytocin increased the availability of the vasopressin receptor was a region associated with pair bonding and reward. Such changes seemed to produce a more social male, better prepared to form social bonds and give sensitive care to his own offspring or siblings.

The Goldilocks Principle

However, like the desired temperature of porridge in the children's tale, Goldilocks and the Three Bears, there is a "just right" range of experiences and hormones in early life that promote survival and reproduction. In our studies of prairie voles, we discovered that even apparently small events, such as a momentary disturbance of the family within the first day of life created life-long differences in brain development and the genes for the oxytocin receptor.

As one example, young prairie voles exposed to moderate social stimulation in early life are gregarious. In comparison to less social species of rodents, prairie voles begin life with more oxytocin, both in their blood and brain, and more oxytocin receptors in brain regions necessary for social awareness and attachment. Prairie voles exposed to a single oxytocin treatment around the time of birth also showed – in later life – an even friendlier behavioural pattern with less anxiety and fear of novelty.

In some cases, neonatally oxytocin-treated voles also formed adult pair bonds more quickly. Especially in males, increases were seen in the oxytocin receptor after receiving small amounts of exogenous oxytocin, possibly allowing these males to be more sensitive to the benefits of oxytocin. The biological basis of the "Goldilocks principle" includes re-programming of neural pathways that rely on oxytocin and vasopressin.

Should we "mess with mother nature?"

Prenatal and postnatal experiences differ among species and within a species among individuals and between the sexes. Variations in early stimulation and hormones, such as oxytocin contribute to these differences.

Moreover, oxytocin and perinatal social experiences also are widely manipulated. Among these manipulations are different styles of parenting, and birth interventions, such as Caesarean-sections, applications of extra oxytocin to hasten birth, or blocking oxytocin receptors (sometimes used to prevent premature labour). All of these hold the potential to influence a broad range of processes relevant to the health of both the mother and baby.

Perhaps even more remarkably, the genes that control the oxytocin receptor can be epigenetically "tuned" by either experience or hormones, including oxytocin itself. Birth and oxytocin both sculpt the brain and body. During the perinatal period infants receive behavioural and physiological messages that help the new born adapt to and cope with an everchanging environment.

However, these properties also give birth, parenting and natural and medically-manipulated oxytocin the power to alter physiology and behaviour for both the present generation and into the future. Studies of oxytocin-vasopressin pathways are offering new insights into the pervasive health benefits of optimal early experiences. This research also provides warnings that manipulations of these systems hold the potential for unexpected outcomes.

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Supporting vision research in the U.S. that encompasses visual impairment diseases

Here, Open Access Government explore how the National Eye Institute in the U.S is supporting vision research that encompasses visual impairment diseases of people of all ages

The National Eye Institute (NEI) was established on August 2nd, 1968. The U.S. Congress passed Public Law 90-489, which authorised the formation of the institution. It was President Lyndon B. Johnson, who signed the legislation on 26th December of the same year, at which moment the NEI began to function. The NEI has supported research into vision consistently, through around 1,600 research grants and conducting their own research that encompasses the visual impairment diseases of people of all ages.

Currently, Dr Paul A. Sieving is the NEI Director. During his time, he has established a programme to develop treatments for eye diseases, the NEI Audacious Goals Initiative (AGI) for Regenerative Medicine – this research focuses on how to restore the function of critical nerve cells in the eye and visual processing system. Dr Sieving particularly focused on these systems after they are damaged by disease, searching for strategic ways to reverse vision loss in age-related macular degeneration and glaucoma.

The NEI has created many research outputs, three of which we discuss below:

Zebrafish can regenerate from blindness

An NEI study in 2017 examined how decreases in neurotransmitter GABA trigger stem cell production in the retina, which used blind zebrafish to attempt a reversing of the injury. They explored regeneration in the zebrafish retina, which happens naturally. Meanwhile, in humans, the same injury seems irreversibly damaging. The scientists found that GABA could be the influential factor in the regenerating process. This finding translated to human eyes could prove to be substantially useful.

Children can survive epilepsy surgery with full vision

Recently, in June 2019, an NEI-funded study explored the impact of brain surgery to halt seizures. The procedure is infamously risky, with the understanding that visual perception could be significantly impaired. A new report from Carnegie Mellon University in the U.S. presented a study of children who had undergone the surgery, which then revealed that the lasting effect on visual perception could actually be imperceptible – even when the children had tissue in their visual centres taken away.

Nitisinone increases melanin in people with albinism

A clinical study in February 2019 happened at the NEI itself, to suggest that the drug Nitisinone increases melanin production for some individuals who have oculocutaneous albinism type 1B (OCA-1B), which causes pale skin, hair and poor vision. A Melanin increase could significantly protect people with this condition against the UV rays of the sun. The scientists found a darkening skin and hair but are hoping to pursue a darkening of the imagining of the iris, over time. This could change the lives of people who currently have no cure.

The last word goes to Paul A. Sieving, Director of the National Eye Institute, who comments on the possibilities of NEI: "This is a remarkable time of discovery. We can view the functioning eye in greater and greater detail and gain a better understanding of the biology, at the level of cells, genes and proteins, that makes vision possible – and how things can go wrong with disease or trauma."[1] ■

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Understanding chronic autoimmune uveitis through ophthalmology research

Andrew Taylor, Professor of Ophthalmology, highlights the research involved to help understand the molecules that mediate ocular immune privilege so they can be adapted as therapy for chronic autoimmune uveitis

Current therapy uses steroids, which have been the standard approach for over six decades. The recent use of humanized antibodies, biologics, to suppress key cytokines in the inflammatory pathway is providing an alternative to steroids; however, like steroid therapy carry serious side-effects from susceptibility to infection to even death. Ironically steroid therapy carries the risk of sight-threating cataracts and glaucoma.

Nearly 17% of patients suffer chronic uveitis and are resistant to steroid therapy. This leaves them with months to years of finding the right concentration of a biological to manage uveitis with minimal side-effects. The objective of this therapy is to suppress inflammation to give the ocular tissue a chance to recover, and possibly reassert its normal anti-inflammatory mechanisms. Meanwhile, each episode of uveitis further diminishes vision leading to blindness and reduced quality-of-life.

One of the ultimate goals of autoimmune disease therapy is to find an approach that would return the immune system to treating our own tissues as self. Such a therapy would not only suppress inflammation; it would induce what could be considered hitting the reset button of the immune system to prevent recurrence of autoimmune disease. Studies into the mechanisms of ocular immune privilege are revealing molecules that have the potential to reset immunity. Not only can these molecules be used as therapy, but they are also well tolerated and are molecules naturally expected to be expressed in a healthy eye.

Originally, the concept of ocular immune privilege was a transplantation term defined by Sir Peter Medawar as a tissue site where incompatible grafts survive indefinitely. Today, the definition of immune privilege includes a tissue microenvironment that actively suppresses the induction of inflammation and promotes immune tolerance. Immune tolerance is where immune cells regulate the activity of other immune cells.

Immune privilege is mediated by molecules expressed on cell membranes and secreted by cells within the eye. The result is that for most of us we have a lifetime of vision not threated by inflammation and autoimmune disease. Our studies into these molecules of ocular immune privilege have demonstrated the role of several that hold a central role in ocular immune privilege and a role in immune regulation systemically.

One of these molecules is the neuropeptide alpha-melanocyte stimulating hormone (α-MSH) and its melanocortin receptors (MCr). This neuropeptide first described for its ability to regulate pigmentation has roles in metabolism, immunity, and general wellbeing. It and its receptors are highly conserved and are expressed in every animal. When we started studying the soluble molecules of ocular immune privilege, we had found that aqueous humour, the fluid that fills the anterior chamber of the eye, did not suppress T cell activity. It changed T cell activity from proinflammatory to anti-inflammatory.

Of the many molecules we found in aqueous humour that suppress inflammation, only α-MSH made T cells expected to mediate inflammation suppress inflammation. In addition, we found that α-MSH like aqueous humour makes other activated immune cells, like macrophages, to make anti-inflammatory cytokines and suppress inflammation. Removal of α-MSH from aqueous humour eliminated the ability of aqueous humour to mediate anti-inflammatory activity. The results alone are enough to support melanocortin-based therapies to suppress uveitis; however, while we were studying the use of α-MSH in therapy more was discovered, suggesting that melanocortin-based therapy can promote immune tolerance, the necessary reset of immunity.

The best-used mouse model of autoimmune uveitis is called experimental autoimmune uveoretinitis (EAU). EAU has served as an important

model in understanding the activity of immune cells in autoimmune disease, testing for new therapies, and understanding the mechanisms of immune privilege. One interesting feature of this model is that unlike in humans, mice resolve uveitis on their own without intervention with resistance to a recurrence of the disease. An important feature of post-EAU is the expansion of regulatory T (Treg) cells specific to antigens within the eye. We found that α-MSH mediates the expansion of these eye-specific Treg cells.

Moreover, we found that α-MSH through the melanocortin five receptor (MC5r) activates an antigen presenting cell (APC) that in a process called counter-conversion coverts T cells that would mediate autoimmune disease into T cells that suppress autoimmune disease. These T cells are called inducible Treg cells, and they protect against reactivation of EAU. Treatment of EAU with α-MSH accelerates recovery from EAU, induces the expansion of the inducible Treg cells, and protects retinal structure from inflammation. The melanocortin-based therapy may very well reestablish ocular immune privilege. Even if α-MSH is one of many molecules of immune privilege with the ability to induce tolerance, our findings demonstrate that using the melanocortin pathway is potentially an effective therapeutic approach to treat autoimmune uveitis, and preserve vision.

The molecular mechanisms of ocular immune privilege are a wealth of potential therapies to be exploited to suppress uveitis. Our findings that activation of the melanocortin pathway through the neuropeptide α-MSH is not only essential for ocular immune privilege but that it can be used to suppress autoimmune uveitis. This is a new therapeutic approach using our body's natural molecules of ocular immune privilege, in our studies the neuropeptide α-MSH, to change the behaviour of immune cells to suppress inflammation, and autoimmune uveitis. In addition, there is a strong possibility that melanocortin-based therapy moves us closer to the ultimate goal of resetting immunity to prevent and stop chronic autoimmune uveitis.

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An introduction to earthquakes in the U.S.

The U.S. Geological Survey (USGS) introduces what an earthquake is and what causes them to happen, plus the depth at which they occur

An earthquake is caused by a sudden slip on a fault. The tectonic plates are always slowly moving, but they get stuck at their edges due to friction. When the stress on the edge overcomes the friction, there is an earthquake that releases energy in waves that travel through the earth's crust and cause the shaking that we feel.

In California, there are two plates – the Pacific Plate and the North American Plate. The Pacific Plate consists of most of the Pacific Ocean floor and the California Coastline. The North American Plate comprises most the North American Continent and parts of the Atlantic Ocean floor. The primary boundary between these two plates is the San Andreas Fault. The San Andreas Fault is more than 650 miles long and extends to depths of at least 10 miles. Many other smaller faults like the Hayward (Northern California) and the San Jacinto (Southern California) branch from and join the San Andreas Fault Zone.

The Pacific Plate grinds northwestward past the North American Plate at a rate of about two inches per year. Parts of the San Andreas Fault system adapt to this movement by constant "creep" resulting in many tiny shocks and a few moderate earth tremors. In other areas where creep is not constant, strain can build up for hundreds of years, producing great earthquakes when it finally releases.

At what depth do earthquakes occur? What is the significance of the depth?

Earthquakes occur in the crust or upper mantle, which ranges from the earth's surface to about 800 kilometres deep (about 500 miles).

The strength of shaking from an earthquake diminishes with increasing distance from the earthquake's source, so the strength of shaking at the surface from an earthquake that occurs at 500 km deep is considerably less than if the same earthquake had occurred at 20 km depth.

Also, the depths of earthquakes give us important information about the Earth's structure and the tectonic setting where the earthquakes are occurring. The most prominent example of this is in subduction zones, where plates are colliding and one plate is being subducted beneath another. By carefully plotting the location and depth of earthquakes associated with a subduction zone, we can see details of the zone's structure, such as how steeply it is dipping and if the down-going plate is planar or is bending. These details are important because they give us insight into the mechanics and characteristics of the deformation in the subduction zone.

The deepest earthquakes occur within the core of subducting slabs – oceanic plates that descend into the Earth's mantle from convergent plate boundaries, where a dense oceanic plate collides with a less dense continental plate and the former sinks beneath the latter. The plate boundary contact between two such plates generates very large, shallow subduction zone earthquakes such as the Sumatra 2004 M9.1 event and the 2011 M9.0 Japan earthquake and is only active to relatively shallow depths – approximately 60 km. However, because oceanic slabs are relatively cold with respect to the surrounding mantle in deeper subduction zone environments, faults within the core of these slabs remain brittle and can generate earthquakes to depths of as much as 700 km (e.g., Pacific Plate beneath Japan and Kamchatka and beneath Tonga).

As the slab descends into the mantle, rheology changes (viscosity characteristics) cause the plate to bend and

deform and generates these earthquakes. The trend of such events can be seen in cross-sections of subduction zones and are known as "Wadati-Benioff Zones".

Within continents and along continental plate boundary transform faults such as the San Andreas, faults are only active in the shallow crust – perhaps to depths of approximately 20 km.

Accurately determining the depth of an earthquake is typically more challenging than determining its location, unless there happens to be a seismic station close and above the epicentre. So generally, errors on depth determinations are somewhat greater than on location determinations.

Are earthquakes associated with variations in the geomagnetic field?

Electromagnetic variations have been observed after earthquakes, but despite decades of work, there is no convincing evidence of electromagnetic precursors to earthquakes. It is worth acknowledging that geophysicists would actually love to demonstrate the reality of such precursors, especially if they could be used for reliably predicting earthquakes!

Learn more: USGS Geomagnetism Program

How is hydraulic fracturing related to earthquakes and tremors?

Reports of hydraulic fracturing causing felt earthquakes are extremely rare. However, wastewater produced by wells that were hydraulically fractured can cause "induced" earthquakes when it is injected into deep wastewater wells.

Wastewater disposal wells operate for longer durations and inject much more fluid than the hydraulic fracturing operations. Wastewater injection can raise pressure levels in the rock formation over much longer periods of time and over larger areas than hydraulic fracturing does. Hence, wastewater injection is much more likely to induce earthquakes than hydraulic fracturing.

Most wastewater injection wells are not associated with felt earthquakes. A combination of many factors is necessary for injection to induce felt earthquakes.

Learn more at the USGS Induced Earthquakes website

Do earthquakes large enough to collapse buildings and roads accompany volcanic eruptions?

Not usually. Earthquakes associated with eruptions rarely exceed magnitude 5 and these moderate earthquakes are not big enough to destroy buildings and roads.

The largest earthquakes at Mount St. Helens in 1980 were magnitude 5, large enough to sway trees and damage buildings, but not destroy them. During the huge eruption of Mount Pinatubo in the Philippines in 1991, dozens of light to moderate earthquakes (magnitude 3 to 5) were felt by several hundred thousand people. Many houses collapsed, but not primarily because of the shaking. Heavy ash from the eruption (made heavier by rain from a hurricane) accumulated on roofs and crushed them.

Stronger earthquakes sometimes DO occur near volcanoes as a result of tectonic faulting. For example, four magnitude 6 earthquakes struck Long Valley caldera, California, in 1980 and a magnitude 7.2 earthquake struck Kilauea Volcano, Hawaii, in 1975. Both volcanoes were quiet at the time. The Hawaii earthquake triggered a small eruption at the summit of Kilauea. No eruption occurred at Long Valley. ■

Learn more about how the USGS monitors volcano seismicity

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A new turn in the search for the origin of life

Professor Friedemann Freund, SETI Institute, explores a fascinating new discovery in the search for the origin of life, here

Sometime in the distant past, life appeared on planet Earth. Nobody knows when, but it must have been at least 3.5 billion years ago, maybe 3.8 billion or even 4.3 billion years ago, relatively soon after Earth accreted in the disk of gas, dust and planetesimals that circled the early sun.

If there is much uncertainty about the timing of the origin of life, how life actually started is even more uncertain. A sine qua non condition for life as we know it is that, somewhere on the early Earth, blobs of organic molecules must have come together to form a "system" that could copy itself and multiply. No easy task, requiring large, complex molecules made of carbon, hydrogen and oxygen with some nitrogen and sulphur thrown into the mix. Using the chemical symbols of these elements we may call them CHONS.

The challenge is to understand how Nature could have produced the large, complex CHONS, without which the first self-replicating systems could never have formed out of the chaos of the pre-biotic Earth. Those CHONS must have contained hydroxy, carboxy, amino and sulphur functional groups. They must have been able to build vesicles with cell membranes. The vesicles must have had cell membranes pitted with cross-membrane functional groups that allowed protons and ions to flow in and out in such a way as to generate concentration gradients and transmembrane potentials – a form of energy.

Unfortunately, the science community has not yet figured out how Nature might have produced the large CHONS that were surely necessary to form such protocells and to give life a shot at getting started. Smaller organic molecules? No problem. Amino acids are easy to make, for instance by electric discharges simulating lightning strikes on the early Earth. The real challenge is how Nature was able to build much larger multifunctional CHONS.

For decades, the search was on to demonstrate how such CHONS could be assembled under plausible early-Earth conditions, in the atmosphere, in freshwater or the oceans, with help from ultraviolet light or high energy x-rays and gamma rays, at high and low temperatures, at high and low pressures. Despite all efforts the goal remained elusive. The science community started to look elsewhere.

One idea that became widely accepted is that the young Earth had been intensely bombarded by the most primitive meteorites, carbonaceous chondrites, which may have accreted in the interstellar dust clouds, from which the entire solar system formed. We can see these dust clouds in the night sky forming dark bands in the luminous plane of our Milky Way galaxy.

The nano-sized mineral grains in the dust clouds bear the spectroscopic signature of delicate hydrocarbons and, indeed, carbonaceous chondrites that have fallen to Earth in recent decades were found to be amazingly rich in CHONS, including some that form vesicles when extracted with water and others that

contain carboxy, amino, and sulphur functional groups. Such CHONS would have come handy on the early Earth and they could have provided a path towards life. So, there it is – the idea that life on Earth owes its existence to organics delivered from space more than 4 billion years ago. A grand idea, quoted in the scientific literature and widely popularised.

However, when we drill down to its roots, we see that this idea came out the disappointment in the science community that, using the most advanced methods of investigation, some of the best minds in chemistry, physics, geoscience and astrobiology have not been able – despite decades of intense work – to figure out how Nature could have produced these large, complex and multifunctional CHONS, without which life as we know it could not have started.

As so often in the history of the human mind, in times of uncertainty, the imagination may turn to the even greater unknowns. This seems to have happened in the face of widespread frustration over the inability to make real progress in the area of origin of life. In this case, the imagination turned to space.

Maybe out there, in the vast expanse of space, chemical reactions are possible that have no equivalent on Earth. Maybe, when stars reach the end of their life cycle and die in cataclysmic explosions, the mineral grains condensing in the hot stellar outflows are uniquely able to produce those complex CHONS.

Maybe the organics associated with the dust clouds in the interstellar medium are such CHONS. Maybe they became incorporated into the carbonaceous chondrites, those pitch-black, organics-rich clumps of very fine-grained matrix, probably formed in these humongous dust clouds in the galactic plane. Maybe the early Earth did indeed capture many of these carbonaceous chondrites and was seeded with the CHONS, from which life would eventually arise.

Posing the question in this way exposes a flaw in the basic approach taken by so many bright chemists, physicists, geoscientists and astrobiologists, whose goal is to unravel the mystery of the origin of life. For decades their focus has been on chemical reactions that take place in the gas, liquid and fluid phases, including supercritical conditions, at gas-fluid, gas-solid and fluid-solid interfaces, even inside clay minerals.

The condensation of mineral grains in the near-vacuum of space, in the outflow of dying stars, is a distinctly different process. It is the transition from the vapour phase directly to the solid state in the presence of hydrogen, carbon monoxide, water, nitrogen and sulphur. During the process, the gaseous components become incorporated into the solid matrix. The smaller the grains, the more of the gaseous components go in. Once inside, the C, H, O, N and S interact with each other, forming chemical bonds – a step towards CHONS.

Here is where past research to unravel the mystery of the origin of life went astray. Brilliant and dedicated as they were, the scientists involved in this field never considered the possibility that the reactive gases dissolved in the magmas in the depth of Earth – water, carbon monoxide and dioxide, even nitrogen and sulphur – would become incorporated into every mineral grain that crystallizes out of terrestrial magmas. Not in high concentrations but at non-zero levels, nonetheless. During cooling, the C, H, O, N and S inside the solid matrix interact with each other and form chemical bonds – a step towards CHONS.

Therefore, there is no need to look to space and to carbonaceous chondrites to deliver CHONS to the Earth, precious organics from which life might have arisen. There is no need to worry that any such delivery could have happened only during the period of heavy bombardment of the young Earth more than 4 billion years ago. Quite to the contrary, there is the distinct alternative that rocks in the Earth's crust were producing CHONS inside the matrix of their minerals, releasing them as they weathered at the Earth's surface.

Even if the amounts of CHONS per unit volume of rock were very small, billions of cubic kilometres of rocks have weathered over the eons. In the accumulative, they must have injected huge quantities of CHONS into the Earth's surface environment. There was no shortage of potentially life-giving and life-sustaining organics.

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The priorities for domestic and international Arctic research in the United States

The priorities for domestic and international Arctic research in the U.S., including the work of the United States Arctic Research Commission (USARC), are detailed here

The United States Arctic Research Commission (USARC) is an independent agency that provides advice to the President and Congress on both domestic and international Arctic research by reports and recommendations.[1]

Congress created USARC through the Arctic Research and Policy Act of 1984. In January 1985, President Reagan established the agency through Executive Order 12501. The remit of the USARC can be summarised as follows:

- To establish the national policy, priorities and goals needed to put together a federal program plan for basic and applied scientific research in the Arctic, including physical, biological and health sciences natural resources and materials, as well as social and behavioural sciences.
- To promote Arctic research, recommend research policy and to communicate policy recommendations to the President and Congress.
- To work with the National Science and Technology Council and the National Science Foundation as the lead agency tasked with implementing the Arctic research policy and to support collaboration throughout the Federal Government.
- To provide guidance to the Interagency Arctic Research Policy Committee (IARPC) to develop and implement national Arctic research projects and a five-year plan;
- To interact with Arctic residents, international Arctic research programmes and organisations and local institutions, including regional governments to obtain the broadest possible view of research needs.

USARC's has seven Commissioners, appointed by the President and include four members from academic or research institutions; two from private industry and also the indigenous Arctic residents. Serving as an ex-officio eighth member is the Director of the National Science Foundation (NSF). In addition, advisors are appointed when required to give advice and information on specific research needs and issues of concern to the USARC plus they review draft documents and convey important information on a number of scientific and engineering disciplines.

In terms of USARC's activities, we know that they hold business meetings and conduct public hearings in Alaska and elsewhere to gain input, plus they undertake site visits and field trips to research facilities and projects throughout the Arctic region. Added to this, recommendations of USARC on Arctic research policy, for example, are published in their biennial Report on Goals and Objectives for Arctic Research, plus the Commission's Special Report series.[2]

Arctic Scientific Cooperation Agreement

It's also worth noting here that U.S. Secretary of State and foreign ministers of the seven other Arctic governments signed the Agreement on Enhancing International Arctic Scientific Cooperation during May 2017 in Fairbanks, Alaska. This paves the way for access by scientists of the eight Arctic governments in Arctic areas that have been identified by the governments, including access to research infrastructure, facilities and data plus the entry and exit of people, equipment and materials. The agreement entered into force during May 2018 and, "calls for the parties to promote education, career development and training opportunities and encourages activities associated with traditional and local knowledge."[3]

Report recommends Arctic research priorities

In recent noteworthy news, we discover that Fran Ulmer, Chair of the USARC, issued the "Report on the Goals and Objectives for Arctic Research 2019-2020 for the U.S. Arctic Research Program Plan". The report affirms the need for continued scientific research and it gives, for each of the five goals, specific recommendations concerning the motivation for research and examples of current research occurring.

The Report's goals underline these priority areas of research:

- Advance Arctic infrastructure;
- Assess arctic natural resources;
- Observe, understand and forecast Arctic environmental change;
- Improve community health and well-being;
- Enhance international scientific cooperation in the Arctic.

"The rapid rate of change in this region has galvanised attention and support for increased investment in understanding and preparing for the New Arctic," says Ulmer. "Research and innovative technology development can help people adapt to new conditions and challenges. This report illustrates some of the opportunities to engage communities, businesses, researchers and governments in this effort," she adds.

This report guides the development of the comprehensive 5-year programme plan for the overall Federal endeavour in Arctic research. Indeed, this plan is submitted to the President for transmittal to the Congress and is revised biennially and has been prepared by the Interagency Arctic Research Policy Committee (IARPC). The most recent version of the White House IARPC plan is "Arctic Research Plan FY17- FY21.

In closing, we can see that this report is an excellent example of the USARC's unchanging mission "to develop and recommend U.S. Arctic research policy and to build cooperative links in Arctic research within the federal government, with Arctic residents, the State of Alaska, researchers and international partners."[4] ■

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Conserving coastal and marine ecosystems and resources

The National Oceanic and Atmospheric Administration (NOAA) have a mission to understand and predict changes in weather, climate, oceans and coasts, as this article reveals, with a special focus on their work to conserve and manage coastal and marine ecosystems and resources

The National Oceanic and Atmospheric Administration (NOAA) are a U.S. agency that aims to enrich life through science. Their scope of work goes from the surface of the sun to the depths of the ocean floor, as they do what they do to ensure that the public is kept up to speed with the changing environment that surrounds them.

By way of background information, we know that President Thomas Jefferson founded the U.S. Coast and Geodetic Survey (as the Survey of the Coast) to provide nautical charts for the maritime community to ensure safe passage into American ports and along their extensive coastline, way back in 1807. (1)

Today, NOAA's vital work includes severe storm warnings, daily weather forecasts and climate monitoring, as well as coastal restoration, fisheries management support for marine commerce.

Dedicated scientists at NOAA use high-tech instrumentation and cutting-edge research to give citizens, emergency managers, planners and other decision makers with reliable information they need when it is required. (2) Certainly, science underpins all NOAA does, for example, when it comes to weather forecasts and warnings, climate information, coastal management recommendations, fishing regulations and satellites in space. Many of NOAA's scientists are respected as national and international experts in their fields and the quality of their work is considered to be exemplary. (3)

The mission of NOAA can be summed up as follows:

1. To predict and understand changes in weather, climate, oceans and coasts;
2. To share such knowledge and information with other people;
3. To manage and conserve coastal and marine ecosystems and resources. (4)

Coastal and marine ecosystems and resources

This article will focus on the third aspect of NOAA's work mentioned above that concerns managing and conserving coastal and marine ecosystems and resources. We know that NOAA has direct authority to sustain and to regulate marine fisheries and their ecosystems, protect and restore habitats and ecosystems, protect endangered marine and anadromous species, conserve marine sanctuaries and other protected places, respond to environmental emergencies and aid in disaster recovery.

In April this year, a new web-based interactive tool for ocean mapping and planning was created to give everyone from ocean industries to coastal managers, students, plus the public the chance to be an ocean explorer from their own computer. The tool was made by the NOAA and the Department of the Interior's Bureau of Ocean Energy Management.

The new OceanReports web tool, gives users specialised 'ocean neighbourhood analyses' including graphics and maps by analysing no less than 100 ocean datasets at the same time.

Did you know that U.S. ocean waters make up a total of almost four million square miles and is one of the largest Exclusive Economic Zones (EEZ) globally? Did you know that detailed information about habitats and

The Sargasso Sea

Did you know that the Sargasso Sea can be found entirely within the Atlantic Ocean and it is the only sea that does not have a land boundary? The Sargasso Sea is well-known for a genus of free-floating seaweed called *Sargassum*? It's true to say that there are a number of different types of algae located in the world's oceans but the Sea is unique because it harbours *holopelagi*, a species of *Sargassum*. By way of further explanation, *holopelagi* means that the algae reproduces vegetatively on the high seas, as well as freely floating around the ocean. Added to his, we know that other seaweeds reproduce and begin life on the floor of the ocean.

Sargassum hosts an amazing variety of marine species, for example, it is an essential habitat for crab, fish, shrimp and other marine species that have adapted to this environment. In addition, did you know that turtles use *Sargassum* mats as nurseries where hatchlings have food and shelter?

Threatened and endangered eels, as well as porbeagle shark and dolphinfish, as well as white marlin, have made the Sargasso Sea their place of habitation. Humpback and commercial fish, such as tuna and birds migrate through the Sargasso Sea and depend on it for their sustenance.

The Sargasso Sea is defined only by ocean currents which contrasts sharply with the other seas in the world which are to some extent, of course, characterised by land boundaries. The Gulf Stream establishes the Sargasso Sea's western boundary, while the Sea is further defined to the north by the North Atlantic Current, to the south by the North Atlantic Equatorial Current and to the east, by the Canary Current. [5]

species, industries in the area, potential hazards such as undersea cables or shipwrecks, the economic value of ocean commerce and other detailed oceanographic information can be at your fingertips using the Ocean-Reports tool?

"The world's largest collection of 'ocean intelligence' can now be accessed to help sustain and grow one of the world's largest blue economies," says Neil Jacobs, Ph.D., Acting NOAA Administrator. "Whether it's aquaculture siting, marine transportation, or offshore energy, OceanReports puts this data at our fingertips and gives us an edge as we continue to grow our national economy."

In addition, while OceanReports offer an abundance of data for use by science and industry, it's easy to use in the classroom to help students studying biology, chemistry, geography and even other disciplines like economics, according to the NOAA. This excellent work is certainly a fitting example of how the NOAA as a U.S. agency aims to enrich life through science, as this article draws to a close.

"With such a diverse range of ocean uses and stake-holders, the OceanReports tool greatly increases one's ability to understand and manage the resources in the complex ocean environment," comments BOEM Acting Director, Walter Cruickshank. "Our team worked diligently with NOAA to create this tool, which benefits the ocean community in addition to helping BOEM carry out its mission—the responsible development of ocean energy and marine mineral resources for the nation." [6] ■

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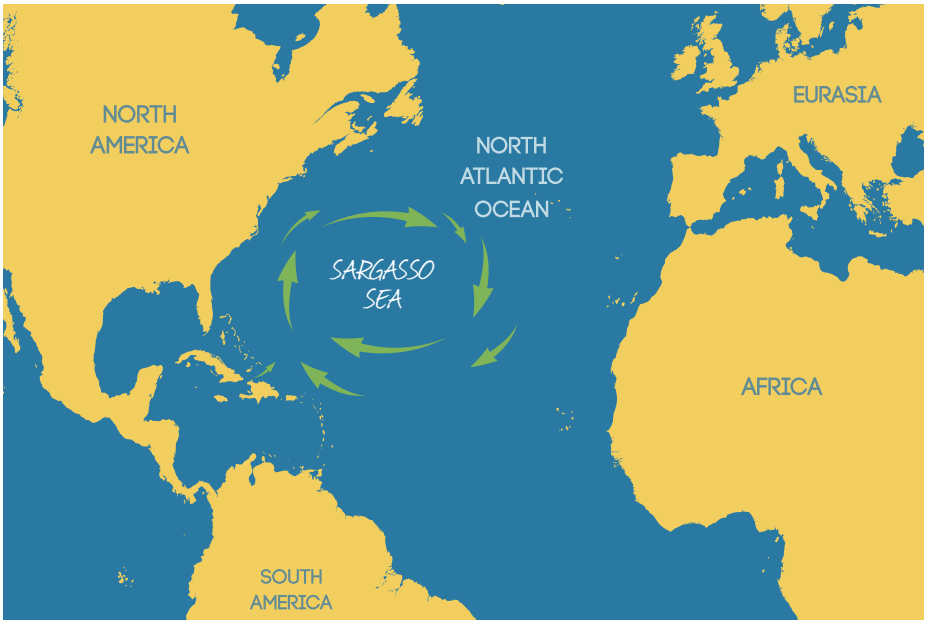
The Sargasso Sea Commission: High seas conservation

Dr David Freestone and Professor Howard Roe explore how the Sargasso Sea Commission could be a new paradigm for high seas conservation

A place of legend, but also a fundamental part of the ocean, the Sargasso Sea encompasses two million square miles in the sub-tropical North Atlantic Ocean, enclosed by rotating currents. The only sea without land boundaries, its importance derives from its interdependent mix of its role in global scale ocean and earth system processes, its socioeconomic values and its role in scientific research.



Two species of Sargassum give the Sea its name. Trapped within the rotating current system and dubbed the golden floating rain forest of the Atlantic Ocean, Sargassum rafts host specialised communities of animals and provide nursery and feeding areas for many endangered and endemic species. Sargassum provides rare open ocean shelter for spawning fish including billfish, tuna, and marlin and young turtles spend their "lost years" sheltered in the mats.

The Sargasso Sea also acts as a crossroads in the North Atlantic for a number of iconic migratory species. Humpback whales migrate annually between the Caribbean and sub-Arctic, and Porbeagle sharks use the area to give birth, but the most mysterious ocean migrants are the endangered European and American eels. Both species live for many years in freshwater before migrating thousands of kilometres to the Sargasso Sea to spawn and die. Their larvae return to the rivers, develop into adults, and migrate back across the Atlantic.

Many aspects of this extraordinary life cycle remain unknown, but recent research identifies their spawning areas within the southern Sargasso Sea. Declining populations of both species in recent years with resulting losses to multi-million-pound coastal fisheries -the Sargasso Sea is vital for the survival of both the eels and the commercial fisheries outside the area.

It is not only eels that are commercially valuable. The Sargasso Sea contributes significantly to global and local economies. The economic value of the Sargasso Sea, which some estimate as millions of pounds, contributes to global and local economies by connections to various fisheries, whale watching, turtle tourism, and the benefits of coral reefs surrounding Bermuda, as well as indirect benefits such as climate regulation, nutrient cycling and habitat services.

The Sargasso Sea is hugely important for our understanding of the role of the oceans in climate change. The Bermuda Institute of Ocean Sciences hosts the longest running time series of open ocean measurements which show rising temperatures and increasing acidification of the ocean since 1954. These data provide indisputable evidence of global warming and ocean acidification, and continue to deepen our understanding of the ways the global ocean works and responds to change.

Climate change alters ocean structure and ecology, which threatens the

Image: © JP Rouja

Sargasso Sea. Plastic waste may end up in ocean gyres, the rotating current systems which include the Sargasso Sea. There is evidence of increased fishing and shipping activity. Sargassum itself may also pose a threat! Since 2011, beaches in the Caribbean, West Africa and South America have been inundated with thousands of tons of Sargassum originating south of the Sargasso Sea.

The culprit is a previously rare form of Sargassum which has suddenly become abundant and may have ecological impacts as it is less attractive to commensal communities and feeding fish. The cause of its increased prevalence is unclear but likely involves nutrient run-off from rivers, dust from the Sahara, increased ocean warming and possible current changes. Currents carry the weed onto beaches, causing huge social and economic problems to local communities and to local ecology.

But the biggest challenge facing the Sargasso Sea is a legal one. The Sargasso Sea falls within the high seas-the 50% of the planet outside national jurisdiction. To address this challenge, five governments convened in 2014 to sign the Hamilton Declaration on Collaboration for the Conservation of the Sargasso Sea and to establish the Sargasso Sea Commission to act as a steward for this extraordinary area. Five more governments have since joined and others may follow.

The Sargasso Sea Commission is a new paradigm for the conservation of areas beyond national jurisdiction, convening stakeholders from multiple countries and organisations to address issues that fall outside national agendas. Parties to the Convention on Biological Diversity have agreed that the Sargasso Sea be included on a list of Ecologically or Biologically Significant Areas. Using this as a basis, in 2015 the Northwest Atlantic Fisheries Organisation declared a moratorium on bottom trawling on Sargasso Sea seamounts in its Area and gear restrictions on midwater trawling.

The Commission is working to protect the Sargasso Sea alongside a number of governments and partners, to protect the migratory range of the European Eel, to regulate vessel activities and to conserve threatened fishery resources. It is also working with NASA which is developing comprehensive satellite imagery of the area. Currently funded largely through support from government supporters and private donors, the Commission seeks additional funding to continue its important work.

SARGASSO SEA
COMMISSION

Dr David Freestone
Professor Howard Roe
The Sargasso Sea Commission

As deep-sea science is out-paced by exploitation, can catastrophe be averted?

Dr Sandra Brooke, Florida State University Coastal and Marine Lab, explores whether the over-exploitation of deep oceans can be averted as deep-sea science continues to be outpaced

Humans have been exploiting the oceans for thousands of years, but focused scientific enquiry into the deep sea did not begin until the early 19th century. In 1843, Edward Forbes proposed his Azoic Hypothesis, which posited that life could not exist below 300 fathoms (550 m).

The Challenger expedition (1872-1876) was the first global survey of the deep-sea, and their dredging operations revealed great abundance and diversity of life far below 300 fathoms. The Azoic Hypothesis became obsolete and dredges were the tool of choice for deep-sea naturalists.

The middle 20th century heralded a leap forward in deep-sea research. The advent of acoustic systems to generate seafloor maps allowed scientists to locate topographic features and plumes from chemosynthetic ecosystems. Rugged ecosystems such as submarine canyons became accessible to science through the use of underwater vehicles.

Over the past few decades, technological advances have created sophisticated mapping, navigation, and imaging systems that have greatly increased our ability to study the deep. New technologies such as autonomous data collectors, new sensors, artificial intelligence (AI) and automated sample processing will continue to advance the pace of marine research.

Large research vessels and sophisticated technologies are extremely expensive, and their use is generally limited to wealthy nations. The deep North Atlantic Ocean is fairly well characterised due to significant investments in deep-sea research by Europe and North America.

Over the past decade, over 500 putative cold seeps were discovered off the western Atlantic margin, miles of deep coral reefs were mapped and explored, dense faunal assemblages were documented within submarine canyons, and many new species were described. By contrast, regions such as the Indian Ocean remain virtually unknown. Vast areas of the deep seafloor have yet to be mapped or explored and we can only guess at the kinds of secrets they hold.

With increasing pressure on financial resources, one could question the wisdom of massive expenditures in deep-sea research. Do we really need to understand a system that most people will never even see? One that is so vast and inaccessible that we couldn't possibly impact it? Why not use our precious funding to study our coastal areas, which are being overexploited, eroded and polluted within sight of human population centres?

The deep sea is not as safe from human activities as one would think. As coastal resources become depleted, nations are moving further offshore in search of unexploited fish stocks, oil reserves, and materials needed to supply the global insatiable demand for technology.

Industrial bottom trawling is the most destructive deep-sea fishing practice, indiscriminately harvesting large quantities of target and non-target species, most of which are discarded. Deep-sea species are slow-growing and long-lived, which makes them highly vulnerable to overfishing.

In addition, large swaths of ancient deep coral habitats have been destroyed by bottom trawling, and recovery has been slow or non-existent. In return for this ecological damage, deep-sea fisheries contribute less than 0.5% of global fisheries landings, and most are heavily subsidised, suggesting they are also economically unsustainable.

Seabed mining for valuable metals is an emerging threat to deep-sea ecosystems such as manganese nodule fields, seamounts and hydrothermal vents. Many mining activities will occur on the high seas and are controlled by the International Seabed Authority (ISA). The ISA is responsible for 'protecting the marine environment from harmful effects', and is working with interested parties to develop mining regulations.

It remains to be seen however, how seamount crusts and active vents can be removed without causing harm.

Image: © Deepwater Canyons 2013 – Pathways to the Abyss. NOAA OER/BOEM/USGS.

The face of a steep wall at the base of Norfolk Canyon (1400 m) with dense clusters of the cup coral Desmophyllum dianthus, a Brissingid seastar, a group of Acesta sp. fileshells and the octopus Graneldone sp

Superimposed on these physical impacts is the looming spectre of climate change, the effects of which we are just beginning to understand.

It is easy to place a value on the exploitation of an ecosystem, but much more challenging to calculate the value of preserving it. For example, some deep-sea ecosystems, particularly isolated hydrothermal vent systems or seamounts have high levels of endemism. Many benthic species use 'chemical weapons' for feeding or defence, and human medicines are often derived from these bio-active compounds. Microbes and metazoans that live in extreme environments can provide the key to evolution of life on earth or create new technologies. What then, is the ultimate cost of not knowing what we destroy?

Research has accomplished much over the past few decades, but cannot keep up with resource exploitation. Virgin fish stocks can be depleted faster than scientific support for protection can be generated. Exploration contracts for mineral extraction have been granted in areas where no research exists. Terrestrial and coastal ecosystems have been mined, overharvested and contaminated for short-term economic gain. Unless something changes, the deep oceans will suffer the same fate. As human populations increase and food security becomes a global issue, sustainable resource management will be critical.

The Magnuson-Stevens Act (MSA) is the primary law governing marine fisheries management in U.S. federal waters. One of the tenets of MSA is the 'precautionary principle', which stipulates that if an activity threatens marine resources, protective measures should be taken, even in the absence of scientific cause-and-effect evidence. This approach removes the burden on science to prove harm from industry activities and recognises the value of caution in an uncertain world.

Unless 'precautionary principles' are applied to ecosystem management globally, we risk squandering priceless and irreplaceable resources. Whether humans can radically change their behaviour on a sufficient scale to prevent an environmental crisis remains to be seen.

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Systems approaches: Making pests run a gauntlet to safeguard crops and forests

Greg Rosenthal of the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service details the importance of the multiple safeguards in systems approaches – when it comes to making pests run a gauntlet to safeguard crops and forests

The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) views global agricultural trade through a plant health lens. The challenge, from this perspective, is how to move billions of dollars' worth of agricultural products across the world's oceans and continents without spreading invasive plant pests. APHIS recognises systems approaches as powerful tools to meet this challenge. A systems approach is a series of measures taken by growers, packers and shippers that, in combination, minimise pest risks prior to importation into the United States.

Systems approaches

Under a systems approach, different steps of the production chain provide opportunities to reduce risks from pests—from pre-planting, pre-harvest, during the growing season, through harvest, to the packing house, to the exporting country's port, to the importing country's port of entry, and into domestic commerce. The idea is to apply enough measures that together ensure an appropriate level of protection.

Examples of these measures include, among many others: sterilising soil for pests; using only certified seeds for planting; surveying for insects; inspecting and treating crops; sanitising equipment moving between fields; harvesting before pest risks emerge; employing pest-proof structures; inspecting, cleaning, and disinfecting commodities at packing houses; placing commodities in pest-proof packaging; conducting cold treatments in transit; inspecting commodities at the port of entry; and establishing end-use restrictions, such as human consumption versus animal consumption versus planting, flour milling only for certain grains, or juicing only for certain fruits.

Countries around the world are using and mutually recognising systems approaches as a way to facilitate safe trade. The International Plant Protection Convention (IPPC) formally adopted the concept in 2002. The IPPC is an international agreement among 183 countries, including the United States. It provides the world with plant health standards and critical tools, such as systems approaches, for negotiating technically sound international trade requirements. The U.S. Plant Protection Act of 2000 defines systems approaches for APHIS.

> "Systems approaches like this one help make global trade safe, fair, and predictable. For imports and exports, they are here to stay."

Benefits of systems approaches

Systems approaches have many advantages. They can work when a single pest mitigation measure will not be effective or feasible. This is particularly important now that, because of human health and environmental concerns, many countries discourage the use of methyl bromide—traditionally a single and extremely effective measure. In addition, if one measure fails in a systems approach, the remaining measures provide redundancy to ensure an appropriate level of protection.

For example, U.S. imports of bell pepper from Spain are allowed under a systems approach that includes production in pest-proof greenhouses, registration and oversight by Spanish agricultural department authorities, regular greenhouse inspections and pest

monitoring, pepper packing requirements, and use of insect-proof covering for transit to the United States.

In addition, two APHIS programs certify exports to and allow imported nursery stock from Canada under systems approaches. These programs promote trade consistency between our two countries. APHIS also accepts imported plant cuttings grown under systems approaches from APHIS-certified foreign facilities producing these commodities.

Systems approaches can leverage the industry's current best practices. That means growers can address pest concerns in a way that doesn't add burdensome requirements. Because participants across a supply chain take steps to address pest concerns before a commodity ships to the importing country, systems approaches can also facilitate the smooth entry of commodities into the importing country.

Taking systems approaches a step further

Over time, APHIS' experts observed that many import requests for plants in growing media (PIGM) were very similar to each other. They realised this similarity offered an opportunity to streamline how they evaluate and process many of these import requests. Normally, APHIS prepares an environmental assessment (EA) unique to each country's request for a specific plant genus in growing media, such as peat or coal cinder. The EA assesses the potential environmental consequences of the proposed importation. We also prepare a pest risk assessment (PRA) to identify the risks, and a risk mitigation document (RMD) to identify measures to help prevent the entry of pests on the plants.

For most requests, those measures – a systems approach – are identical, although we add specific measures as needed. As a result, we determined that a single programmatic EA could apply to most PIGM import requests. That would reduce the need for repetitive documentation of comparable risks. However, if the PRA and the RMD for a routine request identifies new risks for consideration, APHIS would prepare an environmental document. And if we detect a quarantine pest in imported PIGM, we would stop importing that plant from that country until current or revised pest mitigation measures are shown to be effective.

Using a single programmatic EA would ensure continued levels of safeguarding while facilitating international trade, allowing healthier plant imports, reducing the growing time for plants to reach markets, reducing unnecessary or repetitive environmental and other documentation, and speeding port-of-entry inspections.

On 10th April, we published a draft programmatic EA in the U.S. government's newspaper of record, the Federal Register, and are accepting public comments until June 24, 2019. Once a final decision is made regarding the issues within the EA, that EA will cover all future PIGM import requests that use only the default systems approach measures. If a particular import request requires additional measures, we will prepare another environmental document that evaluates those measures. The required documentation will depend on the type and magnitude of risk from the additional measures.

The two sides of systems approaches

APHIS regularly authorises imports of fruits, vegetables, nursery stock, and other agricultural commodities under a systems approach. We also negotiate the use of systems approaches with our trading partners when they consider U.S. requests to export commodities to their markets. For example, our cherry exports to Japan must comply with a systems approach that includes, among other measures, orchard registration with APHIS, pest trap use, specific inspection and processing procedures at the packing house, carton labelling, and inspection upon arrival in Japan.

Systems approaches like this one help make global trade safe, fair, and predictable. For imports and exports, they are here to stay. ■

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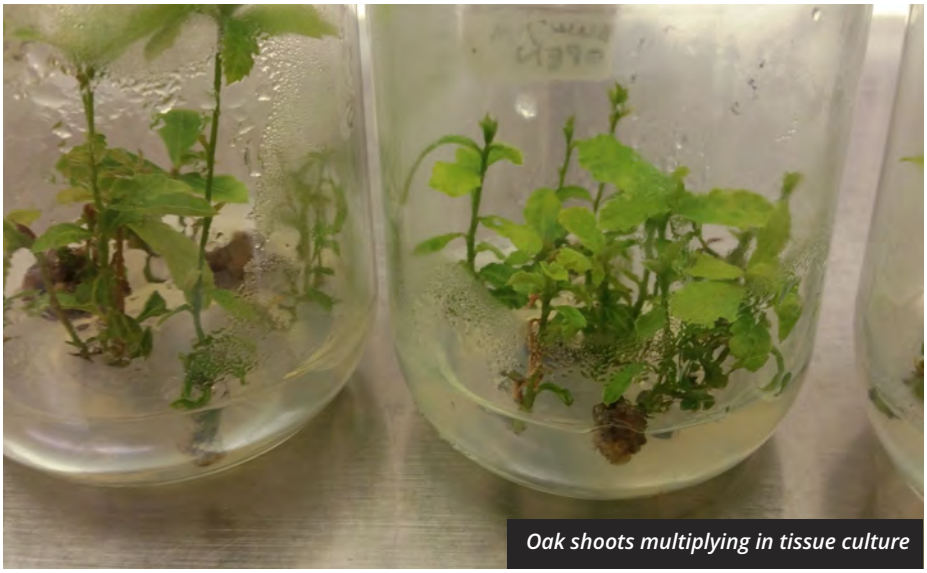
Building better oaks for the urban environment

Dr Nina Bassuk, Urban Horticulture Institute, School of Integrative Plant Science explores how building better oaks will help improve the future of urban environments

The oak genus (Quercus) has over 500 species of trees and shrubs native to regions across the northern hemisphere. It is difficult to overstate their ecological, economic and cultural value. Oaks provide an essential source of timber for furniture, flooring, interior finishing and veneer. Cork is sourced from oak and the impervious heartwood of oak is used for shipbuilding and wine and whiskey casks. Oaks are prominent in many forest ecosystems and their acorns are a vital food source for wildlife, high in fat and nutrients.



Oak shoots multiplying in tissue culture

In addition, oaks have an important role to play in urban and suburban landscapes as they are durable, long-lived and majestic trees. They can be an outstanding feature in any park with a large and spreading growth habit. The grand size, longevity and sturdiness of oaks have made them a familiar symbol in many cultures around the world.

Genetic diversity of oaks

Even within a species, oaks exhibit wide variability in phenotypic traits, e.g. leaf size, shape and colour. Furthermore, oaks are found in many different climates throughout the northern hemisphere. They range from the humid, sub-tropical regions of Central America or Asia to the semi-arid terrain of California or the Mediterranean and to the furthest reaches of deciduous forest in the north.

The genus Quercus is divided into two subgenera: Cyclobalanopsis and Quercus. The latter is then subdivided further into four sections: Protobalanus, Cerris, Quercus (white oaks) and Rubrae (red oaks). The section Rubrae includes many red oaks with which we are familiar e.g. Q. rubrum (red oak), Q. velutina (black oak) and Q. palustris (pin oak). The section Quercus includes species of white oak familiar in northern climates such as Q. robur (English oak) Q. alba (white oak), Q. bicolor (swamp white oak) and Q. montana (chestnut oak). Oaks readily hybridise between species within their respective sections and intermediates are often found within overlapping geographic ranges.

The number of species counted within the genus Quercus contained around 300 in 1862 compared to over 500 species counted in 1998). Although interspecific hybrids are not immediately considered a new species, this shows the complexity of delineating species within the genus. Oaks are often discussed in many studies on plant evolution and speciation because of their ability to hybridise.

Within just the white oak section, species are found growing from Cuba to central Mexico to Northern Canada, making the genetic potential of this group appealing. For example, species within this group found in the northern latitudes have cold tolerance while those growing in southern regions like Q. virginiana (live oak) show incredible drought and wet soil tolerance. Q. bicolor is native to the northeast and tolerant of heavy, compacted soils, while Q. minima (dwarf live oak) grows along coasts and shows salt tolerance. Therefore, the wide variety of traits in white oaks, as

Rooted oak from tissues culture

well as their interspecific hybridisation, makes them a desirable group for selection for growth in urban environments.

Selecting oaks for the urban environment

Trees growing in an urban setting face distinct challenges from trees growing in the wild. These challenges include limited soil volume, soil compaction, road/sidewalk salt, soils with high pH and drought stress. Many native oaks are sensitive to alkaline soils because important nutrients (especially iron and manganese) become less soluble and available for absorption by plant roots at a pH higher than 7.0. This nutrient deficiency results in chlorosis (yellow leaves). Unfortunately, alkalinity is a frequent characteristic of many urban soils.

At Cornell University's Urban Horticulture Institute, (UHI) hybrids between many different species of white oak were created between 2004-2006. The maternal species were located on the Cornell campus in Ithaca, New York and include several native and purported hybrid white oaks:

- Quercus bicolor
- Quercus gambelii x macrocarpa
- Quercus macrocarpa
- Quercus macrocarpa 'Ashworth'
- Quercus montana
- Quercus muehlenbergii
- Quercus x warei 'Long' (Regal Prince®).

Pollen from approximately 40 different species from Europe, Asia and North America were used for hybridisation. Some of the paternal species include Q. virginiana (live oak), Q. lyrata (overcup oak), Q. robur (English oak), Q. fusiformis (Texas live oak), Q. polymorpha (Mexican White Oak). As a result of the breeding programme over 350 unique hybrid genotypes were developed. Over the years these hybrids have been evaluated for tolerance to cold temperatures, drought and high pH soils. We have also evaluated their overall growth habit and form and we noted any issues with pests or diseases. Many hybrid trees showed good form and vigor.

Oak selection and propagation research

Another aspect of this project involves propagation research. Oaks are notoriously difficult to propagate asexually. Once hybrids are created, they must be propagated asexually in order to maintain hybrid characteristics. Using acorns for propagation would negate the hybrid qualities due to pollination by nearby oaks. Difficulty in asexual propagation impedes the selection of hybrids, as it is difficult to propagate clones of each genotype for testing in the field.

Therefore, as we evaluate our hybrid genotypes for desirable growth characteristics, we also consider whether it is possible to propagate them asexually. To introduce a superior tree into the nursery trade, we need to be able to propagate it in large numbers.

So far, propagation approaches have included the use of modified stool beds and tissue culture. By using very small expanding buds, we are able to grow many hybrid oaks in tissue culture, which has the potential of rapidly increasing our numbers to that these trees can be introduced to the nursery trade. This work has taken over 25 years is the result of many researchers improving our understanding of these hybrids over the years. We are confident that we may have some superior urban tolerant oaks to introduce in the near future.

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The Urban Horticulture Institute
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Hydrogen helping the environment, reducing carbon emissions

Morry Markowitz, President of the Fuel Cell and Hydrogen Energy Association details how policies have been implemented that increase the role of hydrogen in various applications – including transportation as one method reducing carbon emissions

Over the past several years, countries, states and other jurisdictions around the world have implemented policies increasing the role of hydrogen in various applications – transportation, stationary power and energy storage – as one method reducing carbon emissions in these sectors.

However, with the number of hydrogen-powered fuel cell systems already in operation on the road in vehicles and deployed on the ground in stationary systems steadily climbing, with more to come on the horizon, many are asking, "is hydrogen really clean?" The plain and simple answer is yes!

In the transportation sector, there are a lot of misconceptions about hydrogen and its use as a fuel. To understand why governments, industry and consumers are increasingly working to utilise this energy powerhouse to meet environmental goals, we must start with the basics. Fuel cell vehicles, or FCVs, are electric vehicles. However, rather than getting power from the grid to recharge, an FCV generates electricity onboard the vehicle, combining oxygen from the air with stored hydrogen fuel, with the only tailpipe emission being water vapour. FCVs are the only zero-emission vehicle platform now and for the foreseeable future, that replicates today's drivers' experience of being able to travel 300-400 miles on a tank of hydrogen fuel and then refuel in just three to five minutes.

Hydrogen is the lightest and most abundant element in the universe, however, as hydrogen is not naturally occurring, it can only be obtained from other sources. The most common methods of hydrogen production are either reforming of conventional hydrocarbons, typically natural gas, or through electrolysis, a process

Morry Markowitz

where an electric current is run through water to produce a stream of hydrogen and oxygen.

When using renewable electricity from solar or wind to power electrolysis or renewable biomethane from landfills or wastewater treatment plants, hydrogen production is completely decarbonised. Just as battery electric vehicles are getting cleaner as the utility grid adopts more renewable power generation, so too is hydrogen production driving its emissions lower.

As some critics have pointed out, certain methods of generating hydrogen do produce some greenhouse gas. However, as the overall goal is to reduce harmful emissions in the transportation sector, many studies, including those by the U.S. Department of Energy's Argonne National Laboratory, have demonstrated that no matter the source of hydrogen, FCVs still dramatically reduce carbon emissions compared to gasoline vehicles. In fact, FCVs are comparable in emissions to battery electric vehicles (BEVs) that use grid electricity.

Another common misunderstanding is the claim that the process of producing hydrogen from natural gas uses more energy than what would be left in the hydrogen generated – meaning it would be more economical to use the natural gas directly as a fuel for an internal combustion engine car. While some energy is lost in reforming natural gas into hydrogen, this argument discounts the extremely inefficient process of combustion engines and does not consider the much higher efficiencies of fuel cell electrochemistry. An FCV using hydrogen derived from natural gas would allow a vehicle to travel two to three times further than a compressed natural gas vehicle using the same amount of fuel. FCVs offer a much more efficient and environmentally friendly means of using domestically-produced resources.

The ultimate goal is to completely decarbonise our transportation system. That is why at the Global Climate Action Summit in San Francisco last fall, several of the largest companies in the fuel cell and hydrogen industry announced an ambitious goal to fully decarbonise hydrogen as a transportation fuel by 2030. This goal would set the stage for a significant environmental impact and put hydrogen-fuelled transport on a much faster path to zero-carbon intensity than the one charted by utilities for the grid.

If the policy aim is to transition to a zero-emission transportation sector, BEVs will not be able to do it alone. Utilising quick-fill centralised fueling stations and the long driving range that consumers are used to, not to mention scalability to all vehicle platforms, FCVs offer a ready choice that fills a need, especially for consumers in multi-family housing, city dwellers, or in locations with limited parking options where charging is not available. While BEVs may be a great choice for some consumers, if we want to have the greatest adoption of zero-emission vehicles, we need to expand the portfolio to include FCVs, too. We are doing that now and the pace of change is only growing.

> "In the transportation sector, there are a lot of misconceptions about hydrogen and its use as a fuel. To understand why governments, industry and consumers are increasingly working to utilise this energy powerhouse to meet environmental goals, we must start with the basics."

Beyond transportation, thousands of hydrogen fuel cells are also being used today to provide zero-emission stationary power generation for a long list of private and public sector customers across the country and around the world. These fuel cell systems are generating clean, efficient, long-lasting and reliable back-up power for communications networks, utilities, governments, railroad and traffic signals and even microgrids.

On-road and off, hydrogen is a clean energy solution that is helping transition to a better future today. ■

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Strengthening cybersecurity in the U.S.

Here, we take a look at the work of the Department of Homeland Security when it comes to strengthening cybersecurity in the U.S., including the Cybersecurity and Infrastructure Security Agency Cybersecurity Division

Daily life, national security and economic vitality and in the U.S. depend on a stable, safe and resilient cyberspace, according to the Department of Homeland Security (DHS).

During November 2018, President Trump signed into law the Cybersecurity and Infrastructure Security Agency Act of 2018. This significant piece of legislation elevates the mission of the former National Protection and Programs Directorate (NPPD) within DHS and sets up the Cybersecurity and Infrastructure Security Agency (CISA).

"CISA builds the national capacity to defend against cyber-attacks and works with the federal government to provide cybersecurity tools, incident response services and assessment capabilities to safeguard the '.gov' networks that support the essential operations of partner departments and agencies."

One can see that such action is necessary because nation-states and sophisticated cyber actors take advantage of vulnerabilities to steal money and information and are working on capabilities to disrupt, destroy, or threaten vital essential services from being delivered.[1]

Cybersecurity Division

The CISA Cybersecurity Division leads efforts to protect the federal ".gov" domain of civilian government networks and works with the private sector – the ".com" domain – to heighten the security of critical networks.[2] This occurs through the four functions listed below:

The National Cybersecurity and Communications Integration Center (NCCIC) aim to lower the risk of systemic cybersecurity and communications challenges in their role as the U.S.'s flagship cyber defence, incident response and operational integration centre.[3] Since 2009, the NCCIC has served as a national hub for cyber and communications information, technical expertise, operating by means of a 24/7 situational awareness, analysis and incident response centre.

The Stakeholder Engagement and Cyber Infrastructure Resilience (SECIR) division within CISA streamlines strategic outreach to industry partners and government, by leveraging capabilities, information and intelligence and experts to meet stakeholder requirements.[4]

The Federal Network Resilience (FNR) Division plays a crucial part in providing direct cybersecurity support, communications and coordination to all Federal Executive Branch agencies. Their aim is to transform Federal Government cybersecurity risk management through operational governance and training, as well as encouraging effective collaboration.[5]

Concerning network security deployment, we know that CISA established the Network Security Deployment (NSD) division to serve as the cybersecurity acquisition and engineering "Center of Excellence" to encompass the entire DHS organisation.[6]

Currently, Jeanette Manfra is the Assistant Director for Cybersecurity for CISA and as such, she leads the DHS in their mission to strengthen and protect the U.S.'s critical infrastructure from cyber threats. As the sector-specific agency for the IT sectors in the U.S., CISA coordinates national-level reporting that is in keeping with the National Response Framework (NRF).[7]

Strengthening America's cybersecurity workforce

When it comes to cybersecurity in the U.S., it's important

to note that in early May 2019, President Trump signed an Executive Order that directs the federal government to take critical steps to strengthen America's cybersecurity workforce. This action will bolster the mobility of the U.S.'s frontline cybersecurity practitioners and support the development of their skills to encourage excellence in the field. In addition, it will help ensure the U.S. retains its competitive edge in cybersecurity. It is also worth noting that today, there is a shortage of 300,000 cybersecurity practitioners in the country.

> "CISA builds the national capacity to defend against cyber-attacks and works with the federal government to provide cybersecurity tools, incident response services and assessment capabilities to safeguard the '.gov' networks that support the essential operations of partner departments and agencies."

Acting Secretary Kevin K. McAleenan explains his thoughts on this Executive Order: "America's cybersecurity practitioners – whether working in the private sector or serving in the federal, state, local, tribal, or territorial governments – constitute a core element in our country's frontline defence and we must urgently bolster them in the face of a myriad of cybersecurity threats. DHS and this Administration are committed to bold action. From enabling movement between the private and public sectors to supporting our workforce's training, education and development, the President's action today sets the course to expand and sustain the workforce and ensure America keeps its competitive edge in the critical field of cybersecurity."[8]

National Critical Functions

In closing, we find out that in early May this year, the CISA releases the inaugural set of National Critical Functions.[9] In summary, these are supported or used by the government and private sector and as such, they are of crucial importance to the U.S, in that their disruption, dysfunction or corruption would have a debilitating impact on security, national public health or safety, national economic security or any combination of these.

Let's leave the last word to CISA Director Christopher Krebs who comments on cybersecurity risk, which is just one part of the CISA's excellent work. "Identifying these National Critical Functions has been a collaborative process between public and private sector partners and marks a significant step forward in the way we think about and manage risk. By moving from an individual, sector-specific lens to a more comprehensive, cross-cutting risk management framework, we can identify and manage risk in a more strategic and prioritised manner."[10] ■

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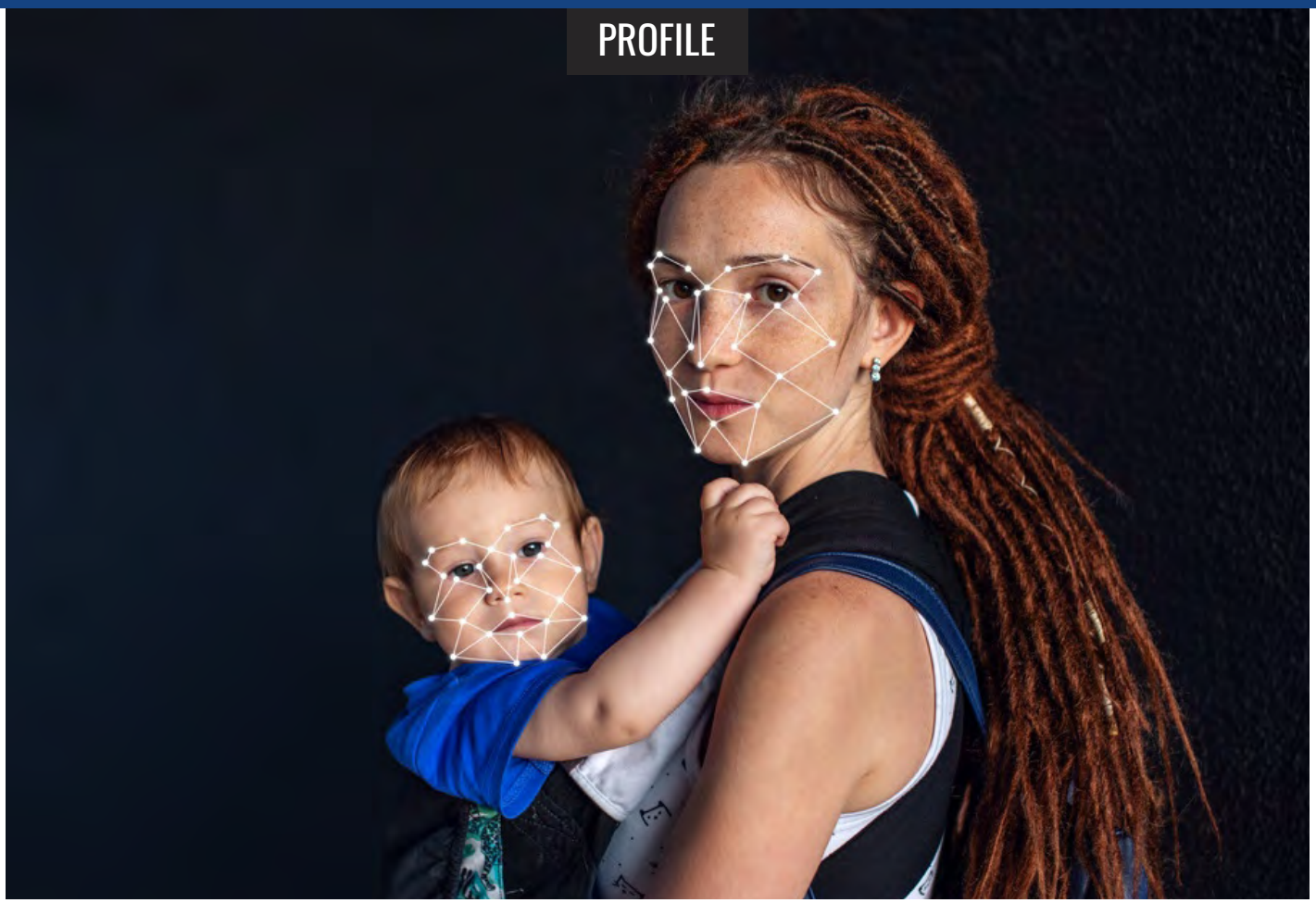

Cybercrime, illegal content online: We don't have to turn a blind eye

Marsali Hancock from EP3 Foundation underlines that we don't have to turn a blind eye concerning cybercrime, illegal content and harmful activities online

As we connect new generations of children and communities online, our unique opportunity is to be the generation that implements new, additional, privacy-protecting designs and protocols. Cybercrime, illegal content and harmful activities don't have to threaten our national security or the physical safety of our children.

Information and communications technologies (ICTs) enable world citizens to instantly access digital systems that have the potential to create better standards of living, improve health, save lives, educate, entertain and inspire. For the three billion of us who have access to the Internet, very few of us could imagine living productive lives without Internet connectivity. And many of us live, eat and breathe access to online systems that define careers, family life and for many, our very identity.

The world, with its circumference of over forty thousand kilometres, has shrunk to the size of our hand-held devices and we are able to go anywhere, see anyone and do anything at the touch of a screen. And therein lies not just the bright future of our children but also the concern for their safety and well-being. The vast potential the Internet holds for billions of people across the world is balanced by the responsibility to use this tool in the most effective and responsible manner possible, especially when safeguarding the world's children.

> "As we are at the midpoint of connecting the entire world, it's time to consider how we are doing at reducing cybercrime and child exploitation."

Against that backdrop, responsible digital skills and enhanced cyber wellness are increasingly important in

a civil society. Information superhighways bring more than just convenience. Studies suggest that a 10% increase in internet penetration is correlated with a 1.35% increase in GDP for developing countries GDP. However, the superhighways also bring cybercrime, exploitation and radicalisation.

The list of risks could be considered overwhelming. Online predators and cyber-stalkers pursue and prey on children. Impressionable youth are the victims of bullying, cyber-attacks and fraud. Terrorist cells have discovered that the internet can promote their activities and methodologies and also act as an effective recruitment tool among the younger generation. Sexual violence and other harmful products and problematic behaviours are exacerbated by their almost effortless accessibility. Additionally, intellectual property theft and identity theft have repercussions that could harm a person for decades.

As we are at the midpoint of connecting the entire world, it's time to consider how we are doing at reducing cybercrime and child exploitation.

New tools and privacy-protecting data practices are, therefore, required.

When first connected, children need protection. Digital skills, alone, cannot substantially reduce the risks from children's access to harmful content or being targeted and groomed for sexual exploitation and radicalisation. New data paradigms are required to shield them and protect them from their own youthful experiences and indiscretions, including self-generated content. To thrive, they must understand this new environment, but we also need to implement ways to protect them. We cannot completely control what they consume online, but we can protect who sees their actions online.

Every action they take is tracked online, whether it's because of cookies, web beacons, or e-tags. Offline, teens have their movements tracked by new sensors in devices, loyalty programmes or discount codes. Each action carries a code that enables companies to track and sell that data and since it is connected to the child, their actions can be revealed to malicious entities, such as hackers.

It is vital to establish new systems to protect our children and ensure the internet serves as a driver for innovation, scientific research, economic growth and social development. How we manage the internet and the deployment of the Internet of things (IoT), artificial intelligence (AI), blockchain and other distributed ledger technologies (DLT) will determine whether our society is able to move toward an internet that benefits all people around the world.

What better way to do this than to hide the identity of the child and only send out relevant data to companies rather than every action the child has taken?

Rather than tracking everything the child does online, EP3 Trusted Data Networks break down the data to the attribute level, keeping the information, but hiding the identity of the child. This still gives organisations access to important data that could track societal trends but never reveals the child's identity. The only way for the child's identity to be revealed is for a trusted identity to directly ask the child to reveal it. Once they have this layer of protection, guardians and parents can then support and protect their child from risks they can manage, such as cyberbullying.

There are many risks associated with going online, but we can take steps to protect our children from malicious entities. It may be a challenge, but we can do something to protect our children online. After all, "the power of the Internet hinges on users' willingness to trust it" and in the end, use it for the benefit of all. (1)

(1) See Supra. Internet Society, 2017 Internet Society Global Internet Report: Paths to Our Digital Future, (2017) p. 72.

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Decentralising security for mobile devices: Is blockchain the viable solution?

Steven Sprague, Cofounder and CEO of Rivetz reveals a viable solution when it comes to decentralising security. He argues that there is great promise for creating mobile device security with blockchain technology

The world was introduced to the first commercial mobile phone in 1983 with the launch of the Motorola DynaTAC 800x, which stood at a height of 13 inches, weighed 1.75 pounds and took 10 hours to recharge. In the early days of the mobile phone industry, it was incredibly simple for attackers to clone a phone's identity and run up all sorts of charges on your account.

Over the last few decades, mobile has experienced quite a metamorphosis from the "brick" of the 1980s to the compact, feature-packed smartphone of today. Now, mobile is king – people across the globe use their mobile devices not only to communicate but also to read the news, get directions, stream music, check bank accounts, store assets and so much more.

As we increasingly rely on our mobile devices, new avenues of attack continue to emerge. So much of our sensitive personal information and digital assets – such as corporate data and bank account and credit card numbers – are accessible via our mobile devices. They have become treasure troves for attackers.

Blockchain and mobile device security

There is great promise for creating mobile device security by combining secure enclaves – also known as 'roots of trust' – with blockchain technology. Blockchain is a distributed ledger technology that protects a digital transaction through complex mathematical algorithms. Because of the strength of this math, the transaction can only be created by those who hold a valid private key.

Private keys were developed as a means of protecting our digital transactions. A private key is a piece of cryptographic code that allows a user to prove who he or she is – in other words, it's a digital signature that says the user is, in fact, the one who is executing a digital transaction.

Private keys are used to secure a variety of transactions on mobile, including messaging, cryptocurrency and more. Here's the downside: if an attacker steals your private key, they can impersonate you, and then access and abuse your data and digital assets. The prevalence of mobile devices has made them some of the largest repositories for private keys.

The biggest challenge in decentralised cybersecurity is that we cannot prove the transaction was intended. If an attacker steals your private key and transfers $5,000 to a third person, there is no way to prove that the attacker – and not you – performed the transaction. Rivetz ensures an intended transaction by establishing that it occurs from a known device, in a known condition, with an authorised user, under the required conditions. Rivetz performs "device attestation" to ensure a user's devices are in a "known" condition by executing regular health checks to ensure the device integrity. Each device's integrity is recorded on the blockchain so future health checks can be compared with the baseline, establishing that those devices are in a condition the user intended.

As the rise of the internet brought digital fraud and attacks on identity, innovative industry leaders banded together to fight that fraud and formed organisations such as the Trusted Computing Group (TCG). TCG developed specifications that have become standard for securing devices, as well as the data and identity on those devices, such as personal computers and laptops.

Trusted computing uses hardware to protect users. It ensures a device will consistently behave in the expected ways, protected by a secure enclave or a 'root of trust' embedded within the device's hardware. A root of trust is isolated from the device's software operating system (OS), allowing it to execute code that cannot be seen by the OS. One such root of trust developed by Global Platform is the Trusted Execution Environment (TEE), which

enables trusted computing technology for mobile devices. The TEE already is built into the hardware of more than 1 billion mobile devices. Today, most private keys are generated within software, which is much more susceptible to attack than hardware. The TEE is capable of protecting a user's private key within the device hardware, a method that is far more secure than performing these operations in standard software.

A single system of security may not be enough to protect against the variety of cyber-attacks possible today. It is more pressing than ever to provide multi-layered protection of digital assets across two or more security domains. That way, even if an attacker were to breach one point of security, the other(s) still would need to be compromised, offering an extra layer of protection for important digital assets – whether that's your personal information or your hard-earned money.

One of the most ubiquitous roots of trust is the subscriber identity module, or SIM card. The SIM is a protected hardware environment and was created to combat mobile fraud and to protect the device identity. With the pervasiveness of both the TEE and the SIM, Rivetz saw an innovative opportunity to use these isolated roots of trust to work together to protect mobile users. In conjunction with ElevenPaths, the cybersecurity unit of Telefónica, the world's third-largest mobile carrier with more than 300 million subscribers, Rivetz uses both the TEE and SIM to protect our private keys – introducing the Dual Roots of Trust.

The solution leverages the TEE along with the SIMs deployed by Telefónica. With Dual Roots of Trust, Rivetz-enabled apps generate private keys in hardware, then cryptographically distribute those private keys between the TEE and the SIM. This delivers built-in security from both the mobile carrier and the device manufacturers, to create decentralised key protection.

By distributing a private key across these two roots of trust, attackers would have to breach both secure systems in order to steal a single private key. As an added security feature, two different entities – or independent control planes – aid the user in controlling their private keys. Through a special application authorised to perform activities inside the TEE, the user remains in control of the secrets stored in the TEE. If your mobile device is lost or stolen, a simple interaction with your mobile carrier can disable the SIM, permanently or temporarily until the device is found. So even if a thief has your device, you remain in control and your private keys are still safe.

The Rivetz solution has an unlimited number of use cases, such as sensitive work apps, mobile wallets, social media accounts and mobile banking. One of the most unique applications of Dual Roots of Trust is the ability to provably control specific applications on a device. This feature is especially useful for enterprises. Let's say a company has its own proprietary Rivetz-enabled app that employees use for work on their personal devices. If an employee is terminated or leaves, the company has the ability to revoke access to that app on the former employee's personal device with Dual Roots of Trust.

As our mobile devices have become more important to our everyday lives and contain so much of our personal and private data, we need better ways to protect ourselves. The solution lies in the roots of trust that already exist on millions of mobile platforms: the SIM and the TEE are two of the most common secure enclaves. Dual Roots of Trust is the next step in ensuring our assets stay safe.

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Achieving excellence in science, technology, engineering and mathematics education

Here, we examine the mission of the National Science Foundation's Directorate of Education and Human Resources to achieve excellence in science, technology, engineering and mathematics education

Within the National Science Foundation (NSF), the Directorate of Education and Human Resources (EHR) has a clear mission for excellence to be achieved when it comes to supporting science, technology, engineering and mathematics (STEM) education in the U.S. The notion here is that this aim applies at all levels and in all settings so that the development of a well-prepared and diverse workforce of scientists, technicians, engineers, mathematicians and educators are supported.

The goals of EHR can be summarised as follows:

1. To get the next generation of STEM professionals ready and to retain and more Americans for careers in STEM.

2. To encourage a robust research community that can undertake a rigorous evaluation and research that support excellence in STEM education.

3. To increase the scientific, technological and quantitative literacy of everybody in the U.S to help them be responsible citizens and live productive lives in today's technological world.

4. To broaden participation and close achievement gaps in all STEM fields.

Capacity-building strategies of EHR include facilitating the translation of research into practice and creating supportive learning environments and STEM pathways by developing models of reform/systemic change at both institutional and multi-institutional levels through partnerships, networking, alliances and collaborations.[1]

Graduate Education (DGE)

Under EHR, The Division of Graduate Education (DGE) aims for innovative, inclusive, high-quality graduate education in the STEM fields. DGE is in charge of innovative cross-Foundation programmes that directly or indirectly support U.S. citizens in their thirst to become the leading engineers and scientists of the future. Certainly, DGE supports research that generates exciting new ideas for graduate education in the years ahead.

> "The program supports advances in fundamental research on STEM learning and education by fostering efforts to develop foundational knowledge in STEM learning and learning contexts, both formal and informal, from childhood through adulthood, for all groups and from the earliest developmental stages of life through participation in the workforce, resulting in increased public understanding of science and engineering."

An example of their work is the Graduate Research Fellowship Program (GRFP), which directly supports graduate students in the STEM fields and is the oldest federal fellowship program in existence. Another aspect is the NSF Research Traineeship Program (NRT), which sets out to ensure that graduate students in research-based master's and doctoral degree programmes develop the knowledge, skills and competencies required to pursue STEM careers. One final example to look at here is the CyberCorps: Scholarship for Service (SFS) program and one of the aims here is to increase the number of qualified employees working for federal, state, local and tribal governments in cybersecurity.[2]

Research on Learning in Formal and Informal Settings (DRL)

Also under EHR, Research on Learning in Formal and Informal Settings (DRL) essentially invests in projects to make STEM learning for all people more effective. Promoting innovative research, development and evaluation of learning and teaching across all STEM disciplines by advancing cutting-edge knowledge and

practices in both formal and informal learning settings sums up its mission.

The EHR Core Research (ECR) program of fundamental research in STEM education provides funding in critical research areas that are essential, broad and enduring. On their website, DRL elaborates further about what they do.

"EHR seeks proposals that will help synthesise, build and/or expand research foundations in the following focal areas: STEM learning, STEM learning environments, STEM workforce development and broadening participation in STEM.

"The program supports advances in fundamental research on STEM learning and education by fostering efforts to develop foundational knowledge in STEM learning and learning contexts, both formal and informal, from childhood through adulthood, for all groups and from the earliest developmental stages of life through participation in the workforce, resulting in increased public understanding of science and engineering."[3]

STEM achievement gaps

In a major analysis of university faculty and students in STEM, Indiana University social psychologists found out that professors' beliefs about intelligence play a measurable role in the success of all students, particularly underrepresented minorities taking their first college-level STEM courses.[4]

"In a university-wide sample, we found that all students – and black, Latino and Native American students in particular – earn significantly higher grades in STEM courses when their professors believe intelligence is a malleable quality that can be developed over time, compared to when their professors believe intelligence is a fixed trait that cannot change very much," says author Elizabeth Canning, at the IU Bloomington College of Arts and Sciences' Department of Psychological and Brain Sciences.[5]

The need for more scientists and engineers

Finally, in other news, the need for more scientists and engineers is highlighted as a persistent issue plaguing industries across the U.S. We learn that a number of initiatives have been created to prioritise STEM in schools to help educators prepare more diverse students and workers for STEM fields. However, these efforts might be falling short when it comes to the representation of people of colour, according to a Researcher at the University of Missouri.[6]

"People buy into these notions that only certain people can access certain spaces and do certain things," Morton says. "When somebody tells a black woman that her STEM studies are too ambitious, they are inferring that STEM careers are reserved for people who don't look like her. However, the women I spoke to were very strong-willed despite these challenges and asserted that they would write their own stories and not buy into other people's narratives."[7]

Closing remarks

The aforementioned examples of news from the STEM field take us back to the earlier point about the mission of the NSF achieve nothing but excellence when it comes to supporting STEM education in the U.S. ■

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Interactive-engagement methods in education: Can we teach students to think like scientists while learning science?

Eugenia Etkina, Distinguished Professor of Science Education at Rutgers, The State University of New Jersey argues that interactive-engagement methods lead to better learning gains than traditional transmission-mode methods and discusses fundamental differences between various interactive engagement techniques

In the past 20 years, the educational community has accumulated enough data to say with confidence that interactive engagement methods lead to better student learning gains than traditional transmission-mode methods (Michael, 2006; Freeman et al., 2014). As Mitchell Waldrop (2015) said: "At this point, it is unethical to teach in any other way." But what is this way? There are many models of interactive engagement methods. One popular approach is the "flipped classroom" (Fulton, 2012) where the students read the textbook (or watch a video with the instructor explaining the material), then come to class and discuss what they read through answering questions posed by the instructor. They often work in pairs and participate in voting for the best answer.

An example of a flipped classroom in physics education is the method of Peer Instruction (Mazur, 1997). While the students in these classrooms work collaboratively answering questions and lecturing is limited, the knowledge that students begin with comes from authority. Students get acquainted with physics concepts by reading the book or watching a video with an authority figure on the screen. While such methods lead to more learning than traditional lecturing, what message about physics are they sending to the students? One answer is that science is an area of study that can be learned by reading the book and discussing what you read in class. Is this the message we want our students to get from our science classes?

Physics, chemistry, biology are experimental sciences. As the history of physics (Holton & Brush, 2001), the writing of physicists about their work (Born, 1943) and observations of this work in real time (Poklinek Cancula, Planinsic, & Etkina, 2015) show, the origin of every physics idea can be traced to experiments. The same is true for biology and chemistry. Sometimes an anomalous or interesting experimental result made scientists question what they observed. Then they (or somebody else) tried to explain and quantify the observed phenomenon. Multiple hypotheses were tested experimentally and those that were not ruled out remained and are now in the textbooks. When students start learning a concept by reading the textbook, they see the final outcome of this process not knowing where it came from. But maybe they learn where ideas come from by doing experiments in instructional laboratories? Research shows that this is not the case (Holmes, Olson, Thomas, & Wieman, 2017). Traditional labs that provide step-by-step instructions do not engage students in the development of new concepts, they mostly focus on the "verification of theory".

But why drag our students through "discoveries" if they can quickly learn the right concept and practice applying it? This seems much more efficient and practical. However, it turns out, that being able to investigate phenomena, to cope with multiple solutions, to evaluate assumptions, to test different ideas are exactly the skills that will make our students successful in the future (OECD, 2018), not using the facts explained to them by somebody else. Future employers will need people who not only have disciplinary knowledge but also epistemic knowledge (how to "think like a mathematician, historian or scientist") (OECD, 2018, p.5).

But how is it possible to create an environment in which students can "discover" and learn physics for themselves in ways similar to how physicists work—to own it, so to speak, within a reasonable time? An example of such an environment or an interactive method of teaching is the Investigative Science Learning Environment (ISLE) (Etkina & Van Heuvelen, 2007; Etkina, 2015). There are three key features of this approach, detailed below, which mirror the features of a scientific

inquiry while at the same time allowing students to develop traditionally valued physics knowledge (normative concepts).

1. Students develop normative physics concepts as their own ideas by repeatedly going through the following steps

(a) Observing pre-selected phenomena (experiments) and looking for patterns;

(b) Developing multiple explanations for these patterns;

(c) Using these explanations to make predictions about the outcomes of testing experiments that they design;

(d) Deciding if the outcomes of the testing experiments match the predictions;

(e) Revising the explanations if necessary, examining assumptions or going back to collect more observational data and;

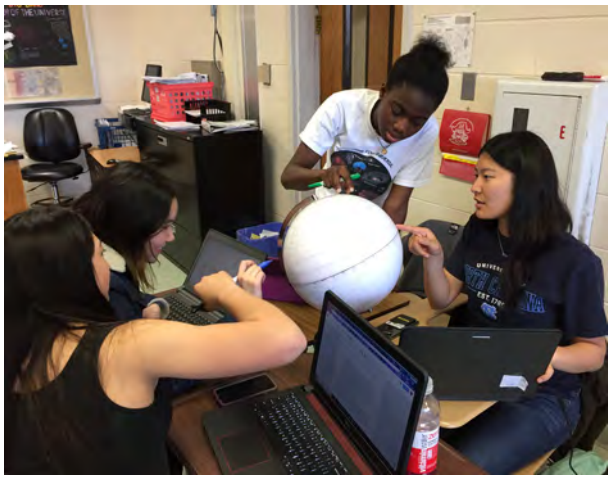
(f) Applying tested and not ruled out explanations for practical purposes (building devices, determining the values of physical quantities, etc.).

2. While engaged in steps (a) – (f) students represent physical processes in multiple ways, developing productive tools for qualitative reasoning and problem-solving.

3. While engaged in steps (a) – (f) students work collaboratively in groups of 3-4 using small whiteboards and then share their findings, designs and solutions in a whole class discussion.

Only after all these steps the students read the textbook and compare the ideas that they have constructed on their own with the ideas presented in the book. The combination of these features applies to every conceptual unit in the ISLE learning system.

While it might seem impossible that the students can learn all of the general physics following the sequence outlined above our experience and the experience of many teachers across the world shows that it is. ISLE was originally developed by E. Etkina and later enriched through collaboration with A. Van Heuvelen, S. Brahmia, D.T. Brookes, G. Planinsic, X. Zou and many others. It is being used in high school and college classrooms and teacher preparation programmes. We developed a plethora of educational materials to help implement this approach, many of which are available on the Internet. In my next editorial, I will show several examples of knowledge construction following the ISLE process and share the resources available.



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The DREAM STEM Project at North Carolina Central University: Retaining talent

Caesar R. Jackson, Professor of Physics explores the DREAM STEM Project at North Carolina Central University, which includes retaining science, technology, engineering and mathematics talent in the U.S.

Science, technology, engineering and mathematics (STEM) educated graduates often become substantive contributors to the economic vitality of the nation and reap higher economic benefits during their careers, yet there are persistent challenges in producing and retaining STEM talent in the United States (U.S.) to meet the future science and engineering workforce demands.

As the U.S. population shifts toward an increasingly multiracial society, the current racial/ethnic gap in science degree production from institutions of higher education forecasts a severe shortage of diverse scientific workers. Although about 28% of all U.S. college students select a STEM major, more than half switch to a non-STEM field or leave postsecondary education without earning any credentials. This departure rate is even higher for individuals from groups underrepresented in STEM, including African Americans.

Historically, black colleges and universities (HBCUs) play a significant role in producing African American scientists. HBCUs were established with the deliberate purpose of serving African Americans and these institutions, despite categorically being underfunded and lacking sufficient resources, serve and are effective in educating more low-income, first-generation students than all other institutions of higher education. Even though HBCUs constitute only 3% of the postsecondary institutions in the U.S., they award 17% of all of STEM baccalaureate degrees earned by African Americans and 24% of the African Americans who earned a doctorate in science and/or engineering received their bachelor's degree from an HBCU.

The U.S. National Science Foundation (NSF), initiated the Historically Black Colleges and Universities Undergraduate Program (HBCU-UP) to assist HBCUs to more fully realise their promise as major contributors to the nation's STEM degree completion goals. The grants awarded from the HBCU-UP are administered by NSF's Division of Human Resource Development within in the Directorate for Education and Human Resources. North Carolina Central University (NCCU), an HBCU located in Durham, North Carolina, was awarded funding from HBCU-UP in 2012 and the DREAM STEM Project was launched at the university.

DREAM STEM – "Driving Research, Entrepreneurship, and Academics through Mastering STEM" – has as major goals, to increase enrolment and retention in STEM degree programmes at NCCU, to increase persistence and graduation rates in STEM and to produce highly-skilled STEM graduates who can create and innovate. The strategic components of DREAM STEM comprise:

1. Entrepreneurship in science education;

2. Development of students' identity as scientists and;

3. Faculty development through teaching and learning research innovation mini-grants.

The entrepreneurship in science education component stimulates entrepreneurial thinking in science students by exercising their creative design abilities, helping them to actualise their intellectual and knowledge potential and demonstrating how to realise and capitalise on opportunities. Students are guided through the research and development (R&D) portion of the science and engineering entrepreneurship cycle where they conceptualise creative solutions to realistic problems and engage in the hands-on design of their innovations. Development of students' innovation design skills is complemented with entrepreneurial thinking training on

how to carry out market analysis, identify financing sources to fund their product and protect their intellectual property. Students' entrepreneurial training culminates with their presentation of a business pitch and demonstration of their product prototype to a public audience. Students' self-belief increased significantly after participating in DREAM STEM entrepreneurial training and students felt more confident in their ability to apply scientific knowledge to develop products and processes, turn ideas into feasible business opportunities, develop a product plan, conduct market analysis and make strong presentations.

Student's science identity development is thought to derive from three overlapping constructs: performance, competence and recognition. The DREAM STEM Project accentuates students' science identity through earned academic scholarships, honours and awards (Performance); participation in undergraduate research experiences (Competence); and exposure and recognition in attending and presenting their work at national professional meetings (Recognition).

It was observed that DREAM STEM students felt a strong sense of belonging (i.e., fitting in) while feeling honoured and affirmed for being one's distinct self (i.e., standing out) and subsequently they expressed greater STEM identification and demonstrated significantly higher academic performance in STEM degree programmes.

The DREAM STEM Project promotes the scholarship of teaching and learning through mini-grant funding awarded to committed STEM faculty who implemented and assessed new and promising pedagogical strategies that stimulated students' active engagement in learning science and mathematics subjects. Gains in students' STEM learning were greatest in STEM courses that included active learning approaches in lecture sessions along with guided inquiry approaches in the associated laboratory sessions of the course.

> "Overall outcomes of the NSF-funded DREAM STEM Project at NCCU include higher enrolment and significantly higher retention, persistence and graduation rates in STEM degree programmes for African Americans students."

In addition, investigation of self-regulated learning behaviours of students in STEM courses at NCCU revealed that self-efficacy for STEM learning & performance had a significant effect on student's effort regulation and self-efficacy was the greatest predictor of the end-of-course grades. Students who exhibited higher academic achievement also exhibited higher self-efficacy, higher effort regulation and higher task value.

Overall outcomes of the NSF-funded DREAM STEM Project at NCCU include higher enrolment and significantly higher retention, persistence and graduation rates in STEM degree programmes for African Americans students. Physics enrolment increased by 82% as a result of a newly created 3-plus-2 dual degree Physics/Engineering program. The first-year retention for DREAM STEM students was 97% compared to 57% for the general STEM population of students. DREAM STEM students persisted in their degree programme to the third year at a rate of 92% compared to 36% for general STEM population and the five-year graduation rate for DREAM STEM students was 80% compared to 30% for the general STEM population.

As a result of the DREAM STEM Project, average degree production increased in Chemistry by 69%, Mathematics by 50% and Physics by 88%. During the grant period from 2012 to 2018, thirty-two (32) DREAM STEM participants completed STEM degrees with 38% in Physics, 25% in Biology, 19% in Mathematics and 13% in Chemistry. The demographics of the DREAM STEM graduates were: 72% African American, 4% White, 6% Hispanic, 3% Asian and 6% two or more races; and 53% were male and 47% were female. DREAM STEM graduates went on to pursue STEM masters and PhD degrees, to become commissioned military officers deployed on technical assignments and to gain employment in high-tech industry jobs.

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An overview of medicinal cannabis research

Dr Mark Ware, Chief Medical Officer at Canopy Growth, provides an overview of the research that already exists around medicinal cannabis and explains why there is a need to educate clinicians further

The medicinal cannabis industry is growing rapidly in the UK with new and established companies entering the market, all aiming to supply patients with new formulations of otherwise old medicine. However, despite regulations allowing for legal use of medicinal cannabis on November 1st, 2018, very few patients are able to access these medicines either privately or on the NHS.

There have been a small number of patients championing access to medicinal cannabis, such as Billy Caldwell and Alfie Dingley, both of whom are among the very few who have managed to obtain a prescription in the UK as of the time of writing.

One factor contributing to the shortage of prescriptions to date is lack of educational support given to clinicians; another is the shortage of clinical evidence supporting the efficacy of different kinds of cannabinoid preparation. As medical training in this area is not standard for clinicians, many are having to do their own research to learn more about the potential safety and efficacy of cannabis.

Additionally, some hospitals have banned the prescription of medicinal cannabis and others have asked for reassurance that their jobs will not be at risk if they prescribe.

While there is a clear case for further research, cannabis and its components have been extensively investigated and used as a medicine for many years, with evolving clinical and real-world evidence suggesting the potential benefit of cannabinoids for those with Multiple sclerosis (MS), chronic pain, cancer treatment-related nausea and epilepsy, among others. However, this evidence is not widely shared or appreciated in undergraduate or continuing medical education for health professionals.

Chronic pain

Relief from chronic pain associated with cancer, musculoskeletal disorders and central and peripheral neuropathies is among the most common reasons cited by patients for the medical use of cannabis. [1] However, clinical trial data are suggestive, but not conclusive, of cannabis treatment of chronic pain. [2] Issues include lack of standardised products, heterogeneity of conditions, small sample sizes and short follow up. Neuropathic pain appears to be the most well-studied condition. Overall evidence suggests that cannabinoids deserve consideration as a treatment option for refractory pain, with increasing calls for cannabinoids to be evaluated as alternatives to opioids. [3]

While a large number of studies suggest cannabinoids can have a moderate effect on pain, more research needs to be done in regard to efficacy, dose, routes of administration and safety.

Epilepsy

A number of recent reviews have shown that cannabidiol (CBD) is more effective than placebo in reducing the number of seizures by 50% or more and improved overall quality of life. [4] Indeed, the U.S. FDA recently approved a prescription form of CBD for refractory childhood epilepsy conditions.

Multiple sclerosis (MS)

Spasticity and pain in MS have been well studied as targets for cannabinoid therapy and in a review of 17 studies, use of cannabis-based products have been found to be associated with improved patient-reported spasticity in the long term. [5]

Addiction

A 2016 survey of consumers attending a Michigan medical marijuana dispensary suggesting that medical

cannabis use in pain patients was associated with a 64% reduction in opioid use. [6] Likewise, analyses of prescription data from U.S. Medicare enrolees in the U.S. (with medical access to cannabis) suggest that access to cannabis is associated with a significant reduction in the prescription of conventional pain and other medication. [7] In the context of an evolving crisis of mortality associated with opioid abuse, the role of cannabis in reducing harms associated with substance abuse deserves urgent consideration.

Adverse effects

Cannabis products are generally well tolerated, however common side effects for CBD or high THC (tetrahydrocannabinol) products include nausea, vomiting, diarrhoea, fatigue and dizziness. [8] The role of cannabis in patients with mental health disorders deserves careful study.

Dr Ware finishes: "Overall, cannabis may have benefit to very ill patients who are refractory to conventional therapy. More research into the efficacy and side effects of a variety of cannabinoids is clearly needed. However, there are many patients in the UK who cannot and will not wait for further clinical research and these patients deserve and need their clinicians to feel confident enough to prescribe cannabis. With better information and guidance, clinicians and patients can work together to evaluate whether cannabis may be appropriate for them." ■

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Ways to characterise how ice caps and glaciers change

Martin Sharp, Professor at Department of Earth and Atmospheric Sciences,
University of Alberta, explains ways to characterise how ice caps and glaciers change

There are several ways to characterise how ice caps and glaciers change. Early work emphasised changes in glacier length derived from repeat measurements of the position of a glacier's terminus at a specific time of year (such as the end of the summer melt season). Note that numerous distinct glaciers may drain, in different directions, from a single ice cap and that these may not all change over time in the same way. Records of year-to-year changes in the annual maximum extent of a given glacier allow the identification of periods of advance, when the glacier terminus moves down-valley over time because the transport of ice to the terminus by flow exceeds the loss of ice there by melting and periods of retreat, when it moves up-valley because ice is removed more rapidly by melting than it is transported towards the terminus by glacier flow. Periods of glacier advance are generally regarded as an indicator of a glacier in good health, while periods of retreat indicate poor health.

Past periods of glacier advance and retreat can be identified by comparing positions of the glacier terminus in historical landscape paintings, terrestrial or aerial photographs, or satellite images that date from different points in time. The limits of past glacier advances are often marked by "end moraines" – ridges of sediment deposited or pushed up by the glacier during those advances. The timing of the advances can be determined from documentary or graphical sources, or by direct dating of either the moraine surfaces, or of organic materials (such as plant remains, soils, peat layers, or tree stumps) that were overrun by the advancing glacier. Knowledge of the timing and rate of glacier changes allows assessment of whether and how they may be linked to past climate changes.

As the Earth's climate warms, we are increasingly concerned about how glacier change will affect the amount and timing of meltwater runoff passing through downstream rivers and lakes and about how glacial melting will impact global mean sea level. To address these two issues, we must quantify past and present changes in the mass of water being exported from glaciers. This requires that we know how the mass of glaciers is changing over time.

To calculate the mass loss from a given glacier over a specific time period, we need to determine how the glacier's thickness and/or volume changed over that period. Historically, this was done in the field by measuring the annual "surface mass balance" of a glacier. This is the difference between the annual addition of mass to the glacier by snowfall during the winter "accumulation" season and the annual removal of mass from the glacier by melting of surface snow and ice during the summer "ablation" (or melt) season. If the annual addition of mass by snowfall exceeds the annual removal by melting, the glacier will grow over time. If mass removal exceeds mass addition, however, it will shrink. Mass removal occurs mainly

by surface melting and meltwater runoff to the ocean. The cumulation of the successive annual mass balances of a given glacier or ice cap over time provides an estimate of the overall changes in the glacier's mass over that period.

Where a glacier terminates in the ocean or in a proglacial or ice-marginal lake, mass loss also occurs by melting of the glacier's terminal ice cliff using heat derived from either the atmosphere (for ice above the sea/lake level) or the ocean/lake (for ice below the sea/lake level). Since glaciers are heated from below by geothermal heat, melting can also occur at the base of the glacier. Rates are typically low relative to surface melt rates, except when the glaciers are on active volcanoes (as are some in Iceland, for instance).

Iceberg calving removes ice from the terminal and marginal ice cliffs of glaciers. It is referred to as "dry calving" if the ice margin is on land and "wet calving" if the bergs are released into a lake or the ocean. For "tidewater" glaciers, which are in direct contact with the ocean, the rate of mass loss into the ocean is affected by variables like the water depth at the glacier terminus (which determines whether the terminus is grounded on bedrock or floating), the water temperature relative to that of the ice (which affects the energy available for melting where ice and water are in contact) and whether there is active meltwater outflow beneath floating sections of the glacier terminus. This outflow might entrain warmer lake or ocean water as it rises through the water column and brings it into contact with the floating ice, thereby accelerating the melting of that ice. Whilst a cover of floating sea ice or lake ice on any water body in front of the glacier terminus may buttress the glacier's flow and limit the rate at which it loses mass by iceberg calving, the break-up and/or melting of such ice may trigger glacier advance and iceberg calving.

To study how glacier change affects global mean sea level or regional water resources, we must quantify changes in the mass of the entire population of glaciers and ice caps in the region of interest. To do this, we use airborne or satellite remote sensing methods such as laser or radar altimetry, or satellite gravimetry. With altimetry, repeat measurements of the surface elevations of glaciers in a specific region are used to estimate the change in regional ice volume over time. Converting this volume change to an estimate of ice mass change involves multiplying the volume change by appropriate densities for the snow and/or ice that were added to, or removed from, the glaciers. With gravimetry, we determine changes in the mass of ice in a specific region from measurements of the perturbations in Earth's gravitational potential that are caused by the redistribution of mass that results from the melting of land ice and transfer of the resulting water to the ocean (or, if the mass of land ice is increasing over time, from the accumulation of snow on the ice cap or glacier). With this method, we are effectively using repeat measurements of the weight of the glaciers and ice caps in a region to document changes in ice mass over time.

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