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NORTH AMERICA ANALYSIS

NEUROBIOLOGICAL RESEARCH DRIVES THE ABILITY TO TREAT MENTAL ILLNESS

JEFFREY BORENSTEIN, OF THE BRAIN & BEHAVIOR RESEARCH FOUNDATION (BBRF) ARGUES THAT RESEARCH DRIVES THE ABILITY TO TREAT MENTAL ILLNESS AND DETAILS WHY FUNDING INNOVATIVE NEUROBIOLOGICAL RESEARCH IS A PRIORITY

IN THIS ISSUE

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INTRODUCTION

Welcome to the April 2019 edition of North America Analysis.

One of the highlights in this issue is the special focus we have on neurodegenerative diseases, which includes comment from Jeffrey Borenstein, of the Brain & Behavior Research Foundation (BBRF). In his article, he argues that research drives the ability to treat mental illness and details why funding innovative neurobiological research is a priority.

In this vein, further insight comes from Rachel Conant, Senior Director, Federal Affairs, Alzheimer's Association, who explains how bold action by the U.S. Congress delivers victory to the millions of people living with Alzheimer's.

Elsewhere in this volume, I thoroughly enjoyed speaking with Dr Carolyn M. Hutter, PhD, Director, Division of Genome Sciences at the National Human Genome Research Institute (NHGRI). You can find out what she told me about the important role of research when it comes to applying genome technologies to studying disease.

We also feature an in-depth look at a new and exciting era in the field of polar science, and it is indeed an honour to have this article authored by Kelly K. Falkner, Director of the Office of Polar Programs (OPP) at National Science Foundation in the U.S.

Turning to Canada, I was delighted to interview Canada's Ambassador for Climate Change, Patricia Fuller, who reveals how the country is taking action to reduce emissions and tackle climate change.

I trust that you enjoy the many compelling and thought-provoking comment pieces in this edition. Please do contact me if you have any suggestions for future articles, or perhaps you'd like to provide any feedback you may have on this document. ■

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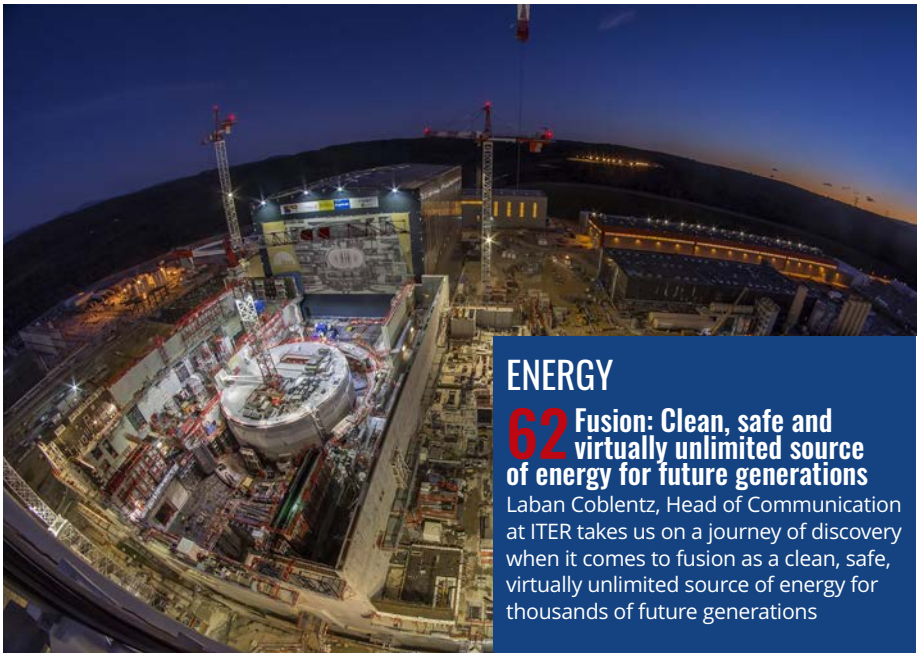

ENERGY

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CANADA

Employing "living biobanks" to advance biomedical research

A group of seasoned experts from the International Society for Biological and Environmental Repositories explain the notion of employing "living biobanks" to advance the field of biomedical research

Technological advancements over the recent decades have enabled the long-term storage of high-quality biological material at very low temperatures. We can now store biological material for a great length of time in biobanks: where biological samples (bodily fluid or tissue) and associated data are collected, annotated, transferred, stored and redistributed for future research in order to improve our understanding of health and disease. The process which enables the preservation of structurally intact living cells and tissues is called "cryopreservation." More specifically, during cryopreservation, biological materials are cooled to cryogenic temperatures, commonly to -196 °C/-321 °F the temperature of liquid nitrogen. At these low temperatures, biological activity slows considerably, effectively halting the biochemical reactions that lead to cell death and DNA degradation and allowing for near indefinite storage of the samples.

Recent scientific advances in cryopreservation have enabled the prospect of establishing "living biobanks" that store viable, functional tissue or replicable cell types for years to decades. This could have a significant impact across basic biological research, medicine and the biopharma industry; however, the effects of such applications are underexplored. For example, banking and long-term storage of stem cells or stem-like cells in different stem cell platforms represent a fundamental resource, preserving the original features of stem cells for patient-specific clinical applications.[1]

The International Society for Biological and Environmental Repositories (ISBER) recently held a roundtable discussion at the 2018 annual meeting on this concept, building on a National Science Foundation (NSF, U.S.)-funded technology road mapping process, the recent "Organ Banking Summits" held at Harvard and Stanford Universities, and roundtable discussions were held at the White House and on Capitol Hill during the last several years. Further demonstrating the application and promise of these technologies, the National Cancer Institute (NCI) recently launched a new project entitled "The Human Cancer Models Initiative (HCMI)" which is a collaborative international consortium that is generating novel, next-generation, tumour-derived culture models (living biobanks) annotated with genomic and clinical data.

The "Apollo Program" of living biobanks

The above meetings focused on developing a mini-"Apollo Program" in cryopreservation to lengthen the shelf-life of living tissues and whole organs. Early proofs of concept for such research advances include the banking of whole sheep ovaries (resulting in live births), human digits, human cartilage, and a rabbit kidney at deep cryogenic temperatures and storage of organs such as rat hearts and rat livers at high subzero temperatures. The U.S. government is currently funding dozens of labs to develop cryopreservation methods for living tissues. This concept has received significant support from diverse stakeholder organisations such as (i) the International Society for Cryobiology, which has co-organised several meetings and sessions on the concept, and the (ii) American Society of Transplantation, which launched a new branch of its organisation focused on this concept. A number of organisations were signatories to a consensus article in Nature Biotechnology outlining the vast potential of these advances to change the landscape of medicine and biomedical research.[2]

Researchers agree that many biobank tissues represent "low hanging fruit" in this effort, as the technical hurdles are much lower for collections of cells or simple tissues than for larger vascularized tissues or whole organs. There are a great number of tissues (or cells) and/or

biologics that could soon be stored in "living biobanks". These can include solid tumour biopsies, organ and brain slices, resected brain tissue, cadaveric donor skin, cadaveric bone marrow, reproductive organs and tissues, pancreatic islets, a variety of neonatal tissues, and blood vessels.[3]

"The U.S. government is currently funding dozens of labs to develop cryopreservation methods for living tissues. This concept has received significant support from diverse stakeholder organisations such as (i) the International Society for Cryobiology, which has co-organised several meetings and sessions on the concept, and the (ii) American Society of Transplantation, which launched a new branch of its organisation focused on this concept. A number of organisations were signatories to a consensus article in Nature Biotechnology outlining the vast potential of these advances to change the landscape of medicine and biomedical research."

Potential impacts

The awaiting scientific discoveries are only one of the essential steps towards a great many potential applications. Techniques currently developed within the context of living biobanks and cryopreservation of living tissue can be applied in preclinical testing, designing disease models, biomarker discovery, toxicity (safety) evaluation of pharmaceutical agents, greatly improved tissue quality for immunohistochemistry (IHC) leading, for example, to precision medicine approaches in the diagnoses and treatments of cancer types.[4]

This same concept is already being applied to cell lines such as tumour and primary epithelial cells, for example, patient-derived xenograft models, organoids, conditionally reprogrammed cells, induced pluripotent cells, and other cancer precision medicine applications, these represent an unexhausted resource of living biobanks. However, these concepts are applied in very many different ways by the academic and private sectors, representing an actively growing field that has yet to reach clinical consensus or maturity. ISBER is launching a special interest group to explore these and other applications. This group will unite stakeholders in these diverse areas, who will aim to provide (hopefully universal) recommendations to guide the development of new biobanking technologies and ultimately the establishment of the first living biobanks.

Even without further advances in cryopreservation technology, the existing technological opportunities today can greatly expand the number and applications of living biobanks. However, key challenges need to be overcome in order to capitalise on these opportunities, including a clearer articulation of both the scientific and clinical impact, as well as of the prioritisation of funding and regulatory actions required to allow this emerging field to reach its full potential. ■

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Neurobiological research drives the ability to treat mental illness

Jeffrey Borenstein, of the Brain & Behavior Research Foundation (BBRF) argues that research drives the ability to treat mental illness and details why funding innovative neurobiological research is a priority

Since the war on cancer was declared 50 years ago, billions of dollars have rightfully poured into cancer research. Comparatively, mental illness which affects the lives of one in four people, receives a mere fraction of that amount of money for research. It is impossible to overstate the economic, social and personal toll mental illness takes on individuals and society. Mental illness is a real, treatable, medical condition that affects the brain. We know that living with a mental illness is not a choice, or something that's in someone's control – just like having any other medical condition.

The time has come to declare war on mental illness and place a priority on funding innovative neurobiological research for better prevention, diagnosis, early intervention, and treatment. The field of psychiatry and neuroscience has seen tremendous scientific advances, but we need to expand basic, translational and clinical research to better understand the workings of the brain and why things go wrong and test new medical and psycho-social approaches.

We also need to raise awareness, eliminate stigma, and remove barriers to treatment.

A growing global problem

While we are making progress, the evidence is overwhelming that mental illness is a significant public health crisis.

Suicide is now the 10th leading cause of death among American adults and the second leading cause of death for young people ages 10 to 24. Suicide rates have risen for every age group, except older adults. And a recent study in the British Medical Journal found that incidents of self-harm among girls aged 13 to 16 increased by 68% over a four-year period.

We also continue to see an increase in psychiatric illnesses among veterans, and the rising death toll from alcohol and opiate abuse has decimated families and entire communities. Millions of people with serious mental illnesses go untreated, and U.S. prisons and jails have tragically become de-facto psychiatric hospitals.

Globally, psychiatric illness has become one of the major conditions affecting the health of the world population. The World Health Organization (WHO) predicts that by 2030, depression will be the leading cause of disease burden.

Supporting science research for recovery, BBRF funds the most innovative ideas in psychiatry and neuroscience to better understand the causes and develop new ways to effectively treat brain and behaviour disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, ADHD, anxiety, borderline personality disorder, obsessive-compulsive disorder, addiction and post-traumatic stress disorder. BBRF grants support a broad range of the best ideas in brain research and our grantees have taken substantial steps forward on the path to developing new treatments and finding cures for mental illness.

The Brain & Behavior Research Foundation (BBRF) supports cutting-edge research that offers the greatest potential for breakthrough discoveries. These discoveries are changing what it means to live with mental illness. BBRF grants are focused on four priority areas: basic research to understand what happens in the brain to cause mental illness; new technologies to advance or create new ways of studying and understanding the brain; diagnostic tools and early intervention to recognise early signs of mental illness and treat as early as possible; and next-generation therapies to reduce

symptoms and ultimately cure and prevent brain and behaviour disorders.

BBRF grants enable outstanding young scientists to begin a career in research as they look to answer important questions or help identify new potentially game-changing targets for treatments.

In fact, a RAND Europe analysis of the global mental health research funding landscape found that we are the top non-governmental funder cited in published articles and virtually every scientific journal in psychiatry, neuroscience, molecular biology, and genetics includes articles on the research achievements of BBRF grantees. Most importantly, BBRF grants have a proven multiplier effect and have led to additional funding from the government, university and industry sources. In fact, the $394 million in grants BBRF has awarded since 1987, has resulted in more than $3.9 billion in additional funding for scientists.

Advances from BBRF grantees continue to define the leading edge of all research in the mental health field. Examples include the use of Clozaril for the treatment of schizophrenia, transcranial magnetic stimulation for depression and other conditions, deep brain stimulation for treatment-resistant depression, the ongoing development of rapid-acting anti-depressants, magnetic stimulation therapy that can be used to treat depression without causing the memory loss that can happen with electroconvulsive therapy (ECT), and optogenetics which helps scientists around the world to better understand the brain.

Increase funding for mental illness now

Now, more than ever, it is important to reduce stigma, prejudice and stereotypes about mental illness and encourage people who have a psychiatric condition not to suffer in silence, but to seek help. By educating the public about the scientific and biological basis of psychiatric disorders, and the amazing progress we are making in brain and behaviour research, we hope to change the culture. With so much that needs to be done, how do we make people pay attention to this issue? How do we increase funding for research and make mental health a top priority so that help is available to all who need it?

> "Globally, psychiatric illness has become one of the major conditions affecting the health of the world population. The World Health Organization (WHO) predicts that by 2030, depression will be the leading cause of disease burden."

Only through a combination of public and private funding for high-risk, high-reward research will we generate significant scientific discoveries that change the lives of people with mental illness and their families and impact our larger society.

Our scientific understanding of how the brain works and what happens when illness occurs is helping to change people's attitudes about mental illness. Research has led to tremendous improvements in how we treat psychiatric conditions and the availability of better treatment has also changed people's attitudes.

Research offers hope for further advances in treatment and ultimately cures and methods of prevention and is the key to helping people with a mental illness live full, productive, and happy lives. ■

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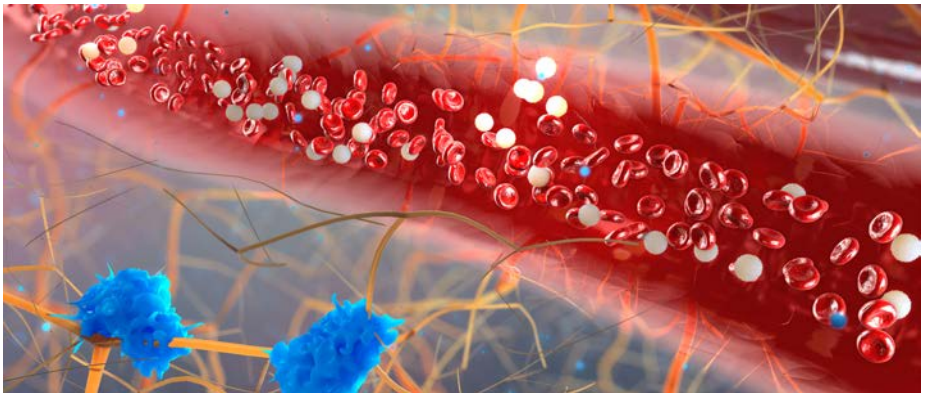
The vascular origin of mental health disorders

Anju Vasudevan from McLean Hospital/Harvard Medical School looks at the progressive change in thought around brain blood vessels and their direct contribution to mental health illness

The cerebral cortex is essential for the integration and processing of information that is required for most behaviours. The exquisitely precise laminar arrangement of neurons, axon collaterals and dendritic processes arise during embryonic development when neurons migrate successively from proliferative ventricular zones to coalesce into specific cortical layers. Abnormalities in neurons and defects in cortical inhibition have long been implicated in the etiology of schizophrenia, autism spectrum disorders (ASD), anxiety and depression.

Brain development, however, like a gem that is cut with many facets that sparkle, is not limited to neuronal changes but is also supported by concomitant development of its vasculature. Correct functioning of the cerebral cortex necessitates the concerted assembly of both vascular and neuronal networks. Here, I will discuss the progressive change in thought with respect to brain blood vessels and its direct contribution to mental health illness from the earliest developmental time points.

Until a decade ago, blood vessels in the embryonic forebrain were believed to be a homogenous population of vessels, responding passively to the metabolic demands of growing neuronal populations. Our work depicted the diversity in embryonic forebrain vascular networks, by differentiating them as pial versus periventricular, based on anatomy, origin,



growth patterns and developmental mechanisms[1]. The tapering vessels joining the periventricular and pial vessels may represent the earliest arterial-venous communication. The periventricular vascular network develops in advance of and is independent of neuronal development by embryonic day 11 to act as a substrate and provide critical guidance cues to instruct key events that follow in the embryonic telencephalon, for instance, neurogenesis (birth of new neurons), radial migration of projection neuron precursors and tangential migration of GABAergic interneurons[2,3].

Interestingly, the periventricular vascular network not only acts as a physical substrate for neuronal migration but also holds the key to several novel developmental mechanisms and pathways. Gene expressions for biological processes and canonical maps containing genes controlling neurogenesis, neuronal migration, chemotaxis, and axon guidance were enriched in periventricular endothelial cells, when compared to pial endothelial cells, signifying new and unknown roles[3].

Pial endothelial cells, on the other hand, showed enrichment in inflammation and pathological process categories. When genes expressed in periventricular endothelial cells were classified according to disease categories, an enrichment was observed in psychiatric disease categories[3]. Our studies, therefore, implicate a new cellular substrate – periventricular endothelial cells as being contributory to a wide swath of neuropsychiatric diseases with schizophrenia, epilepsy, bipolar, mood, depressive disorders and autism topping the list, shedding light on a new problem.

Certainly, the problem is very significant because it means that we have focused on psychiatric illnesses from a neuronal perspective extensively when intrinsic defects within blood vessels may be the actual trigger. These results also highlighted the great need to validate and understand the functional significance of novel genes expressed in periventricular endothelial cells/blood vessels and its specific contribution to psychiatric disease symptoms.

So, we went on to investigate why genes traditionally believed to be confined to GABAergic interneurons were enriched in periventricular endothelial cells – among them were *Gad1* and *Gad2* – these encode GAD proteins that synthesise GABA, $GABA_A$ receptor β3 subunit (*Gabrb3*) and vesicular GABA transporter (*Vgat*). We designed strategies to specifically render endothelial $GABA_A$ receptors dysfunctional or turn off GABA release from endothelial cells[4]. This led to the discovery of the novel vascular GABA signaling pathway operating via forebrain endothelial cells that has an intricate and powerful control of prenatal brain development events – angiogenesis, neurogenesis and neuronal migration. Changes in this pathway left lasting signatures on cortical circuitry and blood flow in the postnatal brain with consequences for behaviour[4]. Dysfunction of endothelial $GABA_A$ receptors was sufficient to cause behavioural abnormalities similar to psychiatric disease that was characterised by one or more of these core symptoms – impaired social recognition, reduced social interactions, communication deficits, increased anxiety or depression.

On the other hand, complete loss of endothelial GABA release resulted in significant abnormalities in developmental milestones and led to a model reminiscent of childhood epilepsy or autism spectrum disorder. Alterations in postnatal behaviour were characterised by periods of quiescence, interrupted by tremors and a reduction in voluntary movement and the mice failed to survive beyond two months of age. For the very first time, our studies describe how intrinsic defects within telencephalic vasculature/endothelial cells from the earliest developmental time points can independently mould neuronal signaling pathways with far-reaching consequences for brain development and behaviour[4]. It also highlights how variations in vascular GABA levels can cause diversity in psychiatric symptoms[4].

We expect our work to bridge a gap between vascular biology and psychiatry. Abnormal vascular pathologies and disturbances of cerebral blood flow have repeatedly been observed in patients with schizophrenia, autism, anxiety and depression using old and new technologies. However, these disturbances were usually linked to inflammation or changes in neural plasticity. Our project uncovers a direct cause of change in blood flow in psychiatric disorders that originate from intrinsic defects in blood vessels from the earliest developmental points. There is a great need to better understand the spatiotemporal regulation of endothelial cell gene expression and function in brain vascular networks at both developmental and adult stages in normal and disease conditions. The neuro-vascular communication initiated in the prenatal period is likely to acquire greater complexity after birth. Blood flow may provide spatial and temporal information, modulating excitation and inhibition in cortical circuits, thereby affecting representation. Therefore, if there is an intrinsic defect within brain endothelial cells, it has to be identified and corrected for the restoration of brain health.

We hope to apply this new scientific knowledge not only to gain a deeper fundamental understanding of novel origins of psychiatric disease but also to generate new and effective treatments. In ongoing projects, we are tapping into the potential of embryonic periventricular endothelial cells/angiogenesis, in multiple ways to prevent the origin of diverse psychiatric symptoms by rescuing vascular defects in the prenatal brain or by developing vascular therapies for repair and regeneration in the postnatal and adult brain. We envision a future where the 'healing touch' of angiogenesis therapy will bring relief to patients suffering from mental health disorders. Determination of brain blood vessel health should, therefore, become a part of our routine health visits and check-ups.

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Bold action by Congress delivers victory to millions living with Alzheimer's

Rachel Conant, Senior Director, Federal Affairs, Alzheimer's Association explains how bold action by the U.S. Congress delivers victory to the millions of people living with Alzheimer's

With a strong bipartisan vote in an otherwise partisan environment, the U.S. Congress just delivered a victory to millions of Americans currently living with Alzheimer's disease and their caregivers.

By passing the Building Our Largest Dementia (BOLD) Infrastructure for Alzheimer's Act (P.L. 115-406), Congress has authorised $100 million over five years (FY20-FY24) to build and enhance the U.S.'s public health response to the Alzheimer's crisis.

Public health initiatives work at the community level to protect and improve the health and safety of the entire population. This means safe water to drink, vaccines to prevent deadly diseases, interventions to reduce smoking, and emergency preparedness tools to save lives.

Thanks to Congress, working together in bipartisan fashion, we can now also add to that list a nationwide public-health infrastructure that is expanding to promote prevention and improve quality of life for those living with Alzheimer's.

Alzheimer's poses a significant threat to our nation, killing more people than breast and prostate cancer combined. Alzheimer's is the sixth-leading cause of death in the United States, devastating more than 5 million Americans currently living with the disease, as well as their more than 16 million unpaid caregivers.

The Alzheimer's Association estimates that these unpaid caregivers provided 18.4 billion hours of care valued at over $232 billion in 2017. Equally as staggering is the financial burden Alzheimer's places on American society, with the direct costs of caring for those with the disease totalling $277 billion in 2018 alone. Unless something is done, the Association projects those costs could rise as high as $1.1 trillion by 2050.

But now, thanks to the BOLD Infrastructure for Alzheimer's Act, millions across America have reason to be hopeful.

By creating a modern public-health infrastructure, the new law will help: improve early detection and diagnosis; reduce both health disparities and risks associated with avoidable hospitalisations and cognitive decline; enhance support to meet needs of caregivers; and support care planning and management.

To help develop this infrastructure, the BOLD Infrastructure for Alzheimer's Act authorises $100 million over five years to accomplish three critical initiatives:

1. Establish Alzheimer's Disease and Related Dementias Public Health Centers of Excellence across the country. These Centers of Excellence will increase the education of public health officials, health care professionals, and the public on Alzheimer's, brain health, and health disparities. The Centers will also provide technical assistance to public health departments across the country in implementing effective Alzheimer's interventions and expand innovative public-private partnerships that focus on addressing the cognitive impairment and health disparities.

2. Award funding to State, local and tribal public health departments to implement Alzheimer's public health interventions focused on priorities like increasing early detection and diagnosis, reducing the risk of cognitive decline and preventing avoidable hospitalisations. This funding will also help public health departments implement strategic actions like those identified in the Healthy Brain Initiative's Public Health Road Map.

Image: © William Perry | Dreamstime.com

3. Increase the analysis and timely public reporting of data on Alzheimer's, cognitive decline, caregiving, and health disparities. This data is critical to identifying opportunities for public health interventions, helping stakeholders track progress in the public health response, and enabling state and federal policymakers to make informed decisions when developing plans and policies.

> "Thanks to Congress, working together in bipartisan fashion, we can now also add to that list a nationwide public-health infrastructure that is expanding to promote prevention and improve quality of life for those living with Alzheimer's."

While the CDC is preparing for the Act's implementation, determinations on awards for the Centers of Excellence and public health departments cannot happen until the Centers receive the FY20 funds appropriated by Congress.

That timing will depend on the appropriations process in Congress this year, but it is likely CDC funding will be awarded and allocated in 2020. In the meantime, the Alzheimer's Association – working through its advocacy arm, the Alzheimer's Impact Movement – is continuing to work with allies in Congress and across the country to ensure these initiatives are implemented as quickly as possible.

The sooner we can apply the public-health approach necessary for reducing risk, detecting early symptoms, and supporting caregivers, the sooner we can reverse Alzheimer's devastating trajectory. ■

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Towards Precision Oncology in Breast Cancer: Predicting Response to Neoadjuvant Chemotherapy Using Tumor Vasculature Characteristics

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Breast cancer is a model disease in precision oncology, leading the way in the development of both targeted therapy and prognostic and predictive biomarkers. However, predictive biomarker based treatment selection remains an elusive goal in the management of many women with this disease. Our group has developed a modeling tool to predict the likelihood of response to neoadjuvant chemotherapy using patient specific tumor vasculature biomarkers. Here, we describe a novel integrated study based on a mathematical model utilizing tumor vasculature characteristics paired with patient data analysis to predict response to neoadjuvant chemotherapy in women with high risk hormone receptor positive, HER2 negative early stage breast cancer.

We have pioneered a semi-automated analysis method that allows for increased measurement accuracy and rapid throughput in rendering model predictions, with hundreds images analyzed for each patient (Figure 1). First, we applied a histology-based model to primary resected breast cancer tumors. Second, we then evaluated a cohort of patients undergoing neoadjuvant chemotherapy, collecting

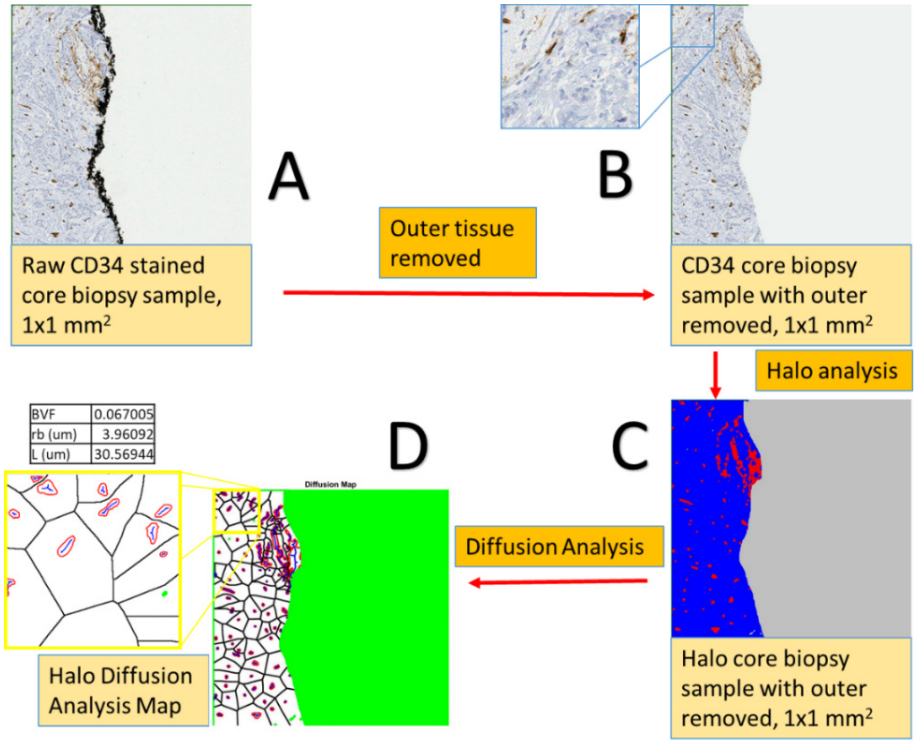

Fig. 1. Diffusion analysis workflow. **A)** *Shows the original CD34 (tumor vasculature) stained histology grid before any processing.* **B)** *Displays the same tissue region as in A, but with the outer inked portion removed due to the increased likelihood of false positives on the perimeter of core biopsy samples.* **C)** *Demonstrates a computerized version of B and differentiates between tissue CD34- (blue), vasculature CD34+ (red), and non-tissue regions (grey).* **D)** *Shows the diffusion analysis of image C, which was performed by code developed in Matlab. Parameters measured are: vessel radius (r_b), blood volume fraction (BVF), and diffusion distance (L). Vessels are outlined in red, and total area of blood vessels in a tissue region is blood volume fraction, BVF. Radius of blood vessels which are measured at each blue point inside of a vessel (outlined in red). An average of all vessel radii in each image analyzed is taken to be r_b (μm). The farthest distance nutrients or drug need to travel from a vessel to reach all tissue, the distance from that point to vessel in red is measured at each point in black, all distances averaged is the diffusion penetration distance, L, measured in μm. White is the tumor tissue region, all of which is considered for analysis. Green is the background/non-tissue region not considered for analysis.*

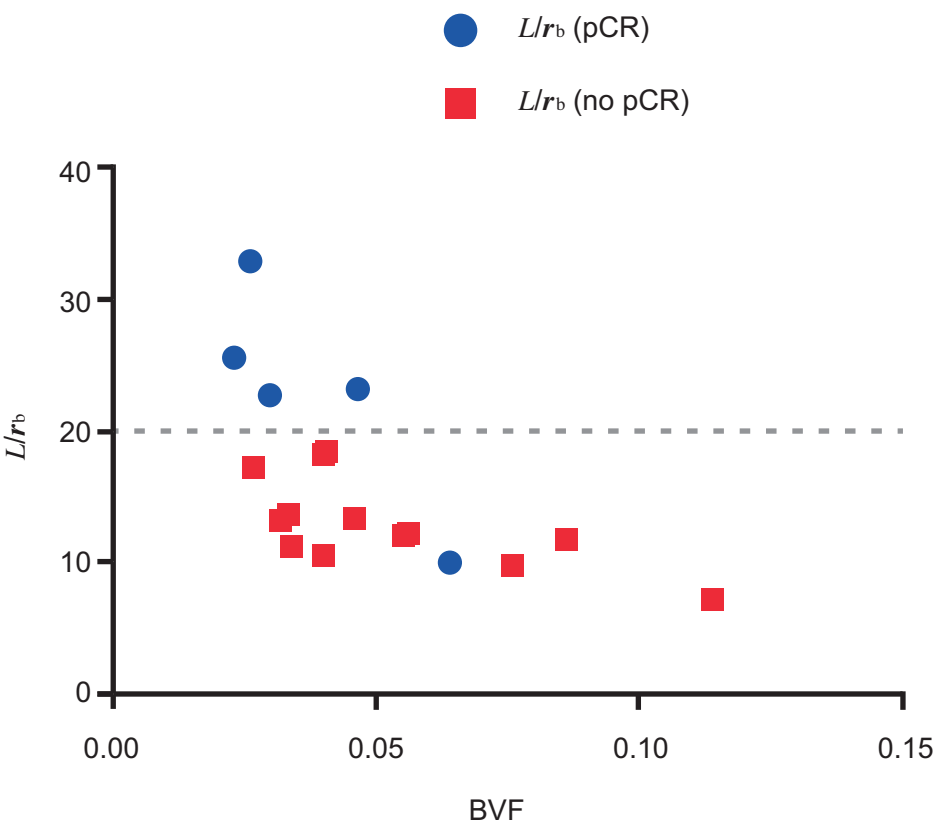

Fig. 2. Histological parameters and their correlation. pCR and L/r_b demonstrate a positive correlation. Dashed grey line separates patient groups with 80% accuracy.

clinically relevant data including pre- and post-treatment pathology specimens, and dynamic contrast-enhanced magnetic resonance imaging. We correlated predicted outcome based on our model with actual clinical outcome, including rate of complete pathologic response (pCR) following neoadjuvant chemotherapy. We found that core biopsy samples of primary breast tumors can be used with acceptable accuracy to determine histological parameters representative of the whole tissue region. We further correlated response to neoadjuvant chemotherapy with the pretreatment tumor vasculature biomarkers and model parameters. Analysis of histology parameters, specifically radius of drug source divided by diffusion penetration distance (L/r_b), a normalization penetration distance, and blood volume fraction (BVF), provides a separation of patients obtaining a pathologic complete response (pCR) and those that do not, with 80% accuracy (P = 0.0269) (Figure 2). With this predictive model, we are able to evaluate primary breast tumor vasculature biomarkers in a patient specific manner, thereby allowing a precision approach to breast cancer treatment.

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Supporting vital Alzheimer's disease research in the U.S and beyond

The work of the National Institute on Aging (NIA) is placed into focus here, with examples of how they are supporting vital Alzheimer's disease research in the U.S and further afield

National Institute on Aging (NIA) is one of the 27 Institutes and Centers of the National Institutes of Health (NIH) in the United States (U.S.). Their work concerns the leading, "a broad scientific effort to understand the nature of ageing and to extend the healthy, active years of life". [1] As a primary Federal agency, the National Institute on Aging supports and conducts Alzheimer's disease research.

When it comes to research on ageing and the health and well-being of older people, the Institute aims to understand the nature of ageing and the process, as well as the diseases and conditions associated with growing older, so that the healthy, active years of life can be extended. The Institute's mission can be summed up as follows:

- Supporting and conducting biological, clinical, genetic, behavioural, social, and economic research on ageing.
- Fostering the development of research and clinician scientists in the field of ageing.
- Providing resources for research.
- Disseminating information on ageing and advances in research to healthcare professionals, the public, and the scientific community.

In addition, we know that NIA pursues their mission by funding extramural research at medical centres and universities throughout the U.S. and further afield; maintaining an active communication and outreach programme; and conducting research at NIA laboratories in Bethesda and, Baltimore, Maryland. [2]

Alzheimer's disease research

Looking at one aspect of the Institute's work, it's worth noting that Alzheimer's disease is a progressive brain disorder that gradually slowly destroys both memory and thinking skills and, eventually, the ability to carry out the simplest tasks, and as such is irreversible. It is the most common cause of dementia in older adults and while it is more common as people grow older, it's not a normal aspect of ageing according to the Institute. [3]

In recent research news, we find out that researchers have been able to map how Alzheimer's pathology spreads across brain networks. Recent advances in genetic biomarker research and neuroimaging and genetic biomarker research have enabled scientists to identify two proteins, tau and beta-amyloid, which are hallmarks of Alzheimer's accumulating in the brain over a period of time. It was also discovered that the patterns of tau and beta-amyloid accumulation were related to specific genetic profiles, which helps us to much better understand Alzheimer's disease risk and possible new avenues for monitoring and diagnosis and monitoring of the disease, in this fitting example of NIA-supported research. [4]

In other topical research news, we learn that taking part in the arts could improve the health, well-being, and independence of older adults. Some specific example identified here include singing group programmes, theatre training, and visual arts for older adults. Lisa Onken, PhD, of NIA's Division of Behavioral and Social Research, shares her thoughts on this most interesting piece of research in her own words.

"Researchers are highly interested in examining if and how participating in arts activities may be linked to improving cognitive function and memory and improving self-esteem and well-being. Scientists are also interested in studying how music can be used to reduce behavioural symptoms of dementia, such as

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stress, aggression, agitation, and apathy, as well as promoting social interaction, which has multiple psychosocial benefits."

Picking up on the point about singing programmes identified earlier in this article, it's interesting to note that in the view of Julene K. Johnson, PhD, of the University of California, San Francisco School of Nursing: "There's a pressing need to develop novel, sustainable, and cost-effective approaches to improve the lives of older adults. Singing in a community choir may be a unique approach to promote the health of diverse older adults by helping them remain active and engaged. It may even reduce health disparities."

Those who took part in the community choir showed positive results within six months, in particular, it increased interest in life and reduced feelings of loneliness. "The study showed increased interest in life because singing in the choir provided a regular, structured activity for participants," notes Dr Johnson. "Access to regular activities in diverse, low-income communities is vital for older adults to remain active and engaged in their community." Looking ahead, we know that NIA is addressing the need for more rigorous research that can demonstrate the efficacy and cost advantage of interventions when it comes to the arts. [5]

In closing, I hope that the examples here demonstrate NIA's endeavour to lead on scientific efforts, for example, around Alzheimer's disease research, to understand the nature of ageing and to further the healthy, active years of life for older adults. ■

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Huntington's disease (HD): Is there hope on the horizon?

Dr Gerry Morrow shares his thoughts on the rare, progressive neurodegenerative illness, Huntington's disease (HD)

Few people predicted a cure for the rare, progressive neurodegenerative illness Huntington's disease (HD). It is one of a range of pathologies caused by multiple repeating three base sequences. Specifically, HD is an autosomal dominant disease caused by an expanded CAG repeat in the first exon of the huntingtin gene (HTT) on chromosome 4. HTT is vital to the viability of neurons. In HD, mutant HTT (mHTT) aggregates in neurons leading to the expression of long glutamine tracts, a cellular proteinopathy, which ultimately causes cell death predominantly in the striatum and cortex of the brain.[1]

Sufferers undergo progressive neurocognitive and psychiatric sequelae, including behavioural and mood changes, movement deficits, choreiform movements and ultimately death.[2]

Age of disease onset is inversely proportional to the length of the CAG repeat meaning that people with a higher burden of CAG repeats are diagnosed under the age of 20, defined as juvenile Huntington's disease. Juvenile HD is invariably more severe, and usually fatal within 20 years of diagnosis. Juvenile HD often presents with parkinsonian type rigidity, dystonia and bradykinesia, seizures and declining educational attainment.[3]

The prevalence of HD is approximately 10 per 100,000, meaning that in the UK there are approximately 6,200 patients living with HD. Of these roughly 5% have juvenile HD, which translates as approximately 300 patients under the age of 20 years.

The diagnosis of HD is made on clinical grounds using the Unified Huntington Disease Rating Scale and subsequent genetic testing.[4]

Previous efforts to treat HD focussed on the pathophysiological pathway with the aim of developing therapies to ameliorate symptoms. Sadly, these have met with limited success.[5] The current focus of research is on a disease modification approach, with the prospect of halting the decline and a potential cure.

Given that the underlying pathology is ascribed to a gene fault, researchers have seized on the possibility of either reducing the volume of mHTT circulating in the cerebrospinal fluid or even preventing the production of mHTT at source.

"The prevalence of HD is approximately 10 per 100,000, meaning that in the UK there are approximately 6,200 patients living with HD. Of these roughly 5% have juvenile HD, which translates as approximately 300 patients under the age of 20 years."

The first of these approaches has reached the phase 3 stage of a clinical trial with a medication called RG6042, which is an investigative antisense oligonucleotide treatment. RG6042 is a complementary molecule to HTT mRNA, which binds to the mRNA and signals protein destruction. Patients in this planned randomised controlled trial will have regular intrathecal administration of the RG6042 medication for two years.

Results from previous trial phases of 46 adults with early-stage Huntington's demonstrated a reduction of mHTT in cerebrospinal fluid (CSF) by up to 60%. This difference corresponds to an estimated 55% to 85% reduction of mHTT in the brain cortex and 20% to 50% in the caudate (a deep region) of the brain.[6] Reducing mHTT should translate into a commensurate reduction in disease impact in HD.

The second option entails a technique called gene silencing. Gene silencing of mHTT involves epigenetic modification of the expression of the mHTT gene. This

Dr Gerry Morrow

leads to inactivation of the mechanism of toxic proteins, which cause the death of neurons. This therapy then prevents the manufacture of abnormal HTT protein.

A gene-silencing treatment called AMT-130 is at an early stage of development. AMT-130 is an artificial microRNA, which targets HTT mRNA. Early results demonstrate effectiveness in animal models of the widespread localisation of AMT-130 in the brain and spinal cord, following a single injection. Phase 1 and 2 studies of this therapy are about to commence shortly.

These interventions of destroying abnormal genetic material and gene silencing, offer the prospect of a perspective shift towards the prospect of cure and that there may be hope on the horizon for patients and families of people with HD. ■

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Providing a path to advanced degrees in biomedical fields

The NYU Sackler Institute of Graduate Biomedical Sciences aims to train the next generation of scientists to make breakthroughs and advances in society at large, explains Naoko Tanese

Becoming an accomplished researcher requires an inquisitive mind and perseverance. It calls for hands-on research experience and active mentorship. Sackler students receive rigorous training to become independent scientists. We also instil in them a strong sense of social and ethical responsibility through interactions with our diverse research community.

PhD programme

Students matriculating at NYU Sackler Institute of Graduate Biomedical Sciences begin their training in an Open Program. While some students enter graduate school with a speciality in mind, in the Open Program students are encouraged to explore multiple fields. First-years wait to select a training discipline until they have taken several courses, completed two or three laboratory rotations, and selected a faculty mentor for their PhD thesis work. They have a full year to make final decisions.

We recently expanded the scope of our program to include new training tracks in Biomaterials Science, Biostatistics, and Epidemiology, in addition to all of the existing traditional disciplines in biomedical sciences. As we recruit students interested in the new tracks, we are faced with balancing the unique background of each student with the spirit of the Open Program. How can the curriculum of an Open Program satisfy students with varying interests and backgrounds?

To address this challenge all incoming students are required to take the course Introduction to Research, which starts immediately after Orientation with an immersive lab experience called Research Adventure. The Introduction to Research course is intended to not only help incoming students begin graduate school with the same basic knowledge, but also to provide them with a sense of community.

The Research Adventure is an intensive, week-long, hands-on research experience, where students working in a team carry out a structured project in a faculty's lab on a topic different from their previous research. This exposes them to new possibilities that perhaps they may not have considered. We continue to evaluate best practices to keep the spirit of the Open Program alive while accommodating the different interests and backgrounds of our matriculating students.

Career

In higher education, there is an increasing trend for PhD students to pursue alternative careers (non-academic positions). For this reason, we strive to prepare them for any career. We emphasise how PhD training teaches students to be critical thinkers, problem solvers, productive team members, collaborators, independent workers, and effective leaders. These are qualities useful to any career path.

NYU's centre for career development offers services such as resume and cover letter preparation as well as networking and interviewing practice sessions. Students participate in many job and internship fairs. We also invite alumni back to give career talks and meet with students to discuss their experiences.

Our students also take advantage of a variety of workshops and courses offered by the postdoctoral affairs office. To improve their career training, they actively engage in career planning while assessing their personal values and translating them to individual goals. They are introduced to all the diverse career opportunities outside of academic research. For those interested in teaching, students learn how to design and implement courses both at the college and post-graduate level. Communication is another skill critical to any career. We host workshops and seminars to help our students with their communication skills, both written and oral, to a variety of audiences.

Inspiring the next generation

The future of our society depends on training the next generation of highly capable scientific workforce. For this

Participants of the Sackler Institute's Summer Undergraduate Research Program

reason, we place a great deal of effort in mentoring young people interested in pursuing careers in science. We are increasingly wary of losing students' interests in STEM – Science, Technology, Engineering, and Mathematics. We are also concerned that not enough young people from diverse backgrounds are entering the STEM field. The current makeup of scientists in biomedical fields does not reflect the composition of the US population.

Numerous studies have reported the benefits of a diverse research community in advancing scientific endeavours. We are committed to making this happen by reaching out to students from diverse racial, ethnic, and socioeconomic backgrounds. One mechanism that has been in place at the Sackler Institute is our Summer Undergraduate Research Program (SURP).

Established in 1990, the SURP has been one of the cornerstones of minority recruitment for MD, PhD, and MD/PhD programs. The purpose of SURP is to give students who have the interest in biomedical sciences an opportunity to conduct research at a major medical centre. Over 700 students have participated in this program and >95% of the participants subsequently entered graduate or professional degree programs. We make an effort to provide a supportive community where students from all backgrounds feel at home. This is critical to our mission to promote diversity and inclusion at the Sackler Institute.

In many ways, STEM training needs to start earlier than college. We have been reaching out to students in nearby high schools to introduce them to scientific research. It's never too early to show them what it's like to be a grown-up scientist. We have visited local schools to give presentations and met one-on-one with young students. We have invited them to research laboratories to observe scientists at work, and in some cases perform experiments as student interns.

Ambitious and determined students commit to commuting long distances for these hard-to-find opportunities to satisfy their curiosity and challenge themselves to unfamiliar but exciting tasks. Some students never give up looking for a chance to enter research labs. This makes it worthwhile to mentor and see them thrive in a new environment. Scientific discoveries are made by following one's passion. We are here to inspire young people to find their passion in the biomedical sciences.

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U.S. research on deafness and communication disorders

The National Institute on Deafness and Other Communication Disorders charts the work of their organisation over the last 30 years that concerns research around the communication sciences, including deafness

Over thirty years ago, in 1988, President Ronald Reagan signed P.L. 100-553 into law, establishing the National Institute on Deafness and Other Communication Disorders (NIDCD) as a new institute within the National Institutes of Health (NIH).

Until that time, research on communication sciences had been supported by the NIH through the National Institute of Neurological and Communicative Disorders and Stroke (now the National Institute of Neurological Disorders and Stroke). Individuals with hearing loss, researchers, clinicians, and professional societies worked together to advocate Congress to authorise a new institute at NIH.

For just over 30 years, the NIDCD has brought national attention to disorders involving hearing, balance, taste, smell, voice, speech, and language. NIDCD contributes to advances in biomedical and behavioural research that improve the lives of the millions of people with these disorders.

Hearing and balance

Hearing loss and balance dysfunction can occur at any age and can affect communication, safety, and quality of life. The NIDCD's robust program of basic and clinical research on hearing and balance includes genetics, genomics, and proteomics. This research focuses, in part, on the identification of genes involved in hearing loss, which can lead to earlier diagnosis and treatment, and to new therapies.

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

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

2018 also coincided with the 10th anniversary of NIDCD's It's a Noisy Planet, Protect Their Hearing.® health education campaign, aimed at increasing awareness of noise-induced hearing loss (NIHL) and how to prevent it. NIHL can happen to people at any age, so the campaign teaches kids and their parents and educators three key messages – turn down the volume, move away from the noise, and wear hearing protectors, such as earplugs and earmuffs.

Balance disorders can be quite disabling, impairing mobility and often leading to falls. NIDCD-supported scientists are examining how the brain interprets information from the ear's vestibular organ. NIDCD clinical researchers are also developing rehabilitation procedures and prosthetic devices to improve the quality of life for individuals with balance disorders.

Taste and smell – the chemical senses

NIDCD-supported research helps us understand how our senses of taste and smell relate to our health and well-being and allow us to interact with our environ-

Image: © Geraldine Dietz Fox, personal communication

Geraldine Dietz Fox, a patient advocate, testifies in support of the NIDCD in the institute's early years. Ms Fox was instrumental in the establishment of the institute

ment. NIDCD-funded scientists study many aspects of taste and smell, from how we first detect odours and tastes through sensory cells in the nose and taste buds in the tongue and mouth to how the brain regions involved in the central processing of incoming taste and smell information function. Scientists are also working to better understand how taste and smell sensory cells are regenerated or replaced across the lifespan by underlying stem cells. These studies may someday help scientists develop ways to restore the loss of taste and smell due to chemotherapy, ageing, injury, or disease.

The NIDCD encourages clinical research to improve the diagnosis, prevention, and treatment of taste and smell disorders in all age groups. More clinical and epidemiological studies will help us better understand how factors such as nutrition, early dietary experiences, individual genetic variation, ageing, infection, and disease affect chemosensory sensitivities and taste and smell disorders.

Voice, speech, and language

NIDCD research is leading to improved identification and treatment of voice, speech, and language disorders such as spasmodic dysphonia, stuttering, and specific language impairment (SLI). In addition, scientists continue to identify genes responsible for persistent stuttering, which may be inherited from family members.

Other ongoing research is focused on ways to improve communication in children with autism spectrum disorder (ASD), including the 25 to 30% of children with ASD who remain functionally non-verbal beyond age five.

NIDCD-supported research also addresses voice, speech, and language impairments linked to injury, stroke, and neurodegenerative disorders. These communication problems – such as aphasia, dysarthria, and apraxia – often lead to increased isolation and poor quality of life.

Future directions

As we head toward new frontiers in scientific discovery and precision medicine, the NIDCD is well-positioned to support innovative studies to produce more sensitive, effective, and individually tailored interventions. NIDCD-supported researchers are dedicated to expanding our understanding of the normal processes of hearing, balance, taste, smell, voice, speech, and language and improving rehabilitation strategies for children and adults who face the challenges of communication disorders.

About the National Institute on Deafness and Other Communication Disorders (NIDCD)

NIDCD supports and conducts research and research training on the normal and disordered processes of hearing, balance, taste, smell, voice, speech, and language and provides health information, based upon scientific discovery, to the public.

About the National Institutes of Health (NIH)

NIH, the U.S.'s medical research agency, includes 27 institutes and centres and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. ■

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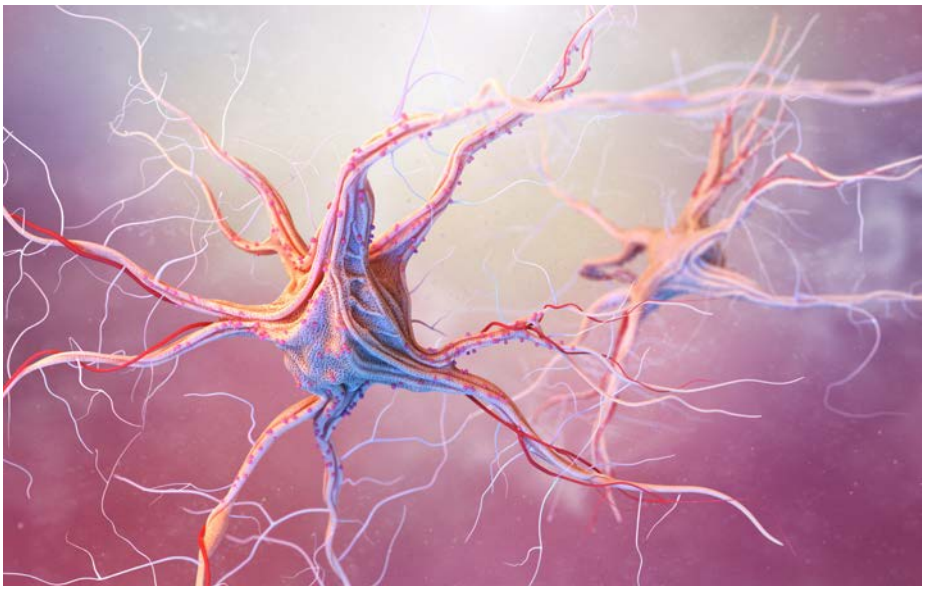
Complexity of neurotrophin signalling in the nervous system

Momoko Takahashi, a Doctoral Student at Northwestern University, explains the complex research of neurotrophin signalling in the nervous system in this report

Ever since Rita Levi-Montalcini, Stanley Cohen, and Viktor Hamburger discovered the first neurotrophin over a half-century ago,[1,2] scientists have continuously worked on characterising this class of proteins, its receptors, and its signalling pathways. What has been revealed is that the complexity of neurotrophin actions are immense; not only do neurotrophins determine the fate of brain cells, known as neurons, they also regulate proliferation, survival, differentiation, migration and neuronal death[3]. Neurotrophins behave differently depending on their location in the nervous system, developmental time period, and species of animal,[4] acting on a multitude of key biological pathways and functions.[5]

Three primary neurotrophins and their corresponding receptors are known today. They are nerve growth factor (NGF) and its receptor, tyrosine receptor kinase A (TrkA), brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase B (TrkB), and neurotrophin-3 (NT-3) and its receptor, tyrosine receptor kinase C (TrkC).[6–12] However, due to the lack of available pharmacological tools, as well as discovery order, the literature on the actions of NT-3/TrkC signalling is less when compared to the other neurotrophins.

The literature that does exist, however, tells a complex story regarding the function of NT-3/TrkC signalling.



Research shows that TrkC induces cell death without NT-3 activation,[4,13] implicating alternate signalling pathway that involves TrkC but not NT-3. Complicating matters more is the fact that TrkC also has multiple isoforms with each behaving differently.[14] Despite these obstacles, recent research strongly suggests that NT-3/TrkC pathway deserves to be studied not only because of its biological, but also clinical significance,[15,16] especially in terms of neurological diseases and the advent of pluripotent stem cells.[17–20] In this research profile, we briefly describe areas of established research in the brain, as well as highlighting mechanisms of NT-3/TrkC signalling in the auditory system – an area of interest for our laboratory.

The hippocampus

In the hippocampus, where neuronal plasticity is heavily dependent on neurogenesis and differentiation to integrate into neural networks,[21] the NT-3/TrkC signalling pathway plays an active role in maintaining network architecture. Learning and memory are reliant on this; animals that lack NT-3/TrkC signalling have deficits in memory tasks.[22] It was recently discovered that NT-3/TrkC also facilitates synaptogenesis by interacting with a molecule known as PTPσ.[23–27] This was a novel discovery because the classical model argues that Trk receptors interact only with neurotrophins. At the cellular level, the story becomes more complex. Injecting NT-3 into hippocampus neurons permits signals to travel backwards from the axon to the cell body.[28] This phenomenon, called retrograde axonal transport, indicates a continued targeted effect in the cell body of neurons, a site where multiple survival-promoting effects are initiated. Not only does the NT-3/TrkC

pathway promote axonal transport, but it also regulates the location of the axon initial segment, altering neuronal excitability and action potential dynamics.[29]

The cerebellum and Purkinje cells

In the cerebellum, the unique and large dendritic architecture of Purkinje cells shed an interesting light onto NT-3/TrkC signalling. With the genetic deletion of TrkC, elaborate dendritic arborisation of Purkinje cells is minimal; however, the fact that dendritic structure is not entirely eliminated suggests that NT-3/TrkC signalling plays another role in dendritic maintenance. Removal of endogenous NT-3 alleviated the reduction of dendritic arborisation, indicating that the NT-3/TrkC pathway controls the neighbouring neuron's dendrite structure in order to maintain a particular density of dendritic architecture within this specific brain region.[30–32]

The auditory system

Several lines of research suggest that the auditory system is dependent on neurotrophin signalling for its proper function and the field of auditory neural science can yield a wealth of knowledge if delved further. Still, the study of NT-3/TrkC signalling in the auditory system can also be a complex endeavour, in part due to the topological gradients of TrkB and TrkC that coexist in same brain regions. For example, the chicken auditory system shows an interesting developmental pattern that is reliant on both Trk receptors.[8] However, a global genetic deletion of either protein can be fatal to the animal, and therefore, methods like the one reviewed in our previous research profile – e.g., focal gene manipulation via *in ovo* electroporation – must be used to further elucidate its functions (please see Open Access Government, January 2019 issue, pages 130-33).

In terms of auditory functions, NT-3/TrkC does several crucial things. It plays a role in regulating action potential properties of auditory neurons in the peripheral pathway;[33] our laboratory has discovered that this happens in the central system as well. Here, neurotrophin signalling regulates action potential kinetics by maintaining a balance between different types of potassium channels.[34] We suggest that this function is critical in establishing normal tonotopic gradients, a biological process required for the neural encoding of different sound frequencies. Similarly, NT-3/TrkC signalling modifies potassium conductance of inner hair cells in guinea pigs, depressing responses and permitting repetitive action potential firing.[35] It also increases calcium currents in the chicken inner ear, promoting more efficient synaptic transmission[36] and in mice, it is involved in synaptic maintenance and neuronal migration of the auditory nerve.[6]

With respect to hearing, correct levels of NT-3/TrkC signalling is required to maintain inner ear health. For example, NT-3 induces synapse regeneration in the inner ear and can repair synapses after acoustic trauma in mice.[15] Similarly, overexpressing NT-3 protects inner ear synapses by promoting its repair after noise-induced synaptopathy in guinea pigs.[37] Conversely, excessive levels of NT-3 in the inner ear can also disrupt the synaptic network of the same species and therefore, negatively affect hearing properties.[38] This suggests that the inner ear requires just the right amount of NT-3 in order for TrkC signalling to be effective in maintaining normal hearing health.

What does this all mean? Few things can be assumed from studies in both normal and abnormal NT-3/TrkC signalling. One conclusion is that due to its ubiquitous presence, a careful study of NT-3/TrkC temporal and spatial expression is necessary before embarking on clinical applications. Nevertheless, research studies in the brain and auditory system suggest that targeting the NT-3/TrkC pathway shows promise as a non-invasive and effective method to treat neurological and auditory ailments.

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Health research: Applying genome technologies to the study of disease

In this interview, Dr Carolyn M. Hutter, PhD, Director, Division of Genome Sciences at the National Human Genome Research Institute (NHGRI) outlines the important role of research when it comes to applying genome technologies to studying disease

On 25th April 2019, National DNA Day celebrates the 66th anniversary of the discovery of DNA's double helix and the 16th anniversary of the completion of the Human Genome Project (HGP). To mark this important anniversary, we spoke to Dr Carolyn M. Hutter, PhD, Director, Division of Genome Sciences at the National Human Genome Research Institute (NHGRI) within the National Institutes of Health (NIH), to learn more about their excellent work, including their role in applying genome technologies to the study of human health and disease. Genomics is a wide-ranging area and this interview covers some fascinating aspects of this, including understanding variation in the human genome and improving human health through genomics research.

By way of background, the NHGRI grew out of the international HGP project. Since the formation of NHGRI in 1997, the Institute has expanded in terms of what they do. Carolyn tells us that NHGRI is guided by a series of strategic plans, the most recent of which was published in 2011 and focuses on thinking about research from the bench to the bedside. She explains this point further, describing the ambitions of the Institute in her own words.

"We continually study everything from the structure of genomes all the way through to the application of genomics in clinical settings. At the moment, we are starting new strategic planning for our Genome 2020 vision. We kicked this off in February 2018 and are planning to have finished in October 2020 which marks the 30th anniversary of the start of the HGP.

"The Institute is part of the National Institutes of Health (NIH), one of the 27 Institutes and Centers within NIH, and our remit is centred around how we use genomics to understand human health. NHGRI doesn't fund all genomics but we consider ourselves to be at the forefront of the field. We recognise that other parts of the NIH are increasingly funding genomics and we collaborate with these groups and a number of international partners."

The Human Genome Project (HGP): From basic to clinical science

With the human genome sequence complete since April 2003, Carolyn then details the various ways in which scientists around the world have benefitted from this in the years since. This goes from basic through to clinical science in terms of how we think about things when it comes to genomics. She says that some argue that the HGP has not yet been completed because we do not yet have full sequencing for very complex areas of the genome. Carolyn then develops this thought further.

"The completion of the HGP really provided this initial backbone for that a much more specific sequencing and understanding of the structure on which of the human genome can be built on. It allows a blueprint upon which all of these other activities can happen. One of these is driving the technology and the innovation needed to sequence genomes, including the complex regions, faster, cheaper and more accurately. Those are the three things that we are always looking for in this area.

"You can also think about what it really means to understand the genome, including 3D or 4D structure of genomes. Another example is projects like The ENCODE Project: ENCyclopedia Of DNA Elements, which are addressing the fact that we have not fully understood what all the genes are doing, or what all the non-coding parts of the genome doing? How do we catalogue them, start to elucidate their function, and put together pieces of that whole picture?"

Understanding variation in the human genome

Carolyn says that you can then layer on top of that additional questions, such as can we understand the variation in the genome? Or what does the variation of the genome tell us about population genetics and population structure or about the relationship between the variation in the genome and disease? She then provides more detail to us about this compelling point in her own words.

"As we start to understand the variation of the genome in relation to disease, we need to move from just saying that a part of the genome is associated with the disease to understanding the causal relationships and

the mechanisms. How do we go from understanding this part of the genome is associated with the disease to translate that into ways that can benefit public health and clinical medicine?"

Improving human health through genomics research

The interview then turns to look at on interesting examples of NHGRI's work to improve the health of all humans through advances in genomics research. Carolyn stresses that their focus as an Institute is on the technologies, methods and resources to move the field of genomics forward. Although NHGRI does not have a disease focus, they do participate in exemplary disease-focused projects. As an example, they partnered with the National Cancer Institute (NCI), another branch of the NIH in the U.S., on The Cancer Genome Atlas (TCGA). Carolyn noted the impact of that project on our understanding of cancer, before moving the conversation to detail more of NHGRI's research work and the priorities for the future in this vein.

"We have a number of Genomic Medicine programmes, such as the Clinical Sequencing Evidence-Generating Research (CSER) program that maps the impact of sequencing in clinical settings. Importantly, we are also building the basic understanding of the relationship between a genome and disease which is fundamentally needed to have an impact in clinical settings.

"Questions about the future priorities for genomics research and its applications to human health and disease are a key part of our Strategic Planning efforts, as mentioned above. We are really excited to have this opportunity to reach out into the community, through workshops and social media, for example, to get feedback. We have internally organised ourselves around key areas that cover basic genomics and technology, genomics of disease, genomic medicine and health, genomics and data science, and genomics in relation to education and societal issues. In all of these areas, we look forward to getting input over the next year and a half on what people see as important questions at the forefront of genomics, and to see what ideas and key areas move to the top.

"One of these key areas we have already identified is the question of how you go from variation to function to disease, and how to study this at scale in order to gain biological insight into the nature of inherited disease, insight into functional mechanisms, and ultimately to provide a rational foundation for clinical applications. We are also seeing a real need to further identify what types of genomics are ready to go into medicine and how do we effectively implement them to get there? We are also addressing how to bring together recent advances in computational biology and big data in an integrative way that allows for innovation in genomics. Important work in all of these areas is already happening, but we need to take these to the next level and draw on the exciting scientific findings that will come out of doing that type of effort well."

Accelerating scientific and medical breakthroughs to improve human health

In closing, Carolyn shares her thoughts on how to accelerate scientific and medical breakthroughs that improve human health. She noted that as a funder, NHGRI spends a lot of time thinking about their need for a really well-balanced portfolio. As such, NHGRI needs to make sure that activity is happening at the right level in all these aforementioned areas.

"Certainly, you don't want to go too far with investments in one specific area, because you never know where you are going to have the most important breakthroughs. This is especially true for a transdisciplinary area like genomics. In addition, we are constantly balancing the need to support fundamental resources and approaches, versus really high-risk approaches where it is less clear that they are going to pay off, but when they do a giant leap is made. Another area we consider is how best to balance large-scale collaborative research and consortia, versus investigator-initiated projects.

"It's important that we have balance in terms of what we are funding and what we are doing in order to enable the scientific advances and breakthroughs." ■

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The biology of "love": Lessons from prairie voles

Sue Carter, Director of The Kinsey Institute, discusses the fascinating nature of prairie voles and explains how they can teach us about the biology of "love"

In both nature and in the laboratory small field mice, called prairie voles form life-long social bonds. Males of this species are amazing parents involved in all aspects of care of the young except nursing. Males even help to "midwife" their partner's labour and help her cut the umbilical cord at birth. Extended families form around the original pair, as prairie vole fathers and then older offspring remain in the natal nest, scrupulously avoiding incest. Males and females are about the same size and they jointly defend their family and resources. Taken together biologists have called this set of behavioural and physical traits "monogamy."

The monogamy paradox

Because prairie vole pairs were sharing a nest and raising babies together, we initially assumed that they also were sexually monogamous. But when we tried to test this assumption, voles of both sexes did not cooperate – often mating with strangers. As DNA fingerprints became available, many prairie voles again failed the genetic tests for sexual monogamy. Similar findings emerged in other apparently monogamous mammals including humans, and most species of birds. Some individuals were sexually monogamous, but when viewed at the level of a species, sexual monogamy was rare or non-existent.

Given the opportunity, both male and female prairie voles were willing to have sex outside of the pair bond. However, once mating was complete, strangers or nonfamily members were often attacked. Like a reality TV show gone wrong, we discovered that male prairie voles were raising, as their own, babies fathered by other males. We slowly began to accept the notion that social attachments are real and have causes and consequences similar to what humans call "love."

"I hope we don't lose sight of one thing. It was all started by a mouse,"
(Walt Disney)

The term monogamy is derived from the Greek for a single wedding or ritual, and does not speak to sexual choices. Considered across the lifespan, many humans have more than one sexual partner. None of this is shocking. But we now understand that the traits of social monogamy are a kind of syndrome with shared neurobiological underpinnings. Our terminology had to be adjusted to admit that what we were observing was more accurately termed "social monogamy."

Hormonal ties that bind

Prairie vole families are bound together by invisible social bonds. As we searched for a mechanism for social monogamy, we found in both male and female voles that pair bonds were cemented by powerful molecules synthesized in the brain. These hormones were released by social experiences, including sexual interactions and even the presence of a baby. In turn these brain-derived chemicals regulate social engagement, pair bond formation and parental behaviour. In addition, following mating, aggression toward strangers increased, and behaviours that looked suspiciously like "jealousy" emerged. However, as might be expected protective aggression toward intruders is based on a somewhat different cocktail of hormones than those needed to create loving relationships between pairs or directed toward a baby.

Two molecules, oxytocin and vasopressin, made primarily in the brain are at the epicentre of social monogamy. However, it has taken decades and the help of prairie voles to untangle these relationships. These deceptively simple molecules are capable of binding to each other's receptors, creating various emotional states that support many behavioural permutations. In addition, oxytocin and vasopressin and their receptors are exquisitely sensitive to experience.

In fact, prairie voles are teaching us that the genes regulating receptors for oxytocin and vasopressin can be switched off or on across the life cycle. Life's most important experiences – sexual experiences, birth, the presence or absence of sensitive parenting, exposure to hormones in early life, extreme stress and traumas – are all "epigenetic" events regulated by

molecular changes with long lasting effects on the genome. This is one of several mechanisms through which the consequences of love protect us across our lifespans, and through which the absence of love leaves us vulnerable.

Love heals and allows us to be human

Studies of prairie voles, and comparisons to nonmonogamous mammals forced us to re-imagine concepts like monogamy and love. Selective attachments, and well as parenting, are supported by a comparatively simple brain and ancient neural and endocrine pathways. Human cognition, a complex nervous system or even gonadal hormones are not essential to allow pair bonds to form or infant nurture to emerge. However, in voles – as in humans – these are influenced by social context including fear, safety, and the emotional history of the individual.

Social behaviours, such as pair bonding and parenting, are hormonally-supported and interact with emotions that facilitate good health, a sense of safety and eventually health and survival. Furthermore, nature is conservative and the same hormones are used over and over again across the life cycle and in different species of mammals, where they support variations in social behaviour and aggression across species and individuals, as well as sex differences in behaviour.

Brain regions involved in pair bond formation and parenting also are shared with other forms of rewarding experiences, and with the neural pathways involved in drug addiction. The absence or loss of love creates vulnerability to substance abuse, depression and other forms of mental and physical illness. Knowledge of these relationships helps to explain why love is rewarding, but also can be addictive, and why the loss of a partner or loved one may be experienced as physical pain or illness.

The biology of "love" is intertwined with the biology of reproduction and basic survival in a dangerous world. This is true of both voles and humans. Love and its consequences operate largely below the level of human consciousness. However, prairie voles have taught us that love is constructed from biological mechanisms that are shared with other mammals. Using insights from prairie voles, we are discovering that the same molecules that support love facilitated human evolution, now allow us to survive and thrive, help create culture, and may even help to explain how and why "love is good medicine."

Suggested reading

Oxytocin pathways and the evolution of human behavior. 2014
https://www.ncbi.nlm.nih.gov/pubmed/24050183

The oxytocin-vasopressin pathway in the context of love and fear. 2017
https://www.ncbi.nlm.nih.gov/pubmed/?term=Carter+love+and+fear

The monogamy paradox: What do love and sex have to do with it? 2018
https://www.frontiersin.org/articles/10.3389/fevo.2018.00202/full

Early nurture epigenetically tunes the oxytocin receptor. 2019
https://www.sciencedirect.com/science/article/pii/S0306453018306103?via%3Dihub

Love as medicine. 2019
http://edition.pagesuite-professional.co.uk/html5/reader/production/default.aspx?pubname=&edid=14e30abb-c333-43f5-b63d-31e069aee049&pnum=182

https://biology.indiana.edu/about/faculty/carter-sue.html

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Progressing science in the U.S. – Enabling discoveries for understanding life

The work of the National Science Foundation (NSF) to advance science is charted here, with a focus on the work of their Directorate for Biological Sciences (BIO) in enabling discoveries for understanding life

The National Science Foundation (NSF) is an independent federal agency created back in 1950 by U.S. Congress, "to promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defence". We know that NSF is crucial because they support basic research and the people that do this to create knowledge that changes the future. [1] The number of research areas supported by the NSF is staggering and includes Biological Sciences (BIO), Education and Human Resources (HER), Geosciences (GEO), Mathematics and Physical Sciences (MPS) and Social, Behavioral and Economic Sciences (SBBE).

Directorate for Biological Sciences (BIO)

Looking at just one of these areas, let's take a look now at the mission of the Directorate for Biological Sciences (BIO) and some examples of the excellent work they support. In short, their work essentially enables discoveries for understanding life itself, indeed, BIO-supported research furthers the frontiers of knowledge when it comes to biology, as well as increasing the understanding of complex systems and supplying a theoretical basis for original research in numerous other disciplines of science.

Within the remit of BIO, research studies encompass biological molecules, communities, cells, organs, organisms, populations, tissues and ecosystems up to and incorporating the global biosphere. The website of BIO provides us with an excellent overview of the major challenges of reaching a coherent understanding of life itself.

"This challenge will require that knowledge about the structure and dynamics of individual biological units, networks, sub-systems and systems be compiled and connected from the molecular to the global level and across scales of time and space. Integral to all activities across the directorate is a commitment to integrate research and education, broaden participation, and promote international partnerships." [2]

In terms of the leadership, we find out that in February this year, the NSF selects D. Joanne Tornow to serve as Head of the Directorate for BIO. Her wealth of experience at NSF includes a focus on accountability, as well as supporting cross-disciplinary, convergent research that plays on the strengths of scientists and engineers to solve problems.

"Dr Tornow is an experienced manager who brings a wealth of knowledge to BIO and the NSF leadership team", says NSF Director France Córdova. "Joanne has spent the past year leading BIO in an acting capacity and has already demonstrated that this critical component of NSF is in good hands. I look forward to seeing BIO's progress under her leadership."

We know that exciting discoveries from NSF-funding include unearthing a new branch on the tree of life with archaea, the revolutionary CRISPR genome editing tool, as well as advancing other scientific areas, and enhancing other fields and making new ones.

"I fell in love with biology in the ninth grade and have been a biologist ever since. I have a long history with the BIO directorate, a place that was my first home at NSF and one of my favourite places to work," Tornow comments. "I am honoured to lead BIO at a particularly exciting time of discovery across the spectrum of the biological sciences." [3]

There are a number of interesting examples of how this support for the biological sciences is being given in terms of projects funded. One is led by University at Buffalo physicist Andrea Markelz who reports the development of a method for rapidly measuring proteins' unique vibrations. [4] By way of background, we know that proteins vibrate with microscopic motions that help them perform essential tasks like photosynthesis and from cell repair, which is true for the cells of every living organism – humans, bees, birds, roses and even bacteria.

> "Within the remit of BIO, research studies encompass biological molecules, communities, cells, organs, organisms, populations, tissues and ecosystems up to and incorporating the global biosphere. The website of BIO provides us with an excellent overview of the major challenges of reaching a coherent understanding of life itself."

New possibilities in biological research could occur, such as studying the microscopic motions of proteins in a more efficient way. The new technique could enable scientists to quickly assess whether pharmaceuticals designed to inhibit a protein's vibrations are working. "Proteins are elegant and robust nanomachines that nature has developed", explains Markelz, PhD, at the UB College of Arts and Sciences. "We know nature uses molecular motions to optimise these machines. By learning the underlying principles of this optimisation, we can develop new biotechnology for medicine, energy harvesting and even electronics." [5]

There are so many other interesting examples of research funded this year, including a study which reveals the way in which a group of deep-sea microbes gives clues to the evolution of life on Earth, according to a paper in the ISME Journal. [6] Another example comes from Rice University and concerns protein signalling in the rapidly differentiating cells of embryos, which are believed to be more complex than previously thought. [7]

In closing, it's amazing to think that the scope of this article only covers a fraction of the NSF's wonderful work. If we think about the wider picture, we know that in fiscal year (FY) 2019, the NSF's budget totals $8.1 billion. Add to this, the fact this funding reaches all 50 states of the U.S. to almost 2,000 universities, colleges and other respectable institutions. Every year, over 50,000 competitive proposals for funding are received by the NSF. 12,000 new funding awards are made annually. Fundamental research and education across all fields of science and engineering, including the biological sciences is set to continue into the future. [8] ■

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Early detection of corneal disease with THz and millimetre wave frequency based thin film measurement techniques

THz and millimetre wave frequency techniques, combined with thin film measurement methods, provide early detection of corneal edema associated with disease in the view of Zachary Taylor, Assistant Professor at Aalto University

The adult human body is ~60% water. Tissue water content (TWC) varies from from 50%-80% depending on age, location on the body, physiologic state, and so on. Many diseases can perturb this fraction and medical research today has dedicated profound time and resources developing diagnostic systems, tools, and algorithms to detect and characterise these abnormal changes in TWC. A system familiar to many is magnetic resonance imaging (MRI), which uses precisely tuned magnetic fields and RF pulses to form volumetrically resolved maps of body water content. Brain tumour imaging, blood perfusion analysis, and spinal joint assessment are among the countless possibilities with MRI generated TWC maps. However, magnetic fields are difficult to characterize at boundaries between tissue and air, therefore, quantitative assessment of surface tissue water content is extremely difficult.

One important, water-rich, surface tissue system not currently accessible with MRI is the cornea. The cornea is the outer most layer of the human eye (Figure 1) and principally composed of collagen and water in mass fractions of ~ 21% and 79% respectively. The tough but optically transparent tissue protects the delicate structure of the eye from the outside environment and is responsible for the majority of the focusing power of the human optical system. The bottom layer of the cornea (endothelium) sits adjacent to a water volume called the aqueous humour (Figure 1). The role of the endothelium is to actively pump water from the cornea and back into the aqueous humour to maintain 79% water and, therefore, ensure optical clarity. Perturbations from the 79% water lead to significant vision degradation.

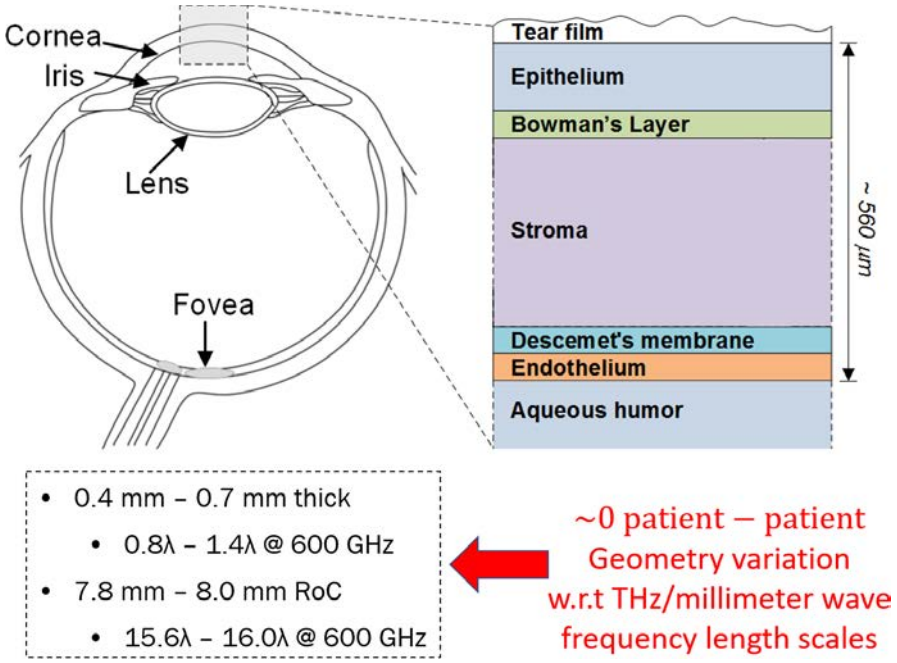

Figure 1: The patient-to-patient geometric variation of the cornea (thickness and radius of curvature) is fractions of a wavelength in the THz frequency range. The average thickness varies by 0.3 mm which is fractions of a wavelength at THz and millimetre wave/. The radius of curvature (RoC) range is even smaller at 0.2 mm.

A common disease that attacks the endothelium's pumping efficiency is Fuchs endothelial corneal dystrophy which affects ~40% of the world's population over 40 years of age. A reduction in pumping efficiency leads corneal hyperhydration and then corneal edema due to uncontrolled diffusion of water from the aqueous humor to the stroma (Figure 1). Edema is readily apparent from increased corneal thickness and significant optical opacity. This gives the cornea a "milky" or glazed over appearance. Corneal edema and, therefore, disease detection via visual assessment of opacity is straightforward but it is difficult to treat the disease at this point in

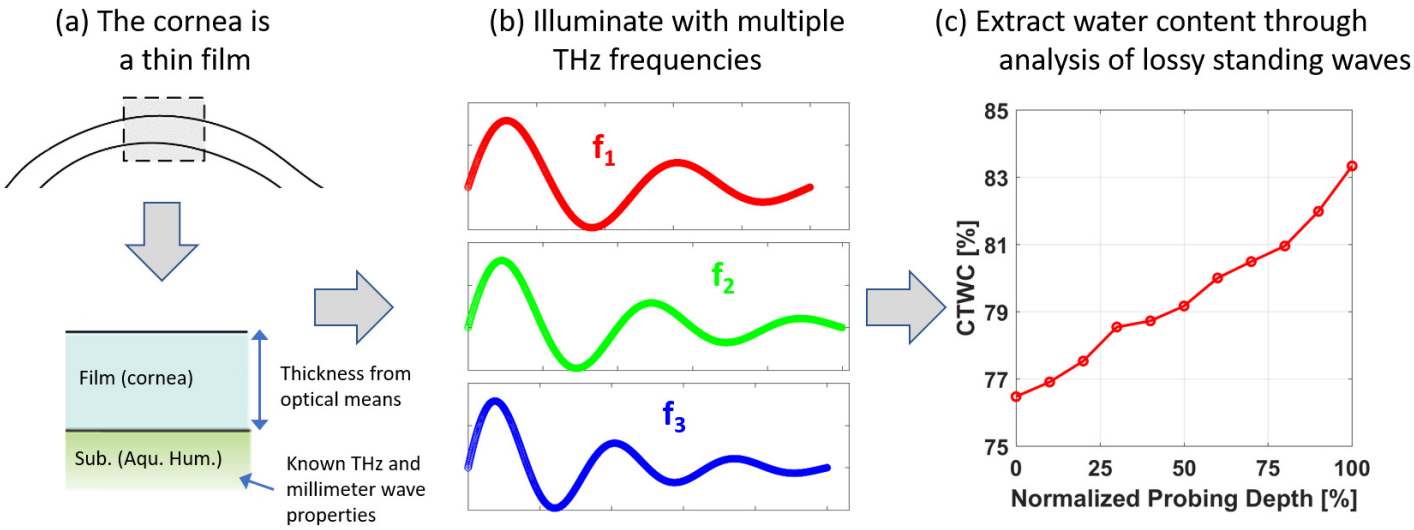

Figure 2: The lack of physiologic variation w.r.t. to THz frequency wavelengths and proximity to a deep (w.r.t λ) body of water allows one to treat that cornea as thin film sitting on top of an infinitely thick, lossy substrate. Analysis of lossy standing waves at multiple frequencies enables extraction of water content gradients in the thickness dimension.

the progression. The definitive treatment for Fuchs dystrophy is called lamellar transplant, where part or all of the diseased cornea is resected and donor or artificial cornea are grafted on. Graft rejection following transplant is not uncommon (1%-12% depending on surgical technique) and failure is typically preceded by the presence of edema in the graft. Detection of graft rejection via visual assessment of corneal edema is too late in the rejection progression to save the graft. Early and accurate detection and quantification of corneal edema, before perceptible changes in optical clarity, are not currently feasible. Development of sensitive and specific corneal edema measurement systems will considerably improve patient outcomes.

Despite efforts in research the clinical gold standard for water content is still pachymetry or a centre of the cornea thickness (CCT) measurement. This method recognises that an edematous cornea must expand (thicken) to make room for excess water and thus a history of steadily thickening cornea indicates compromised corneal health. However, the vast majority of patients do not have detailed CCT histories. Further, sincepachymetry is an indirect measure of water it cannot, in a single time point, ascertain or even infer water content. Studies performed on patients with corneal disease suggest that small, initial increases in CTWC do not produce statistically significant increases in CCT. Some high-resolution microscopy studies have identified changes in cellular morphology in Descemet's membrane (Figure 1) but these are exploratory and the clinical utility is unclear. What is needed is a direct measurement of CTWC that can be decoupled from variations in tissue geometry/morphology. THz and millimetre wave techniques may provide the key.

The inspiration for THz and millimetre wave probing of CTWC r content arose from ellipsometry; a measurement technique used to characterise thin films of materials. Ellipsometry illuminates the target with a laser that (1) has a wavelength on the order of the film thickness, and (2) the speed of light of that wavelength in the film is a very strong function of the film material and any imperfections in the film material. The illumination will bounce around inside the film and create a standing wave. Small changes in illumination parameters, such as wavelength, or angle of incidence create large, detectable changes in the standing wave. It is straightforward to numerically extract the thickness of the film and/or the material properties of the film simultaneously with a very high degree of accuracy.

The cornea is a perfect representation of a thin film (Figure 2) at THz and milimeter wave frequency length scales. It sits on top of a known material with known properties (water) and its physical thickness can be accurately measured via a number of optical techniques. Three key features render cornea a great match to THz and millimetre wave imaging. First, the thickness range, 0.4 mm-0.7 mm (Figure 1), falls right in the middle of our free space THz wavelength range: 0.1 mm-3 mm. Second, the standard deviation in radius of curvature (RoC) is fractions of a wavelength in the band of interest which enable THz and millimeter wave systems to always assume the cornea is a sphere thus allowing for straightforward optical design. Finally, the propagation speed of THz and millimetre wave radiation through physiologic material is an extremely strong function of water content and a weak function of the non-aqueous components (e.g. collagen). Therefore, quantitative mapping of corneal water content , and even water content gradients, can be through resolving the standing waves created by illuminating with an

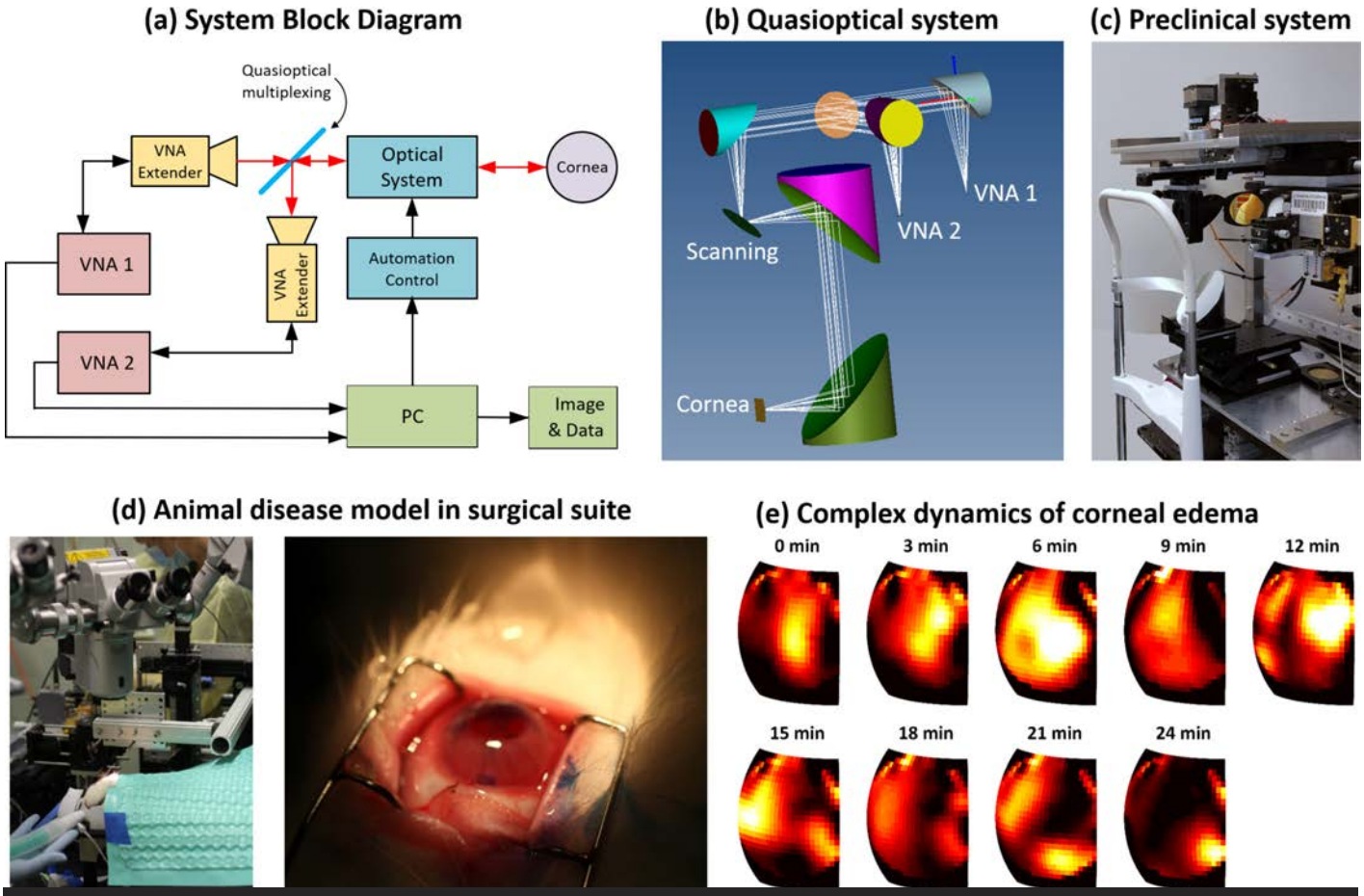

Figure 3: Ongoing corneal imaging work. (a) Block diagram of system in development. (b) Optimised THz quasioptics. (c) Preclinical test system. (d) Descemet's membrane stripping experiment. (e) THz frequency maps of corneal edema formation at numerous time points post stripping

ensemble of frequencies at in the THz and millimetre wave bands (Figure 2).

Our programme was established by an R01 grant (R01EY021590) from the National Eye Institute (NEI) for endothelial disease and graft rejection detection. We were the first to introduce the concept of lossy etalon analysis to THz millimetre wave imaging of cornea and the first to use it to decouple CCT changes from CTWC perturbations in vivo. We are currently able to resolve ~1% water by volume changes in corneal phantoms and are close to demonstrating this capability in in vivo animal models.

A current snapshot overview of the programme is shown in Figure 3. We are building multi-transceiver systems at complementary frequency bands to enhance water gradient extraction (Figure 3(a)) and have performed extensive optical simulations to optimise signal acquisition from curved surfaces (Figure 3(b)). Numerous human imaging systems prototypes have been built (Figure 3(c)) and are currently being tested tested on volunteers. We have also completed surgical trials in rabbit models (Figure 3(d)) and observed corneal edema formation (Figure 3(e)) after removal of Descemet's membrane (Figure 1).

Corneal tissue water content (CTWC) quantification offers a unique opportunity for THz and millimetre wave techniques in medicine. The relative lack or physiologic variation in corneal morphology on THz length scales and the extremely strong dependence of THz properties on water content enable successful application of thin film metrology. Successful clinical translation of this technology will require a multidisciplinary approach combining the fields of RF remote sensing, antenna design, radar engineering, optical techniques. In recognition of these challenges and the broad range of expertise required, we has moved the entire corneal tissue water content imaging programme to Aalto University in Finland.

A?

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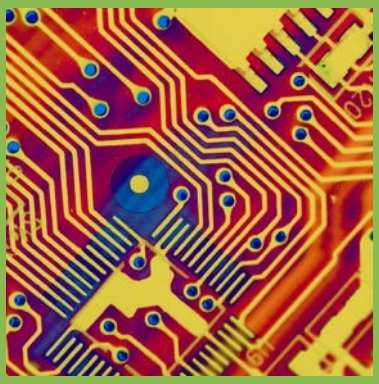





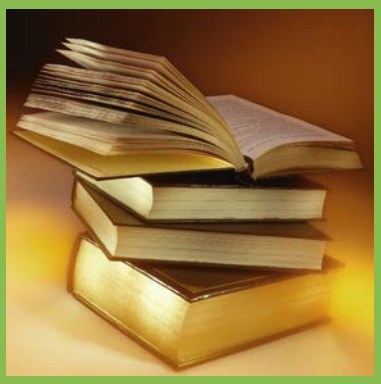

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A new and exciting age in polar science

Kelly K. Falkner, Director of the Office of Polar Programs (OPP), National Science Foundation, shares her thoughts on a new and exciting age in the field of polar science

We are embarked on a new and exciting age in polar science; the National Science Foundation, I am proud to say, is solidly committed to keeping the U.S. at the forefront of this new era.

A bit over a century ago, nations viewed the poles primarily as areas for heroic exploration with designs for geographical conquest. While some nations certainly put a higher priority on science in that context than others, the vast white unknowns were thought of as "places to claim".

Even as recently as a generation ago, attention was not widely focused on the polar regions as scientifically significant; the research may have been interesting to those in the know, but "marginal" compared to advances in other fields and seemingly isolated from other parts of the globe.

I have lived through and continue to experience a sea change in those attitudes – both in my previous professional life as a working polar scientist, and more recently as the director of NSF's Office of Polar Pro-

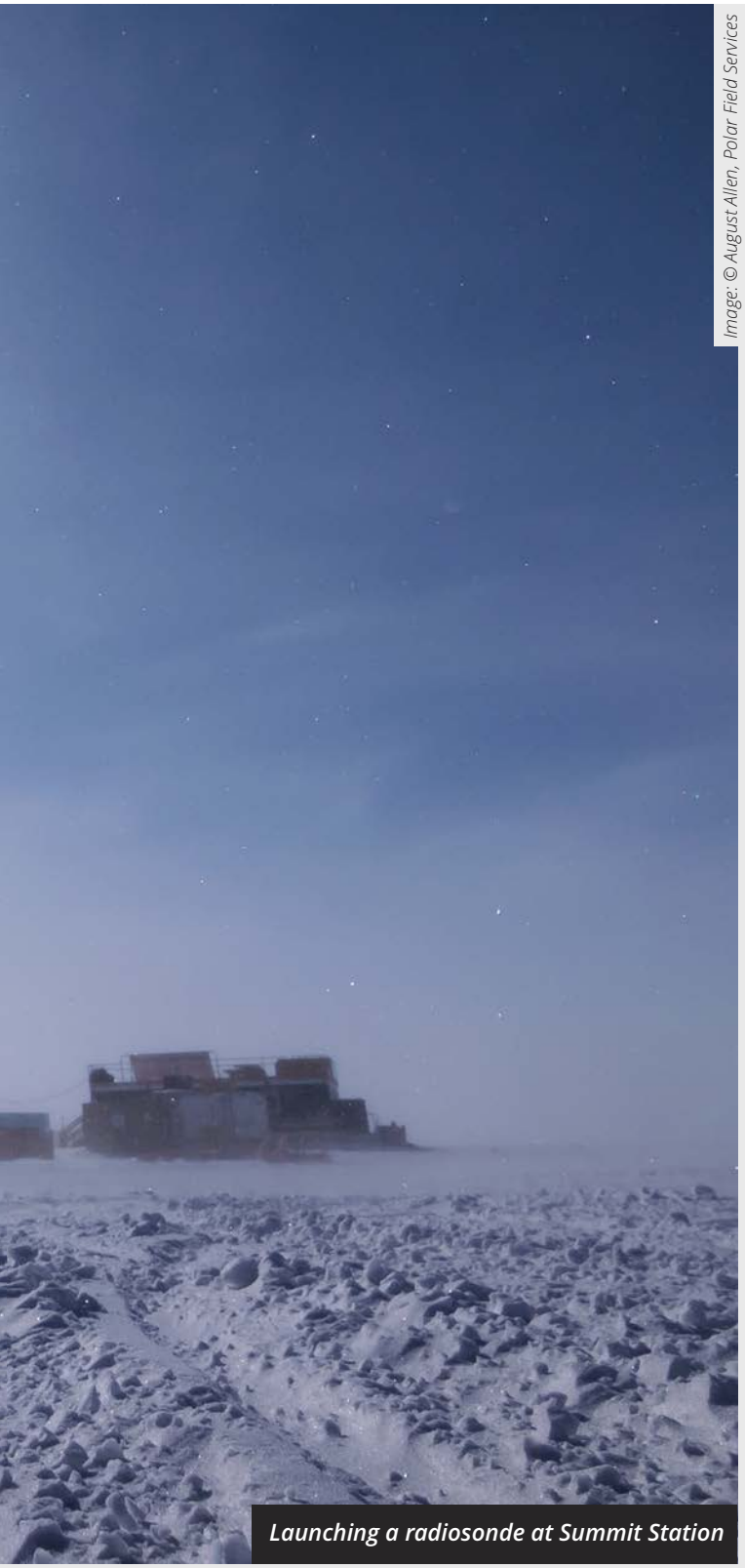

Image: © August Allen, Polar Field Services

Launching a radiosonde at Summit Station

grams (OPP). It is clear today that changes in the polar regions affect the rest of the globe, and the need to understand and try to predict and even remediate those changes has become a national and international priority. Moreover, polar regions provide unrivalled platforms from which to conduct many types of truly ground-breaking research.

At the same time, the face of polar science both literally and figuratively is changing. Women now contribute significantly to research that previously was male-dominated – and even literally off-limits to them – less than 50 years ago.

Technology, meanwhile, continues to open observational and experimental horizons.

Let me give a bit of the context to support these assertions and then touch briefly on some developments underway at NSF that will help polar science evolve to make the U.S. an even more inclusive leader in global innovation.

NSF's involvement in polar science began just a few years after the agency's creation, to help plan and support the U.S. science program for the 1957-58 International Geophysical Year (IGY).

Today, NSF, through OPP, manages the U.S. Antarctic Program on behalf of the Nation. OPP's Arctic Sciences Section supports research throughout the Arctic from Greenland to Alaska, on land, ice, sea and above. At both ends of the globe, we maintain vital partnerships with the private sector and federal partners including research agencies and the Department of Defense to accomplish field-based research. This also entails extensive international engagement.

By nearly every measure, U.S. polar scientists are among the most productive in the world. For example, the U.S. has always and still solidly leads in number and quality of peer-reviewed scientific publications.

To be in this position, we owe a debt to the pioneers of the U.S. polar science presence. Keep in mind the context that the ability to withstand the rigours of polar winters while carrying out research is a relatively recent phenomenon. The first overwintering team at the South Pole consisting of 18 men under the joint leadership of civilian Paul Siple and Lt John Tuck was deployed only in the late 1950s.

Given how logistically challenging it remains to work at the poles even to this day, it would be easiest to continue to do the things we already know how to do. To remain at the forefront, however, we must continue to strive beyond our comfort zones. We must continue to evolve new technologies and capabilities that allow us to tackle

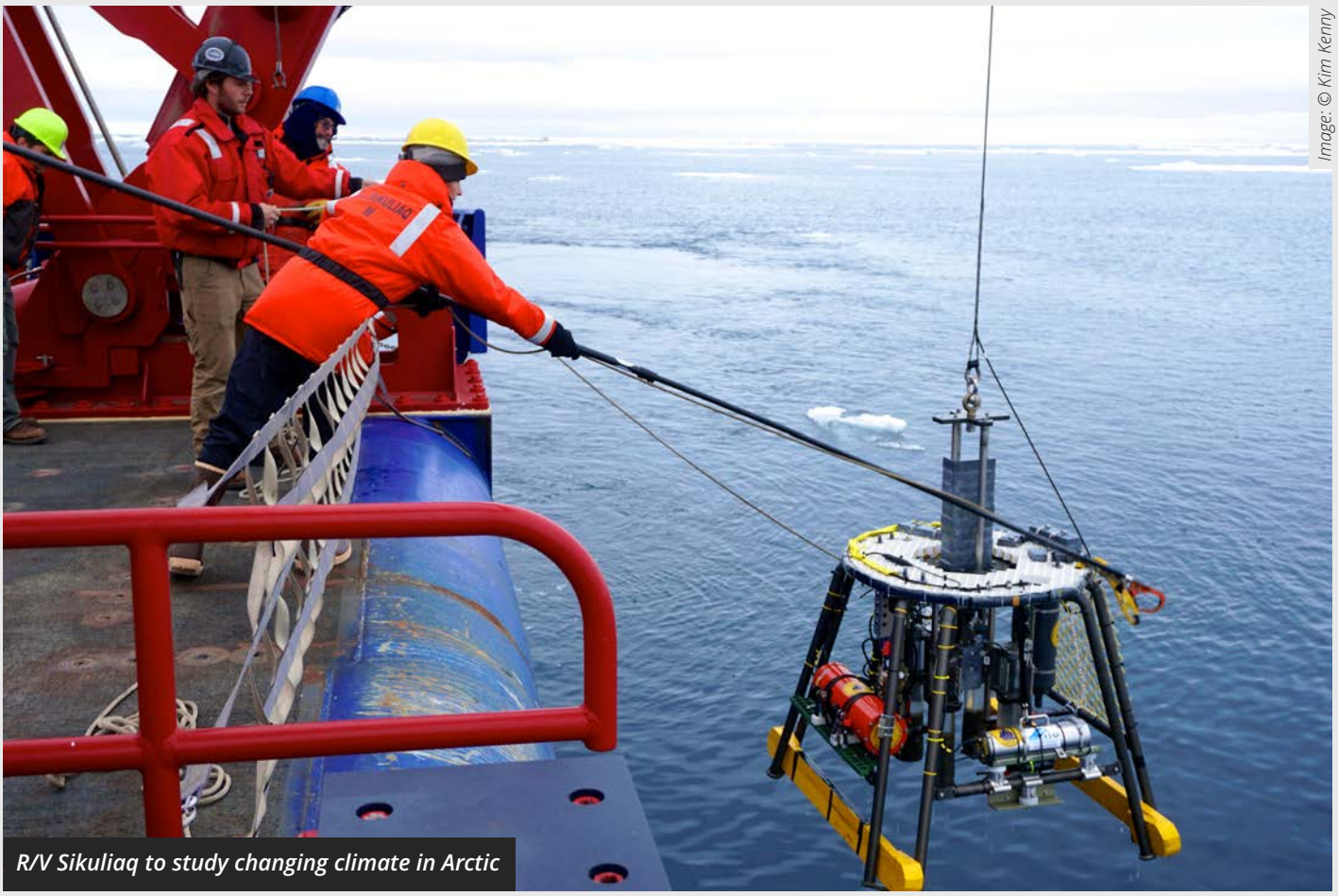

Image: © Kim Kenny

R/V Sikuliaq to study changing climate in Arctic

questions at a much larger scope and scale than ever before. And very importantly, we must continue to engage and support our Nation's most creative and motivated scientists.

Today, polar science remains a vital – and growing – part of the NSF research portfolio. Some current examples of exciting NSF-supported science include:

- Two papers published in Science Magazine in July 2018 described the detection of extremely high energy neutrinos by the IceCube detector at South Pole Station that led to the identification of blazar as the source. We finally achieved at least a first answer to the 106-year old mystery of the origin of cosmic rays!

- State-of-the-art autonomous robots deployed by the Southern Ocean Carbon and Climate Observations and Modeling program, have generated first-ever, year-round coverage of physical and chemical properties of the Southern Ocean, revealing that the system is far more dynamic than previously assumed. Stay tuned to learn what that means for our global climate system.

- A partnership of 17 nations, the MOSAiC Observatory, a ship frozen into the ice, will drift with the Arctic sea-ice pack for a full annual cycle, starting in September 2019, to observe atmospheric and oceanic processes that affect the sea-ice as it evolves from new first-year ice to multi-year ice and, eventually, decays.

- A $25-million joint U.S. and U.K. expedition to the Thwaites Glacier will prod and poke the system from myriad approaches over the next five years in order to understand why it is speeding up and what we can expect in the future. Since the portion of the West Antarctic Ice Sheet held back by the glacier rests below sea level, it is thought to be particularly vulnerable to accelerated melt with the potential to raise sea level by 3-m or more.

- NSF is taking an All-Hands-On-Deck approach to accelerating the pace of Arctic science to address the widescale and rapid changes occurring there, through an initiative we call "Navigating the New Arctic". Or NNA. This is currently among NSF's top ten priority strategic investment areas several of which are expected to complement NNA. We are looking forward

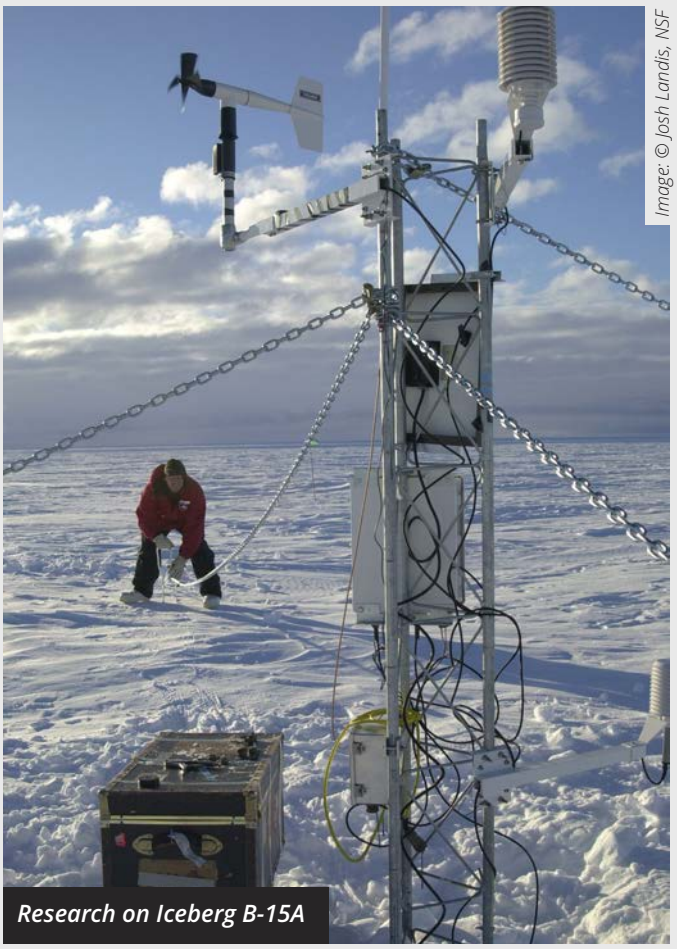

Image: © Josh Landis, NSF

Research on Iceberg B-15A

to the results of a solicitation for proposals backed by $30 million in new funds that closed on 4th March 2019, and targets science at the intersection of the social, natural and built environments.

Meanwhile, the quality and pace of polar science in the Arctic and the Antarctic continue to rely as heavily on critical infrastructure as it did in the IGY. We must be ever forward-looking. As one case in point, NSF has launched new state-of-the-art polar capable research vessel, Sikuliaq, run by the University of Alaska, primarily to explore the Arctic.

At the other end of the globe, at Antarctica's McMurdo Station, NSF's Antarctic logistics hub, expanded as needs arose since it was established during the IGY into a hodge-podge of 104 structures spread out over a 1.5 square-mile campus.

A 2012 Blue Ribbon Panel rightfully pointed out resulting inefficiencies in McMurdo's operations. In February, the National Science Board, NSF's governing body, gave the agency the nod to begin the Antarctic Infrastructure Modernization for Science (AIMS) project, which over 10 years will consolidate the station footprint to enhance safety and flexibly streamline science support for the next 35-50 years.

Last but not least, this coming Antarctic season marks the 50th anniversary of the first women to set foot at the South Pole. Not until 1978-79 did a female overwinter there.

I am happy to report that women now participate in polar science, science support and leadership throughout the world. But the polar research community remains a long way from being as diverse as the society that supports us. Research clearly tells us that diverse groups make more robust decisions. And one never knows from whom the next brightest scientific advance may emerge. Which brings me to my take-home message:

For the U.S. polar science community to meet the needs of the coming century and beyond, we must:

- Nurture a more diverse research and research-support community;
- Keep peering over the horizon for infrastructure & logistics needs;
- Drive innovation in technology, including technologies and approaches to manage and profit from extracting the "big picture from big data;
- Build productive partnerships wherever we do better and more together. ■

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Observations to action: Informing understanding and responses to rapid Arctic change

When it comes to observations to action, The International Arctic Research Center informs understanding and responses to rapid Arctic change, as we discover here

By way of an introduction, the Arctic is the most rapidly changing environment on Earth and is already experiencing transformations in its marine and terrestrial environments and social-environmental systems. Effective responses to such changes require a thorough understanding of drivers and impacts, based on sustained observations that guide model development and improve predictive capacity.

The International Arctic Research Center (IARC) at the University of Alaska Fairbanks was founded to address the key challenges of Arctic observing science, particularly at scales that require international collaboration. One key to IARC's success is rigorous engagement with stakeholders making decisions in and about a rapidly changing Arctic, requiring expertise and resources in science communication and the co-production of knowledge.

IARC research

Marine science

The Nansen and Amundsen Basins Observational System (NABOS) was conceived at IARC in 2002 to track remarkable changes in the Eurasian Basin of the Arctic Ocean. Since then, ten comprehensive multidisciplinary cruises have delivered critical information for documenting and understanding oceanic, atmospheric, and sea-ice change. Moorings anchored to the ocean floor beneath sea ice for several years have provided long-term continuous records, augmented by summer oceanographic surveys to provide spatial context.

Graduate students, high-school teachers, and summer schools are key elements of broad outreach during NABOS cruises. From its beginning to the most recent cruise in 2018, this programme has been a multinational endeavour, with scientists from many different countries working hand-in-hand to measure, analyse, and deliver complex data and information.

NABOS has provided critical information about unprecedented Arctic Ocean changes, likely representing a fundamental shift to a new, less stable, more dynamic marine environment. By the mid-2010s, the halocline in the eastern Arctic Ocean (an oceanographic feature separating surface from deeper waters) had lost its ability to serve as a lid preventing Atlantic Water heat at depth from reaching up to the sea ice bottom. Progressively deeper winter mixing has brought up more heat – diminishing the ice cover. Continued observations and analysis will establish whether this might be the onset of major winter sea-ice loss altering northern hemisphere weather patterns.

Terrestrial research

A massive green band spanning the high northern latitudes, the boreal forest stores immense amounts of soil carbon. Decomposition is slowly releasing this carbon to the atmosphere and exacerbating climate change, wildfires can accelerate this process.

Interior Alaska wildfires are burning bigger and hotter than in the past, and more frequent 'mega-fire' seasons challenge the region's fire managers. With over 80% of Alaska's population residing in or near the forest and wildlands, fire managers need science and technology to operate safely and efficiently. IARC meets these needs by developing locally relevant, accurate models and forecasts of Alaska's changing fire regimes and impacts.

In a large, observation-limited state, this means using a sophisticated modelling approach known as dynamical downscaling. A coarse-resolution global climate model is linked to a regional model incorporating local climate information, providing "downscaled" model output with much finer resolution.

Managers welcome this new tool as part of their ongoing science-based effort to protect life and property in Alaska's unique landscape. IARC is

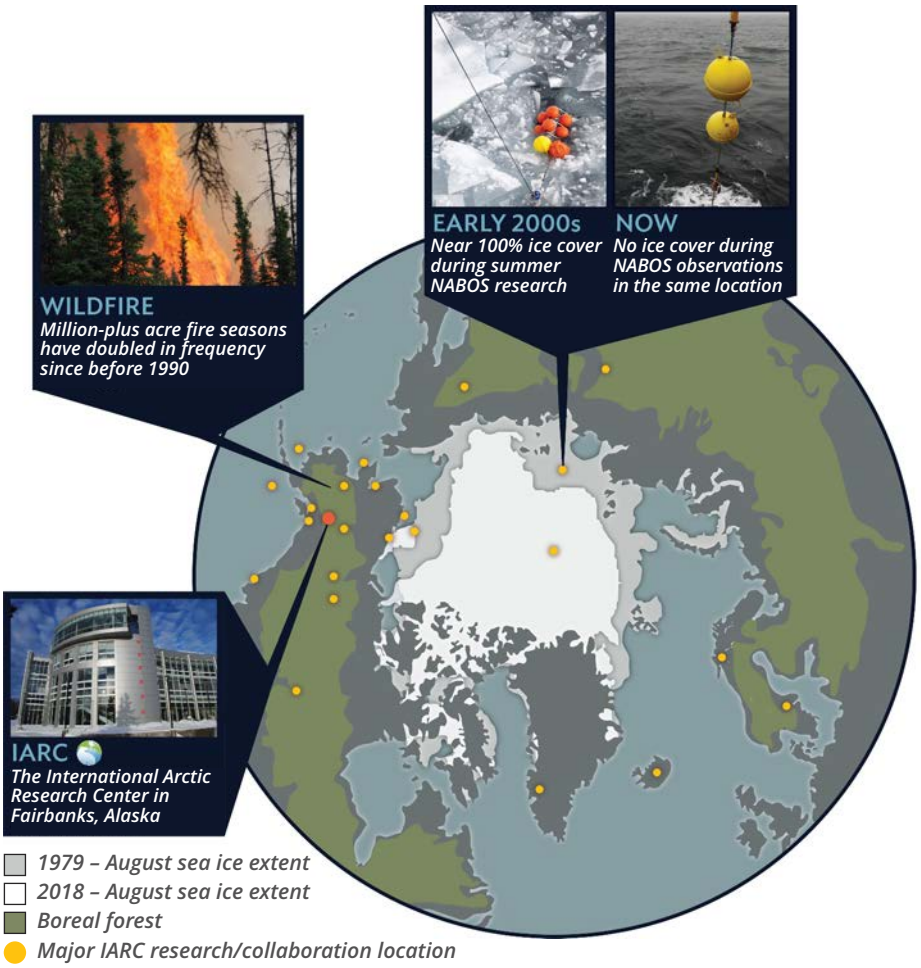

Fig. 1: The International Arctic Research Center has research and collaborations around the circumpolar north to help the world understand transformative changes in the Arctic

also exploring new ways to use fire weather predictions to assess the level of risk for upcoming fire seasons, supporting fire-response logistics and budget planning.

The role of government in responding to rapid Arctic change

The current capacity for local, state, and national governments to respond to a warmer, less predictable Arctic is weak. Observations and models may chart marine and terrestrial trajectories over the next half-century, but governments in the U.S. operate on far shorter time horizons. Furthermore, federalism splits responsibilities for environmental management, resulting in only incremental change for most government policies and services.

IARC supports the use of more observations by the government, across more scales, in the development of programmes and the enforcement of rules. IARC has the ability to translate and communicate complex changes across Arctic environments, so government officials and agency employees charged with fulfilling the mandates of government can connect today's data with future desirable outcomes.

There must be an incentive for understanding: why should any politician care about something that falls outside of their constituents' interests? Because humans are social-environmentally interdependent, even if our governments of states and localities split us up, Arctic warming affects North America and the world as a whole.

These challenges call for models and maps that are time appropriate for government cycles; transmittal of data demonstrating effects of Arctic change on lower latitudes; and linking local and Indigenous knowledge to promote a broader and deeper understanding of change.

Future outlook for the Arctic

Across all facets and functions at IARC and the global North, there is increasing recognition that solutions to Arctic problems require multi-sector, multi-stakeholder/actor approaches. IARC helps chart pathways, by building collaborative networks across the Arctic and non-Arctic nations, and by supporting efforts, such as the Arctic Observing Summit. Disruption from climate change in the North challenges our current institutional systems and governments. Observations of Arctic change both calls for and support key decisions in this decade to forestall future problems.

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Containing radioiodine in a solid phase for radioactive waste disposal

In this report Professor Peter H. Santschi, Texas A&M University at Galveston, highlights the challenges when containing iodine in a solid phase for radioactive waste disposal

Silver-impregnated zeolite (AgIZ) has been used for removing radioiodine from contaminated groundwater and nuclear waste streams and the worldwide inventory of such secondary waste is rapidly increasing. To contain long-lived radioactive iodine (16 Mio year half-life of ^{129}I) from nuclear waste, various methods have been employed, with various success.

One of the ways ^{129}I can be immobilized is through the formation of insoluble silver iodide solid, AgI, which is only possible in the presence of oxygen (Fig. 1). The silver technology is commonly deployed by coating silver on zeolites, AgZ, and then putting it contact with the aqueous or gaseous ^{129}I waste stream. The objective of a recent study [Kaplan et al., 2019] was to quantify the effectiveness of two grout waste formulations for disposing of the used AgIZ (Table 1). The grout formulations were with and without slag, an ingredient used to reduce porosity and to create a strong chemically reducing environment to immobilize redox reactive contaminants).

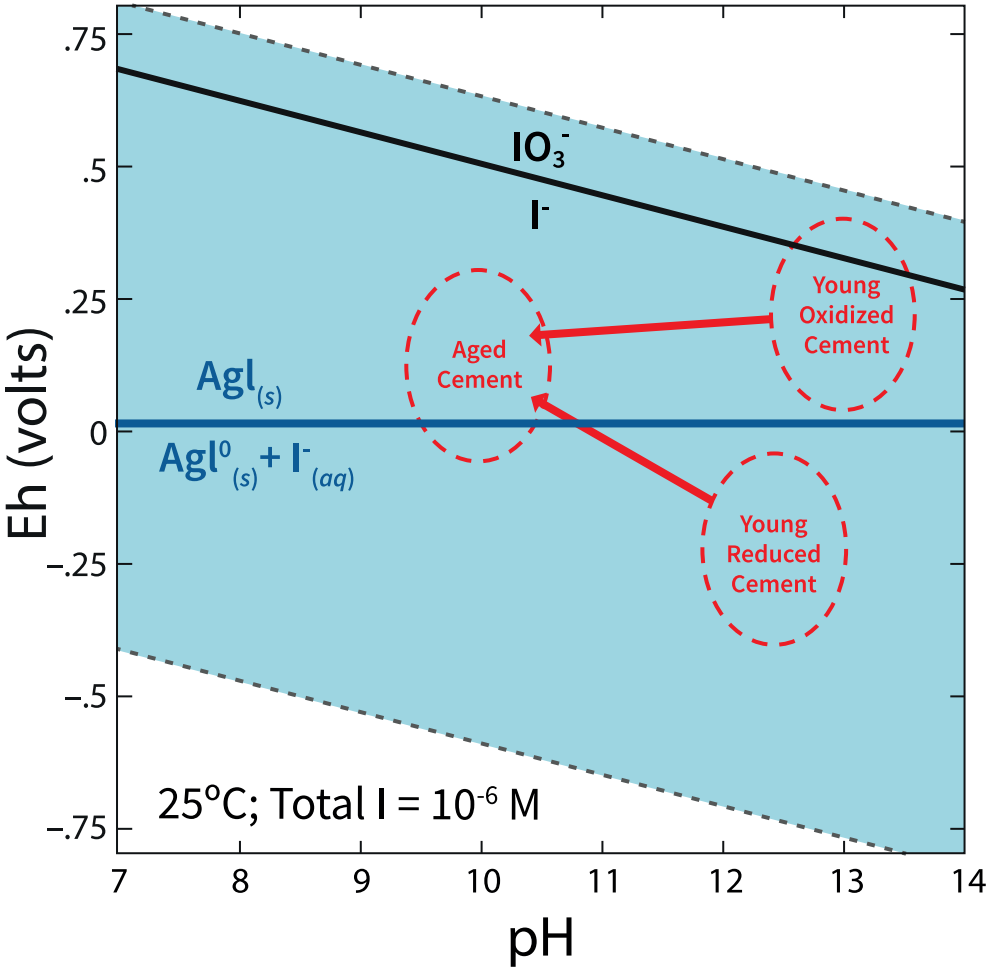

Fig. 1. Pourbaix diagram of iodine speciation showing general regions for grouts with and without slag, indicating that redox potential of 'Young Reduced Cement' containing grout, falls within the zone that predicts reduction of Ag.

A second objective was to determine the iodine speciation leached from AgIZ encapsulated in grout. Iodine commonly exists concurrently as three species in the same environment: iodide (I^-), iodate (IO_3^-), and organo-iodine (org-I). To predict the toxicity and the rate at which ^{129}I travels, it is important to know the iodine speciation in the system. A 60-day kinetic batch experiment demonstrated that AgIZ encapsulated in slag-free grout was extremely effective at immobilizing iodine and silver, a potential non-radioactive carcinogen.

However, AgIZ encapsulated in slag-containing grout, the most common type of grout used for low-level radioactive waste disposal, was entirely ineffective at immobilizing iodine. While the slag-free grout with AgIZ released only 3.3 µg/L total iodine into the contact solution, the slag-containing grout released 19,269 µg/L total

Table 1. Ingredients and proportions used to make the grout samples

Ingredients*	$Grout_{-slag}$ (wt%)	$Grout_{+slag}$ (wt%)	$Grout_{-slag+AgIZ}$ (wt%)	$Grout_{+slag+AgIZ}$ (wt%)
Cement	19	6	16	4
Fly ash	59	32	47	26
Slag	0	31	0	25
AgIZb**	0	0	16	14
Water	22	31	22	31
Liquid:Dry Blend	0.29	0.45	0.29	0.45

** Expressing the above receipts in terms of percent of the dry blend: $Grout_{-slag}$ is composed of 25% cement, 75 wt% fly ash, 0 wt% slag; $Grout_{+slag}$ is composed of 8% cement, 47 wt% fly ash, 45 wt% slag; $Grout_{-slag+AgIZ}$ is 20 wt% cement, 0 wt% slag, 60 wt% fly ash, and 20 wt% AgIZ; and $Grout_{+slag+AgIZ}$ is 6 wt% cement, 36 wt% slag, 38 wt% fly ash, and 20 wt% AgIZ.*

*** AgIZ is the Ag-zeolite (AgZ) amended with I^-.*

iodine. Based on thermodynamic calculations, the strongly reducing conditions of the slag-containing system (Eh was -392 mV) promoted the reductive dissolution of the AgI solid, forming a dissolved form of silver, $Ag^0_{(aq)}$, and releasing iodide into the aqueous phase. The slag-free grout system was maintained under more oxidizing conditions (Eh was 439 mV) and a minimal amount of iodine was released from the grout.

In both grout systems, the aqueous iodine, originally added to the AgZ as iodide, was composed primarily of iodide and org-I, and essentially no iodate was detected. More organo-I was detected in the slag-free than the slag-containing grout system, because the high redox potential of the former system was more conducive to the formation of oxidized I species, such as I_2 and HIO, which may be intermediates in the covalent bonding of iodine with organic carbon in grout. Spectroscopic analysis (X-ray Absorption Near Edge Structure analysis) of the two AgIZ-grout samples indicated that the iodine existed exclusively as silver iodide.

Together, these results show that subsurface grout disposal of AgIZ waste should be done under oxidizing conditions and that radioiodide released from AgIZ can undergo speciation transformations (leading to organoformation) that have important implications on subsequent mobility and estimated risk. **[Kaplan, D.I., Price, K., Xu, C., Li, D., Lin, P., Xing, W., Nichols, R., Schwehr, K.A., Seaman, J.C., Ohnuki, T., Chen, N., Santschi, P.H. 2019. Iodine Speciation in a Silver-Amended Cementitious System. Environment International, in press]**

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Understanding freshwater resource problems

Experts from Stroud Water Research Center and Kansas State University highlight the importance of addressing today's freshwater resource problems and how to achieve sustainable watershed management

Freshwater resource problems are ubiquitous across the globe despite decades of focused watershed management efforts targeting drinking water treatment, water use efficiency and point-source pollution reductions. Severe challenges remain with respect to more diffuse and less easily treated problems that begin with land use and water use decisions by humans living, working, developing and farming watersheds increasingly altered by anthropogenic climate change.

To address today's freshwater resource problems, we must understand the role of humans in freshwater systems, including their culturally influenced decision-making processes. Integrative analysis of natural and social systems has been an international sustainability science goal for many years. However, full integration in regard to the role of culture is often still missing from the complex water sustainability equation.

Achieving more sustainable watershed management depends in large part on the ability to better understand the social learning processes that drive adaptive environmental decision-making, as well as the causal chains linking culturally influenced environmental values to environmental behaviours. Integrative mechanistic models are needed that account explicitly for human-landscape interactions and incorporate detailed, well-developed, coupled models of hydrosystem, aquatic ecosystem, and human system responses to changing climate (Figure 1).

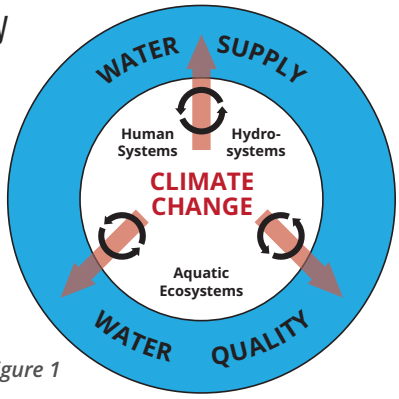

Figure 1

Our research approach interactively couples mechanistic models of three systems – the hydrosystem, the human system, and the aquatic ecosystem – controlling water supply and water quality in the Central Great Plains of North America, a region with long-standing water quality and quantity concerns. In this arid, highly erodible and agriculturally intensive region, historical natural climate fluctuations have been extreme, and the coupling between the dynamic climate and human systems is close, as witnessed during the Dust Bowl environmental disaster of the 1930s. This classic example of the intersection among climatic variables, human land use, and unexpected societal impacts illustrates the economic, demographic, and cultural consequences for a region and nation when unsustainable land use collides with unanticipated climatic change.

We demonstrate our integrative modelling framework in the study of a coupled human and natural system in a surface water-dependent agricultural watershed with a highly climate-sensitive surface water flow regime influenced by human-induced land-use and climate change. The hydrosystem serves as the foundation of our model, which focuses on integrating climate, ecosystem and human decision scenarios as boundary conditions for a watershed response model. This enables us to predict future surface water regimes that inform an aquatic ecological model.

Since cultural influences can drive people to either adopt or reject sustainability policies, our human-systems model empirically includes culture. Humans use culture to learn and inform their decision-making processes, but human culture is often seen as too difficult to incorporate into environmental system models.

At its most fundamental, culture is comprised of shared values, beliefs, and norms through which humans visualise, interpret, or assign meaning to actions, concepts, and their environments. Despite this complexity, developing mechanisms to empirically model the cultural influences that drive region- or community-specific responses to management efforts is critically important.

We model policy decision-making processes grounded in culture within

a framework of coupled human and natural systems, quantifying cultural influence using the Values-Beliefs-Norms (VBN) framework informed by an extensive survey of the local population. Within an agent-based model, agents vote to adopt or reject environmental policies.

Heterogeneity among agents is derived from demographics, VBN factors, and the environment. Each human agent is populated by attributes extracted from an extensive survey of the local population. Attributes include demographic characteristics (gender, education, income, age, and occupation), values characteristics (altruistic toward humans, altruistic toward biodiversity, traditional, self, and openness to change), environmental worldviews, political ideology, and environmental knowledge.

The agents' decision-making processes are informed by cultural, hydrological, and aquatic biodiversity models. The fully integrated model (Figure 2) is then used to evaluate whole-system response to climate variation scenarios derived from historical data and downscaled climate projections. This integrative model represents a functional coupling of natural and human systems, allowing for biophysical feedbacks to directly affect agents' decision-making processes and enabling us to evaluate the sustainability outcomes delivered by different policy scenarios.

Our findings demonstrate that policy support is grounded in cultural values, and cultural differences explain preferences for conservation policies designed to conserve and protect water resources and aquatic ecosystems. The array of values invoked to make decisions about policies, and the social-psychological pathways

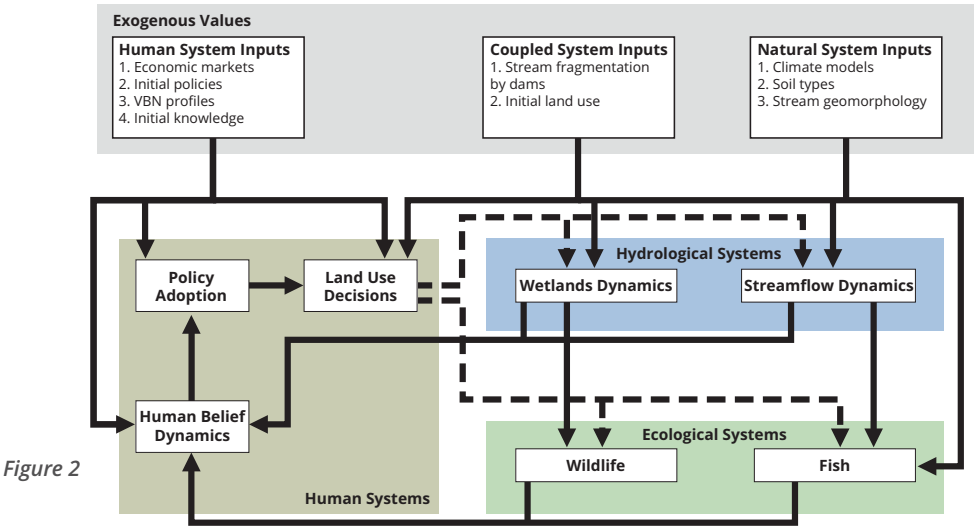

Figure 2

linking values to policy support can vary across policies and types of agents (e.g. farmers and non-farmers).

In contrast, some human system factors, such as financial obligation, are the strongest and most consistent explanation of support for conservation policies among members of both groups. These dynamic linkages between cultural and environmental factors reveal new pathways for actions that support sustainability.

Our results indicate resistance to environmental policy, suggesting that the local cultural framework may result in rejection of sustainability policies and prevention of needed support even under potentially extreme climate conditions.

However, our model also showed that the best opportunities for policy acceptance immediately follow extreme events. This underlines the need for influencing culture and pro-environmental behaviour via interventions and monitoring to benefit from the increased acceptance of environmental policies during and immediately following severe environmental conditions. This work provides the foundation necessary for future research to explore rich questions about coupled system dynamics and sustainability policy.

Funding Acknowledgement:

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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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Marijuana use during pregnancy: The cannabis conundrum

Dennis R. Carty, Ph.D. and Pamela J. Lein, Ph.D., University of California, highlight the rising trend of marijuana use during pregnancy and the implications surrounding it

Many women suffer from nausea and vomiting during pregnancy to the point that these symptoms interfere with daily activities, or in extreme cases, compromise the health of the mother and unborn child. It is perhaps no surprise then that options for relieving these symptoms are a prominent topic in on-line forums for pregnant women. A notable trend in these on-line discussions is increasing advocation for the use of marijuana, also known as cannabis, to relieve pregnancy-induced nausea and vomiting. The mounting interest is driven in part by increasing legalisation and social acceptance of marijuana and approved medical use of cannabis-based products to treat nausea and pain associated with cancer, multiple sclerosis, Crohn's disease and some forms of epilepsy.

Additionally, marijuana is often promoted as a natural remedy with minimal side effects and, therefore, many women perceive it as a healthier alternative to the standard medications used to treat pregnancy-induced nausea. Indeed, 70% of women recently surveyed in the United States believe that there is "slight or no risk of harm" in cannabis use during pregnancy. The truth is that there are more questions than answers about the safety of marijuana use during pregnancy.

While humans have used marijuana (Cannabis sativa) for recreational, religious, and medicinal purposes for several millennia, basic research regarding the therapeutic efficacy and toxicity of the active constituents in cannabis, such as tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), is remarkably limited. The basis of marijuana's biological effects was not determined until the 1990s when neuroscientists discovered two cannabinoid receptors, CB1R and CB2R, in the mammalian brain.

Subsequently, researchers found that these receptors respond to molecules naturally synthesized in the body from fatty acids, which are called endogenous cannabinoids, or endocannabinoids. The endocannabinoid system functions to regulate numerous physiological processes, including body temperature, hunger, processing of sensory information, and cognition.

Cannabis is a complex mixture of pharmacologically active compounds that includes more than 100 cannabinoids in addition to Δ9-THC and CBD, as well as other pharmacologically active molecules, such as terpenes and flavonoids. These compounds interact with the endocannabinoid system to cause the biological effects associated with cannabis.

For example, the binding of Δ9-THC to CB1R causes the "high" associated with smoking or ingesting marijuana. CB1R is widely expressed in the developing brain, and data from experimental animal models indicate that

endocannabinoid signalling plays a significant role in the normal development of the brain. Either overstimulating or blocking CB1R activity during brain development causes "miswiring" of brain circuits. This altered brain circuitry manifests as behavioural deficits in the young animal that persist into adulthood.

CB1R is expressed in the developing human brain by the first weeks of the second trimester. Δ9-THC, CBD and other cannabinoids in marijuana cross the placenta and are transferred into breast milk. Because cannabinoids have a relatively long half-life in the human body, the fetus or breastfeeding infant may be exposed to active cannabinoids for up to 5 days after maternal use of cannabis.

Such observations raise the possibility that marijuana use during pregnancy potentially alters fetal or infant brain development by interfering with the endocannabinoid signalling system in the developing brain. This possibility is supported by data emerging from several large epidemiological studies of cannabis use during pregnancy in North America and Europe.

These studies report an association between maternal cannabis use and increased impulsivity, attention deficit, hyperactivity, delinquent behaviours, and impaired memory in children, and higher rates of depression, drug abuse, memory deficits, and psychosis in adolescents and adults.

A key question is whether there is a safe level of maternal marijuana use. Answering this question requires knowing how much marijuana is consumed by women during pregnancy. However, quantifying marijuana intake is challenging because the potency of cannabis, as well as the ratio of the different active cannabinoids it contains, is extremely variable. With regard to the latter, it is also unknown as to which constituent(s) in marijuana impact the developing brain.

This is a critically important question in light of widespread on-line discussions suggesting that CBD is safer than Δ9-THC. Compared to the significant amount of research on the toxicity of Δ9-THC, which is linked to the dysphoric and other adverse effects of marijuana abuse, there has been comparatively little research on the potential toxicity of CBD.

Recent studies in zebrafish, which have an active endocannabinoid system, suggest that CBD causes abnormal development and lethality at concentrations significantly lower than Δ9-THC. While it has yet to be determined whether CBD interferes with brain development in mammals, including humans, these findings suggest the urgent need for research to characterize the developmental neurotoxicity potential of the individual active constituents in marijuana.

The developmental neurotoxicity of marijuana is also influenced by the production and method of consumption of cannabis products. For example, smoking a cannabis cigarette produces combustion byproducts, including polycyclic aromatic hydrocarbons (PAHs), which are neurotoxic to the developing brain. Vaporizing dried cannabis significantly reduces the production of combustion byproducts, but can introduce neurotoxic metal contaminants into the inhaled product and increase the amount of active cannabinoid consumed.

Concentrates such as oils, tinctures, and edibles avoid the issues associated with smoking or vaping cannabis. However, these methods of consumption do not mitigate the problem of wide variability in the purity of cannabis products.

For example, cultivation practices can introduce contaminants such as microbial impurities, mycotoxins, metals, and pesticides into the final product. Maternal consumption of cannabis products containing these contaminants can result in their transfer to the fetal brain, which is of potential concern since many of these contaminants are known to interfere with brain development.

As cannabis use becomes increasingly acceptable and widespread, increasing numbers of women are likely to use cannabis during pregnancy. While the impact of maternal cannabis use on the unborn child remains an open question, the data that are currently available warrant caution, and underscore the urgent need for additional research to inform ongoing discussions regarding the cannabis conundrum in pregnancy.

UCDAVIS VETERINARY MEDICINE

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Agricultural issues: Protecting the United States from harmful invasive plant pests and diseases

The work of the Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) in the United States covers a wide range of agricultural issues, including protecting the U.S. from harmful invasive plant pests and diseases, as this article uncovers

The U.S. Department of Agriculture's (USDA) Animal & Plant Health Inspection Service covers a wide range of agricultural issues, including protecting the United States from potentially harmful invasive plant pests and diseases. The organisation was established in 1972 to consolidate the USDA's animal and plant health bureaus.

Since then, the scope of agricultural issues the agency oversees has grown exponentially and today covers areas such as wildlife damage and disease management, regulation of genetically engineered crops and animal welfare, and protection of public health and safety, as well as natural resources that are vulnerable to invasive pests and pathogens.

Guarding against invasive species and diseases is a 24-hours a day, seven days a week job for the agency. The potential consequences of, for example, the Mediterranean fruit fly or Asian long-horned beetle, going unchecked could be billions of dollars of production and marketing losses annually.

Similarly, if a disease such as foot-and-mouth or highly pathogenic avian influenza were to become established in the U.S., producers could face devastating losses due to the imposition of trade restrictions by foreign partners.

APHIS has aggressive emergency protocols in place to tackle pests and disease and it works with partners and affected states to quickly manage and eradicate outbreaks as soon as they are detected.

To promote the health of U.S. agriculture in the international arena, APHIS also develops and promotes science-based standards with trading partners to ensure America's agricultural exports, which are worth more than $50 billion a year, are protected from unjustified restrictions.

Under the Plant Pest and Disease Management and Disaster Prevention Programme, the APHIS distributes funding to individual states to expand or enhance pest surveys, identification, inspection, mitigation and risk analysis, as well as public education and outreach.

Since 2009, the USDA has provided around $293.5 million and supported more than 2,340 projects under the Plant Protection Act.

"To promote the health of U.S. agriculture in the international arena, APHIS also develops and promotes science-based standards with trading partners to ensure America's agricultural exports, which are worth more than $50 billion a year, are protected from unjustified restrictions."

Collectively, these projects allow the USDA and its partners to quickly detect and respond to invasive pests and diseases while maintaining the infrastructure necessary to ensure that disease-free, certified planting materials are available to speciality crop producers.

In the 2019 financial year, the USDA is providing $66 million to 407 projects in 49 states, as well as Guam, Puerto Rico and the Northern Mariana Islands.

Image: © Duy Do | Dreamstime.com

The largest single allocation will see $16 million go to California to support projects covering a range of plant health and pest mitigation activities.

This includes $5 million to survey for harmful exotic fruit fly populations in the state, along with $3.5 million to support the activities of detector dog teams in searching for harmful, exotic plant pests in packages at mail and express parcel delivery facilities.

Another $2.2 million will support the National Clean Plant Network (NCPN) foundation plant stocks for citrus, grapes, fruit trees, sweet potato and roses. APHIS provides funding through the network to university and government facilities that develop, maintain and provide clean foundation stock for selected speciality crops. The programme is designed to help protect the environment and ensure the global competitiveness of speciality crop producers. In 2019, APHIS will allocate $6 million to support NCPN projects nationally.

Elsewhere, $1.7 million has been allocated to California's Emergency Plant Health Response Teams for responding to, delimiting the infestation area, and managing outbreaks of exotic plant pests.

"California is a critical partner in protecting U.S. agriculture", says USDA Under Secretary Greg Ibach.

"With this funding, California will be able to better protect its own resources and, in doing so, contribute to USDA's mission of keeping our nation's agriculture economy healthy and strong." ■

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Polder project: Coastal zone of Bangladesh

Professor Robert Aiken discusses work on food networks in this report, specifically the Polder project

"Smallholders manage over 80% of the world's estimated 500 million small farms and provide over 80%of the food consumed in a large part of the developing world, contributing significantly to poverty reduction and food security."[1] As a public agricultural scientist, this is of interest. Food security extends beyond the major food and feed grain crops (rice, wheat, corn, soybean, sorghum), many of which I study. If a substantial portion of humanity depends on food produced by smallholders, what risks do climate changes pose for these community food networks?

The sustainable intensification of smallholder food systems is the focal work of a colleague, Dr Vara Prasad.[2] His network of international collaborators is devoted to understanding the function of community food networks, and opportunities for sustainable intensification to enhance food security. Vulnerability to climate change is an integral aspect of this work.

To gain insight into food networks, I discovered the Polder project, active in the Coastal Zone of Bangladesh. The 1.2 million hectares Coastal Zone is home to 8 million Bangladesh in the delta of the Ganges river.[3] The region, typically within 10 m above sea level, is subject to tidal flooding, saltwater intrusion, and seasonal drought. Food insecurity diminishes the development of half the children in the region.

Image: © SIIL Polder Team

Previous studies indicated that increasing mothers' knowledge of nutrition contributed to improved nutritional status of children and the whole family. The SIIL Polder project established a knowledge hub on nutrition, engaging mothers of primary school children in the awareness campaign and training activities.

Image: © SIIL Polder Team

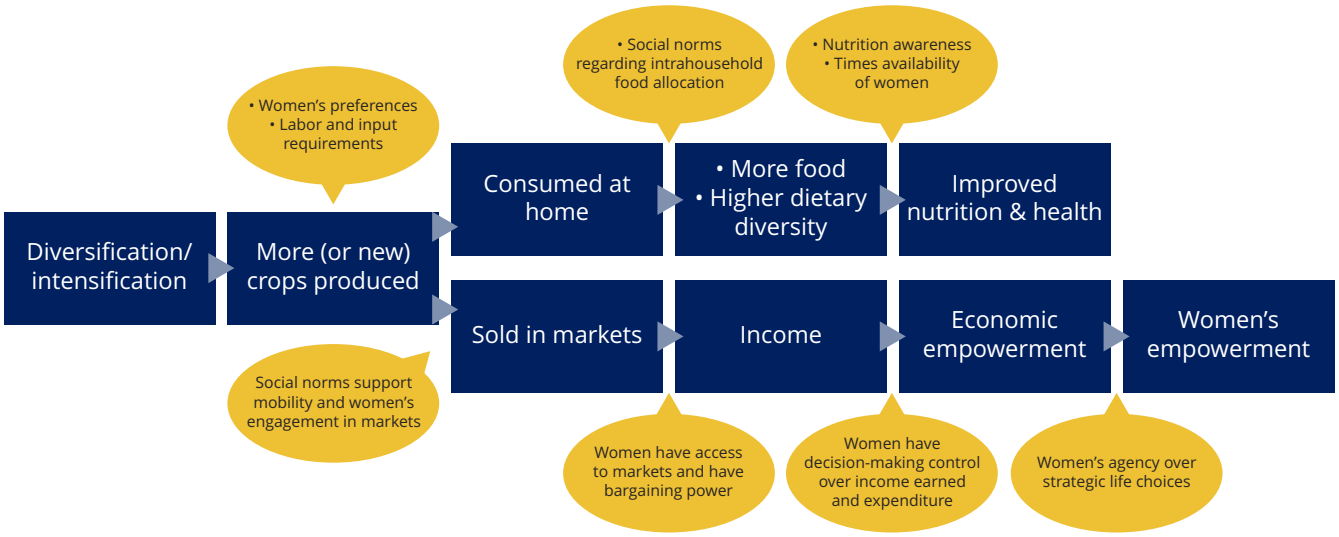
The SIIL Polder project works with communities in managing water governance – timing the opening and closing of sluice gates – in the polders. "Water management has become the key entry point in changing people's lives and triggers socioeconomic development in coastal Bangladesh" according to Sudhir Yadov, a water scientist at the International Rice Research Institute.

Water management is critical for crop growth and food security in the Coastal Zone, utilizing dikes and gates established in the 1960s and 1970s to manage large water catchments, known as 'Polders.'

Another colleague, Dr Krishna Jagadish, directs the Polder project for the K-State Sustainable Intensification Innovation Lab. Krishna's project has established a team of young scientists (nutritionists, water management, agronomy, social sciences, economics, climate-crop modelling) and sociologists who are learning about food networks in one of the nearly 130 plus polders in the Coastal Zone of Bangladesh. Learning hubs form a key component of the adaptive research pursued by these teams. Some of their findings:

Adoption of climate-resilient high-yielding rice varieties can boost grain yields by up to 50%. Incorporating fish production into the flooding phase of paddy rice supports household nutrition.

Successive cropping of hybrid corn and nutritious pulse crops can double annual food productivity. Corn grain can support emerging poultry production enterprises, while stalks provide fodder for livestock.



Crop diversification and intensification affects gender dynamics in the crop-livelihood-food systems of the Bangladesh Coastal Zone. A simplified pathway toward better nutrition, livelihoods, and women's empowerment in rural households. Image courtesy SIIL Polder Team.

Farmers who cultivated different rabi[4] crops (%)		
Cropping Patterns	2015-2016	2016-2017
Climate-resilient high-yielding varieties (HYV) of rice (SIIL intervention area)		
Rice-sesame	30.7	23.9
Rice-mungbean	14.7	32.3
Rice-okra	10.7	15.4
Rice-sunflower	6.0	14.4
Rice-maize	0	4.5
Rice-HYV rice	2.7	3.5
Rice-sweet gourd	0	5.0
Rice-other crops	0	2.5
Rice-fallow	41.3	28.4
Traditional rice (outside of SIIL project intervention)		
Rice-sesame	30.0	17.5
Rice-mungbean	5.0	12.5
Rice-okra	12.5	7.5
Rice-sunflower	0	0
Rice-HYV rice	0	0
Rice-vegetables	0	0
Rice-fallow	52.5	70.0

Impact of the SIIL Polder project on cropping patterns of the Coastal Zone of Banglasesh[5]

The burden of more intensive cropping can fall, disproportionately, on women in the household, often responsible for crop harvest. Mechanical harvest using small reapers can reduce labour requirements by 80%.

Seed storage enterprises – in rat-proof containers, provide income opportunities for women lacking access to land resources. Coordinated water management in the polders is critical for all of these developments. Learning hubs provide critical means of sharing information about new practices, successes and challenges. The students contribute insights into the polder food network while developing professional credentials and experience. Together, the project fosters learning communities where adaptive land intensification help families adapt to changing conditions.

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2 Director, K-State Sustainable Intensification Innovation Lab (SIIL), supported by US AID.

3 Polder Tidings, a newsletter published by the International Rice Research Institute with support from the K-State Sustainable Intensification Innovation Lab (SIIL), funded by US AID. Contact Dr. Krishna Jagadish (KJagadish@ksu.edu) or Dr. Sudhir Yadav (S.Yadav@irri.org) for more information.

4 The rabi season (November – March) is typically cool and dry, winter.

5 Yadav, S., M. Mondal and K. Jagadish. 2017. "Foregoing fallow: Improving productivity of polders in Bangladesh. Polder Tidings Vol. 2 No. 1: pp 4-5. International Rice Research Institute.

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Harnessing the plant microbiome for commercial applications

Philippe Rolshausen, Cooperative Extension Specialist based at University of California, Riverside, explains how the plant microbiome can be harnessed for commercial applications

In the second half of the 20th Century, the green revolution increased agricultural production to feed a globally growing population. It was made possible because of the adoption of new practices, transfer of technology and planting of high-yielding crop varieties. On the other hand, this revolution changed the agricultural landscape and came at an environmental cost because of the increased demand for water and a greater need for agrochemical inputs. Fifty years later, we stand at a crossroad of the green revolution because while we are projected to reach a global population of nine billion people by 2050, we cannot afford to ignore the environmental challenges that lie ahead of us.

Public awareness of environmental risks has expanded consumer demand for organic or sustainably grown food products which, in turn, shifted the standard conventional farming practices to more integrated systems. The use of synthetic chemicals is still a cornerstone of those agricultural practices in order to maximise crop productivity and limit losses caused by diseases. While these practices will not disappear for obvious reasons, research has optimised chemical formulations, delivery and efficiency and as a consequence, reduced the chemical inputs in cropping systems and runoffs in the environment. In addition, it facilitated the adoption of natural biological products that contain living microorganisms. Agricultural biological products have now become an integrated part of pest and disease management practices and nutritional programmes in developed markets, where bioproducts are used in combination with synthetic crop chemistries.

The assemblage of microbial organisms associated with humans or plants is known as the microbiome and can be viewed as an extension of the host genome. There are over a billion bacterial cells that inhabit a gramme of soil or gut. The equilibrium established between those living entities (or homeostasis) is critical for host health and that imbalance between the two entities (or dysbiosis) may lead to a state of stress. The microbiome has been a major focal point of scientific and clinical research and has fuelled the expanding market for plants and human probiotics. The agricultural biologicals market is projected to grow at a Compound Annual Growth Rate (CAGR) of 13.8% to reach $14.65 billion by 2023 from $6.75 billion in 2017. In comparison, the U.S. markets for probiotics is estimated at $49.4 billion in 2018 and is projected to grow at a CAGR of 7% in the next five years. The strategy for a probiotic is to introduce "beneficial" microbe(s) that could provide advantageous traits to the host and improve environmental fitness. Yet the inability to predict or manipulate the behaviour of the introduced microbe and to deliver a consistent response to the treatments have impacted scientific credibility. The advent of "Omics" technologies provide the tools for a broader understanding of the microbial ecosystems and their dynamic interaction with the host. It enabled the screening of large microbial populations and identified individual or groups of taxa with functional capabilities.

The rhizosphere (the soil environment that surrounds the roots) is a microbe-rich environment that includes fungi, oomycetes, archaea, viruses and bacteria. Evidence shows that plants have developed a mechanism for recruiting specific microbes to cope with environmental stress. In this capacity, the host-selected microbes have provided a protective role against invasion by opportunistic pathogens, or drought conditions. Capitalising on those endemic functional microbes would increase the success rate for commercial biopesticides that currently rely on the exogenous application of non-native strains to a crop system. There is broad scientific support for biological controls against plant pathogens. However, those have been established in controlled conditions in in vitro or in planta assays, but under field conditions, very few biological control agents can perform at a competitive level. This limitation combined with the challenge of formulating a product that guarantees a long shelf life of microbial activity has hindered market access of the microbial technologies. Yet there have been a handful of com-

"...we stand at a crossroad of the green revolution because while we are projected to reach a global population of nine billion people by 2050, we cannot afford to ignore the environmental challenges that lie ahead of us."

mercial successes for agriculture with fungal- (e.g., Trichoderma) and bacterial-based (e.g., Bacillus, Streptomyces, or Pseudomonas) bioproducts.

The plant rhizosphere also conveys key nutritional functions similar to those of the human gut. Scientists made the analogy that "plants wear their gut on the outside" because roots are exposed to the fluctuation of the environmental conditions, as opposed to the gut that is internal and, thereby, more environmentally sheltered. The energy production strategy between plants and mammals are, however, different. Plants can internally generate their own carbon energy (or autotrophs) through photosynthesis, while mammals seek their energy from other external sources (or heterotrophs). The mammalian gut has evolved to facilitate the uptake of simple sugars, lipids, vitamins and ions. In contrast, nutrient acquisition by roots to support plant growth is almost exclusively limited to mineral ions and water from soil. The microbial profile of human guts and the plant rhizosphere is qualitatively and quantitatively different because of the contrasting conditions under those two environments (oxygen level, pH, food availability). Despite the fact that those two microbiomes have evolved independently, they have in both cases, helped facilitate availability and assimilation of nutrients to their host. One obvious example is the symbiotic relationship between legumes (peas, beans) and rhizobia. Those bacteria help the plant fix atmospheric nitrogen (78% of the air) in exchange for a carbon supply. Another example is the symbiotic relationship between the plant and mycorrhizal fungi, whereby the mycorrhizae receive carbon from the plant in exchange for increased nutrient uptake (principally phosphorus and nitrogen). Both of those symbiotic microbes have been commercialised as biofertilizers and are being used successfully in agricultural production systems, mostly for annual cropping systems. Our research has also shown that citrus trees are often found in association with mycorrhizae and those fungi appear to support tree health under stress conditions. Our group is investigating if this symbiotic relationship can be established early on at the tree propagation phase in nurseries, rather than at a later stage in the field. In this way, this strategy would promote tree growth early on and sustain orchard longevity.

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Creating urban tree biodiversity within a uniform street tree landscape

Dr Nina Bassuk, Professor at the Urban Horticulture Institute, School of Integrative Plant Science, explains creating urban tree biodiversity within a uniform street tree landscape

Street tree landscapes typically consist of uniform rows of a single species, generally selected for their high branch clearance from the ground, attractive appearance and high tolerance to urban stresses. However, the desire for uniformity, which can be seen in countries all over the world, has created a conflict between the cultural preference for visual uniformity and the practical need for species diversity.

Most cities exhibit a low species diversity when it comes to urban trees. This may be caused by historical convention combined with the assumption that only a few species would adhere to cultural and design norms. However, the over-planting of a limited number of species called monocultures, have brought about the decline of formerly common and numerous types of tree. When a few trees dominate, their diseases and insect pests can proliferate causing tree decline.

Elms, chestnuts, and ash trees have been decimated by the proliferation of insects (emerald ash borer) and diseases (Dutch elm disease, Chestnut Blight). It is clear that design objectives must be balanced against the practical need for species diversity in street tree plantings.

Current strategies

Faced with the difficulty of balancing aesthetic and ecological concerns, current designers all too often short-change or even abandon one or the other objective-genetic diversity or visual uniformity. Where they may have once planted an entire neighbourhood with the same species, those favouring uniformity over practicality might now plant a single species for one or two blocks of a given street. Although this sort of compromise may feel like a bow to diversity, it isn't a true solution to the problem. Planting trees in somewhat smaller 'same species' blocks will not necessarily prevent the kinds of devastation associated with monocultures on a block by block basis, particularly if the species selected have already been heavily planted in the community.

For those favouring an ecologically sensible approach, the alternative to monocultures is sometimes to plant wonderfully diverse selections of trees that share no common characteristics whatsoever. The results of such efforts can be aesthetically disappointing and in a number of cases have led to public outcry.

Unfortunately, this type of plant selection has served to fuel the idea that the only way to achieve uniformity in design is through the exclusive use of one species.

The case for visual uniformity

So, what makes uniform plantings so appealing in the first place? What makes them so difficult to give up? The advantages to uniformity are primarily aesthetic and have a long-standing tradition over many centuries internationally. A street lined with rows of more or less identical trees brings to most observers a sense of order and tranquillity, even the domination of nature. In the most heterogeneous of neighbourhoods, a uniform row of trees can have a cohesive influence, tying together diverse elements and creating a sense of neighbourhood identity. Street trees can also soften the potentially jarring transitions from residential to commercial areas.

Moreover, marching rows of identical trees have been used as a symbol of power by military commanders as they marched their armies down those uniformly designed streets.

The case for species diversity

Unfortunately, the appeal of same species plantings is ultimately outweighed by its disadvantages. Even if aesthetics were the only consideration, the fact that unhealthy or dying trees are unattractive makes the need to diversify unavoidably.

Another factor that makes monocultures impractical is the tremendous diversity inherent in the urban environment. The challenges and stresses for trees can change dramatically within very small distances, often making it impossible for a single species to thrive uniformly throughout a given area. Variables, such as light, reflected tem-

Three species on a street creating a uniform appearance while increasing genetic diversity

American Elms in a monoculture before Dutch elm disease (DED)

After Dutch elm disease (DED) killed all the Elms

perature, drainage, soil compaction, limited rooting space, soil pH, availability of water, exposure to salt, and restrictions to crown development can vary tremendously even from one tree space to the next. A careful assessment of site conditions prior to plant selection rarely points to the selection of a single species. Even those who are aware of this fact often make the mistake of selecting one species that will purportedly survive under any and all difficult conditions. Such widely adaptable species dominate the aforementioned list of overplanted trees that have suffered decline, become unmanageable, or both.

A solution

To avoid similar problems in the future, it is clear that uniform plantings of a limited number of species must be avoided. But, is it possible to gain the practical advantages of diversity without giving up the aesthetic desire for uniformity? Fortunately, the answer is yes. Through the careful selection and grouping of plants, communities of trees can be created which, despite their genetic diversity can satisfy our desire for visual uniformity.

By breaking down the visual characteristics that distinguish one species from another into basic categories, we have selected a set of five criteria for putting genetically diverse species into aesthetically compatible groups. The first criteria concerns height to first branch. The distance from the ground to the first branches of the tree canopy creates the visual and physical envelope that we view or walk under. By keeping this space equal between trees, the walking or viewing experience appears alike between trees. The second and third criteria are tree size and shape. Nothing will create a uniform appearance less than a large tree planted next to a small tree or a narrow tree planted next to a broad spreading tree.

> "Unfortunately, the appeal of same species plantings is ultimately outweighed by its disadvantages. Even if aesthetics were the only consideration, the fact that unhealthy or dying trees are unattractive makes the need to diversify unavoidably."

The other two criteria of less importance are branching density and foliage texture. They are given secondary consideration because they generally are not as obvious to the casual observer and can even become difficult to distinguish as the distance from the observer increases. By using these criteria, it is possible to have greater biodiversity in our cities while acknowledging the desire for visual uniformity.

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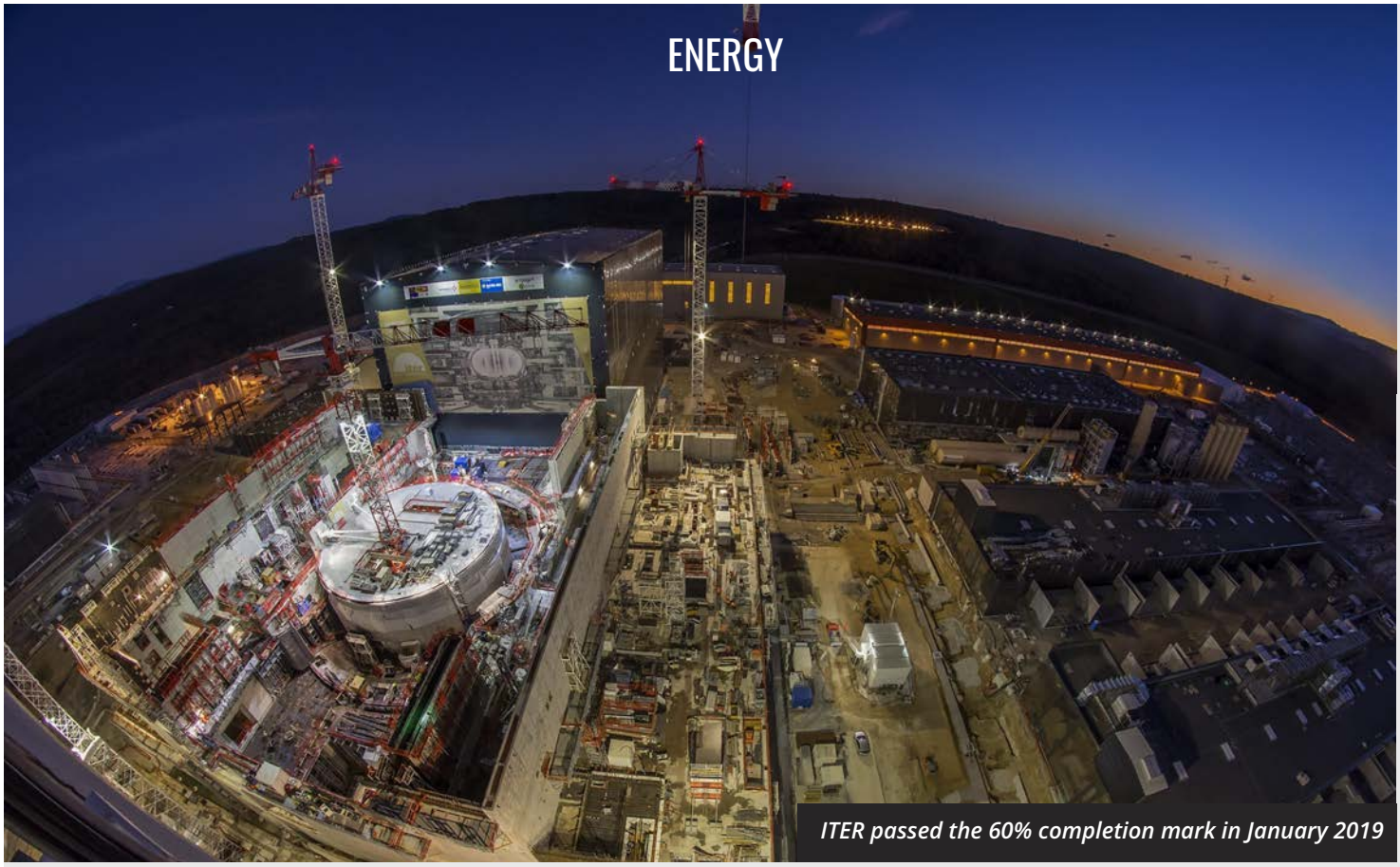

ITER passed the 60% completion mark in January 2019

Image: © ITER Organization

Fusion: Clean, safe and virtually unlimited source of energy for future generations

Laban Coblentz, Head of Communication at ITER takes us on a journey of discovery when it comes to fusion as a clean, safe, virtually unlimited source of energy for thousands of future generations

Cradled in the rolling hills of Haute-Provence in southern France, a slumbering giant is emerging from the earth. Global awareness is also rising: the ITER Tokamak, a collaboration of 35 countries to build the first industrial-scale fusion reactor – literally "a star on earth" – is among the most ambitious scientific endeavours of our time, with high stakes for our future.

While hundreds of tokamaks have been built over the past six decades, none are like this. Still, observers tend to limit their observations of ITER's uniqueness to superlatives. The 150 million °C operating temperature of the plasma. The frigid chill of the superconducting magnets, operating at near absolute zero (-269 °C). The weight of the Tokamak Complex – 400,000 tonnes, heavier than the Empire State Building – resting on 493 carefully positioned seismic pads. The strength of the Central Solenoid structure at the machine's heart, able to withstand twice the thrust of a space shuttle launch. Or the heat flux ITER's toughest surfaces must withstand 20 megawatts per square metre, twice the torrid load a space shuttle endures on re-entering the Earth's atmosphere, but for a sustained period.

These comparisons can be mindboggling. But they do not fully portray ITER's "firsts," nor do they hint at ITER's ongoing, real-time return on investment for its partners. Within this first-of-a-kind machine is a mini-universe of first-of-a-kind components, systems, and technologies.

Consider the ITER magnet system, designed to forge an invisible magnetic chamber inside the metal tokamak, confining the ultra-hot plasma away from the physical walls. To build this first-of-a-kind structure at

Image: © Fusion for Energy

A specialised tool created by Douce Hydro to test the performance of ITER's "pre-compression rings"

ITER's scale required, among other materials, 100,000 kilometres of niobium-tin strand, nearly 500 tonnes. At the outset, worldwide production capacity of niobium-tin stood at 15 tonnes per year. Nine suppliers in six of the seven ITER Members ramped up global output to nearly 150 tonnes per year – each working to precisely the same materials specifications, testing protocols, and quality assurance standards. A global industry was born. For any superconductor application, such as medical scanning equipment, a call for tender could now be placed with equal confidence in Carteret, New Jersey, Xi'an, China, or the Jastec facilities in Japan.

Consider the first-of-a-kind tools demanded by ITER's assembly process. Taekyung Heavy Industries of Korea has manufactured the twin titans in this ITER toolbox: two 22-metre-tall Sub-Sector Assembly Tools, each capable of delicately folding together a 440-tonne vacuum vessel sector, two 310-tonne toroidal field magnets, and segments of the thermal shield into a composite whole, with precision measured in millimetres. To verify the performance of ITER's magnet-protecting "pre-compression rings" – more than a billion glass fibres held together with epoxy resin – a futuristic testing device developed by Douce Hydro of France (pictured above) will exert a force of 36,000 tonnes with a positional accuracy of 0.1 millimetre.

Each such tool – and there are dozens more – demands innovation. And there is more. Across every aspect of the project, in laboratories and fabrication centres on three continents, fit-for-purpose R&D is being used to develop specialised steel alloys, gyrotrons, pellet injectors, power electronics, cryogenic pumps, tritium breeding systems, and hundreds of other first-of-a-kind innovations.

When CEOs talk about the benefit of participating in this project, they rarely focus on a contract's monetary value. They speak of being stretched, of the creativity and innovation ITER demands, of the newly developed industrial capacities that result, of new spin-off technologies with implications and markets well beyond plasma physics or tokamak engineering – and of the increased competitiveness they acquire by being part of this unprecedented project.

The multinational nature of the ITER project is in itself driving first-of-a-kind solutions to logistics, shipping and storage, schedule management, 4D software and data management, multi-sector cooperation, and other challenges of international project management. Given the array of complex cross-border threats facing modern society, from climate change to pandemics, several wise observers have commented that the lessons learned in this area may prove to be among our most enduring and meaningful contributions: learning how to work together, in the most tangible terms, to solve a global problem.

Ultimately, ITER will enable scientists to study a controlled "burning" or self-heating plasma, the gateway to offering fusion as a clean, safe, virtually unlimited source of energy for thousands of future generations. But until that time, even now, the returns on investment are rolling in. ■

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Plasma-Jet-Driven Magneto-Inertial Fusion – A progress report

Y. C. Francis Thio and F. Douglas Witherspoon, HyperJet Fusion Corporation,
provide an update on the progress on Plasma-Jet-Driven Magneto-Inertial Fusion

In this article, we continue our reporting on the progress made on the fusion approach, plasma-jet driven magneto-inertial fusion (PJMIF), which we began in the last of these series of articles [1]. A review of the progress made in the development of the plasma gun needed by PJMIF is given in [2]. Under the ARPA-E ALPHA program launched in 2015 [3], a plasma gun called the ALPHA2gun was developed. The plasma gun development has experienced three development cycles. The first cycle was undertaken with a series of gas valves culminating in Revision 9 (Rev9) using the ALPHA2gun [4].

The second cycle of development introduced Revision 10 (Rev10) of the gas valve, which had substantially improved performance characteristics over the first 9 versions in terms of precision gas mass metering, the speed of opening and closing, reliability, and repeatability. The third cycle of the development of the plasma gun (HJ1) is near completion [5]. Final tuning of the gun is in progress.

In 2016-2018, multiple-gun operations to launch and merge up to seven jets to form a conical section of the plasma liner was performed using the second-generation gun (Alpha2Gun) equipped with the Rev10 gas valve at the Los Alamos PLX-α facility. High-speed framing end-on CCD images of the six Jets merging were acquired, samples of which are shown in Figure 1(a). The images show clearly the formation of primary shocks when the jets first merge. The shocked region of the jet spreads laterally, and soon the shock processes the entire jet. The shocked plasma flows proceed to merge and produce secondary shocks which process the plasma in a similar way as the primary shocks, thus resulting in a cascade of shocks.

This phenomenology was expected theoretically. Computer simulations of the jet merging dynamics agree well with the experimental results as shown in Figure 1(b). Reasonable agreement between the computer simulations and the experimental results is obtained when 10% random mass variations and 1 μs random timing variations in the arrivals of the jets are introduced into the computer simulations.

The shock cascade raises an important physics issue. The shocks heat up the plasma liner, increasing its internal pressure, which resists the self-compression of the liner, thus reducing its efficacy in compressing the target plasma when it is used to implode a target plasma. A dimensionless quantity that may be used to gauge the severity of this effect is the Mach number, which is the ratio of the plasma liner flow speed to its internal sound speed. The heating of the plasma liner raises its internal sound speed, thus lowering the Mach number of the flow.

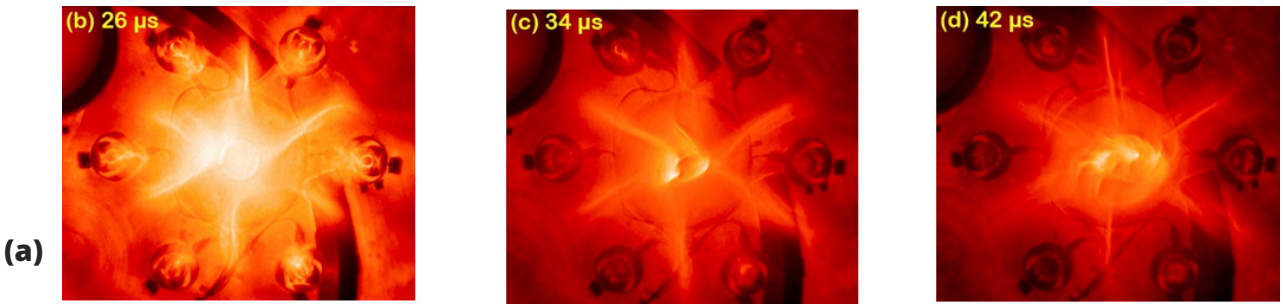


Fig. 1. Merging of six jets to form a conical section of a plasma liner: (a) High-speed framing end-on CCD images (false colour) of six jets merging at 26 μs, National Laboratory. Reproduced from W. Shih, R. Samulyak, S. C. Hsu, S. J. Langendorf, K. C. Yates, and Y. C. F. Thio, Phys. Plasmas, 26, 032704 (2019) doi:1

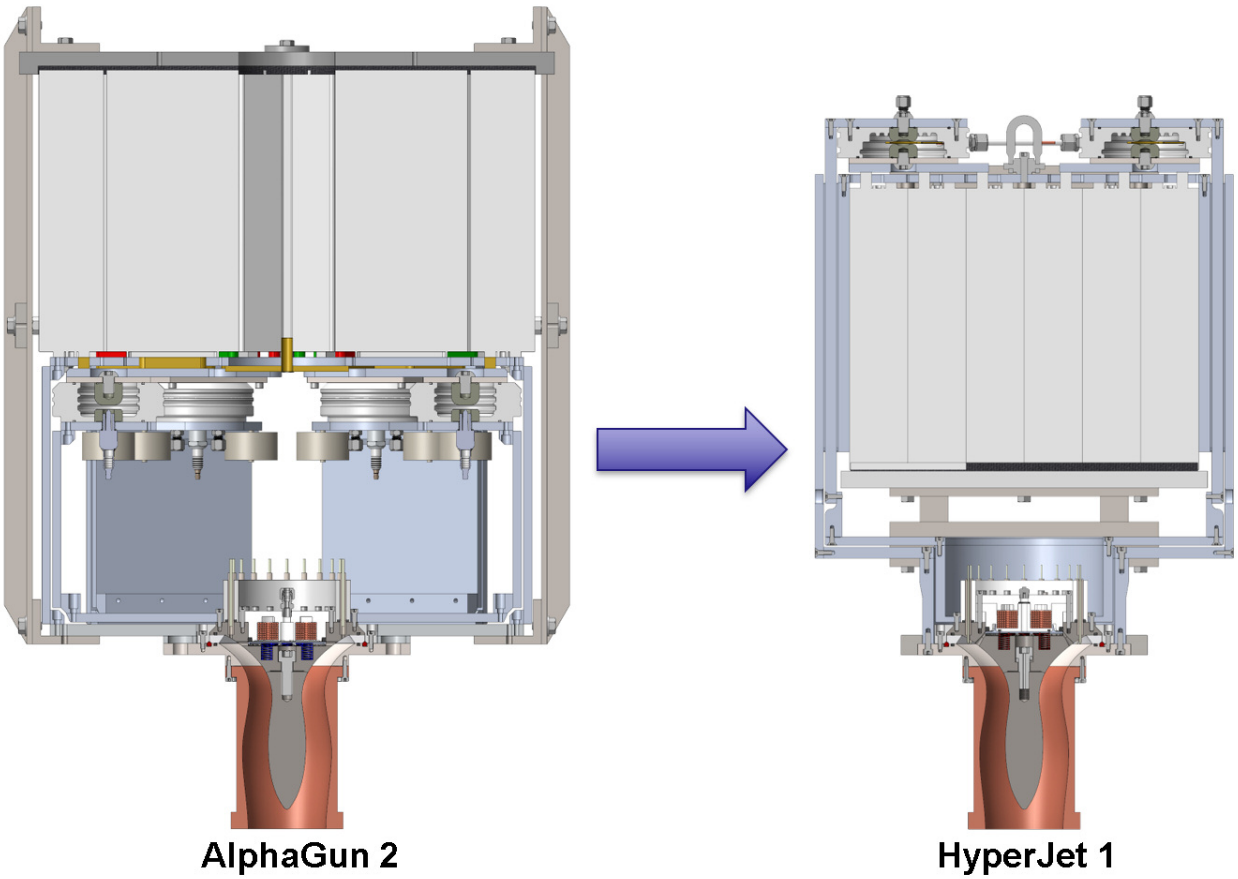
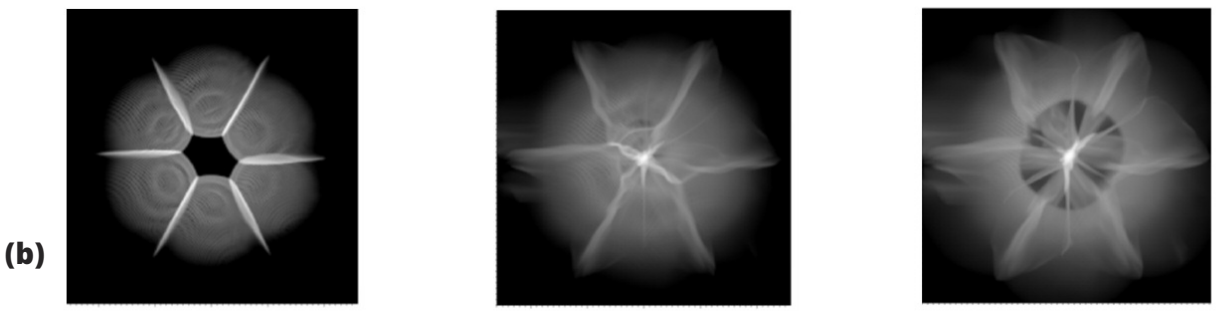


Fig. 2. The footprint and volume of the capacitor module are significantly reduced from Alpha2gun to HJ1.

The heating of the liner by the shocks is mainly experienced by the ions in the liner, while the electrons remain cool. If the electrons can cool the ions at a sufficiently high rate, it is possible that the plasma liner may recover its high Mach number at some point after merging. By studying how the Mach number of the liner evolves in time, we can better assess the effect of the shock cascades caused by the jet merging on the imploding efficacy of the plasma liner. This is an important piece of physics we wish to extract from our multiple jet merging experiments.

We found indeed that the rate of cooling of the ions by the electrons was sufficiently fast for the ions to recover its Mach number from a temporary depression during the traverse of the plasma liner towards the centre before it was expected to engage with the target in an actual liner-on-target implosion in a typical PJMIF scenario [7, 8].

Over the last 12 months, HyperJet Fusion has been engaged in the development of a third-generation plasma gun (HJ1), introducing the following new features [5]:



34 μs, 42 μs after launching of the jets. (b) Computer simulations of the six-jet merging experiments using the code, FronTier, of Brookhaven 0.1063/1.5067395, with permission from AIP Publishing.

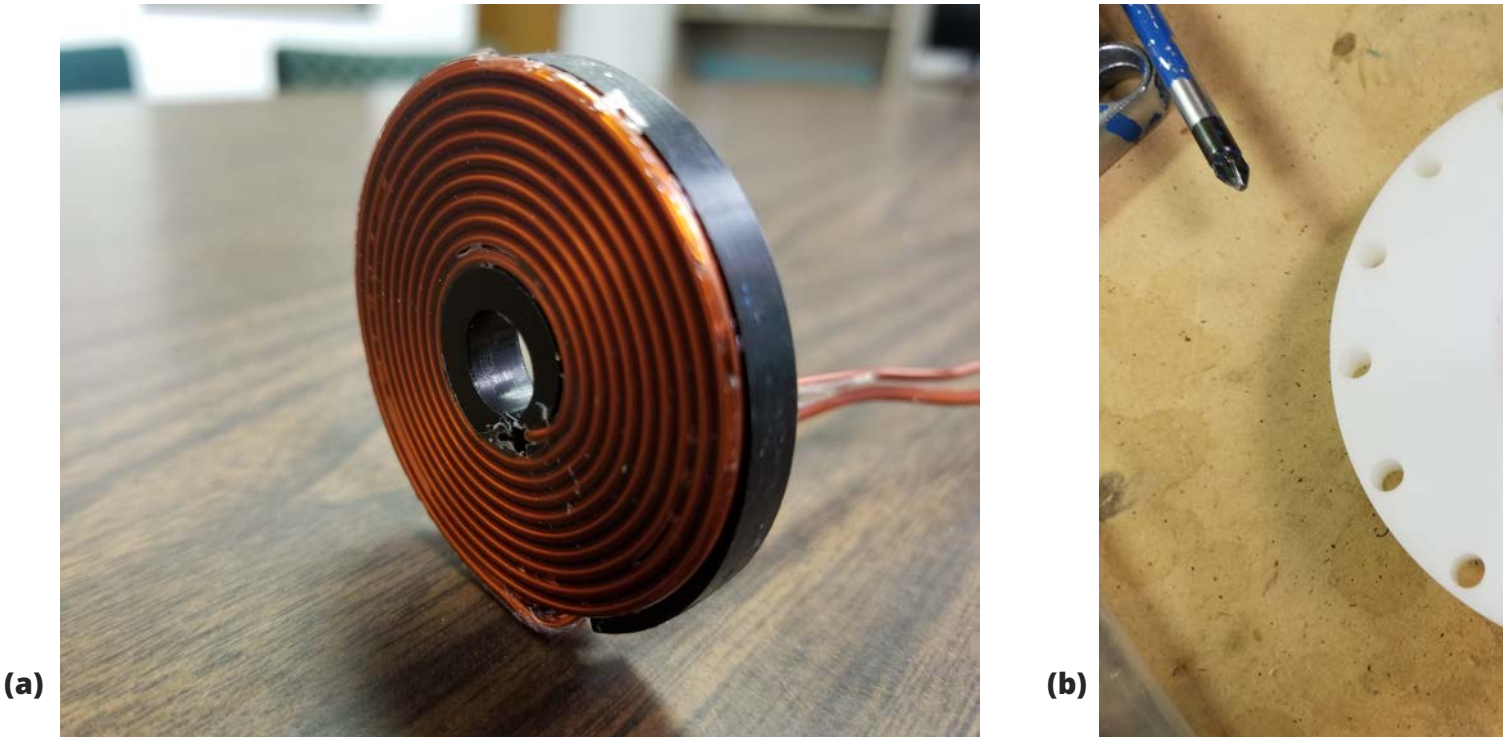


Fig. 3. The new HJ1 gas valve and pre-ionizing technique: (a) the gas valve drive coil is planar, axisymmetric, precision wound and highly reproducible. (b) The

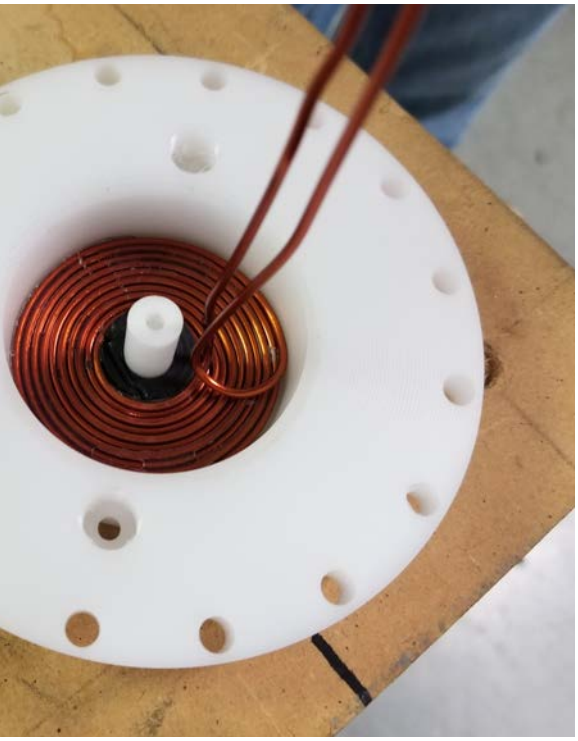
The footprint and volume of the capacitor module driving the gun is considerably reduced going from Alpha2gun to HJ1 as shown in Figure 2. This is necessary in order to field all 36 guns on the PLX tank. The space between the transmission plates in the manifold is completely filled with a solid insulator, thus, providing robust and reliable electrical insulation without any voids, preventing any spurious arcing breakdowns in the transmission manifold. The tighter configuration also results in lowering the internal inductance of the transmission manifold. We expect that, as a result of the lower parasitic inductance, HJ1 should have higher electric-to-kinetic efficiency.

The gun makes use of a gas valve to dispense working gas into the gun. The gas valve is opened by an electromagnetic propulsion subsystem consisting of a drive coil and an aluminium flyer plate (a coilgun). To open the gas valve, a large pulse of electrical current is passed through the drive coil, which induces a large eddy current in the flyer plate. The drive current in the coil and the induced eddy current in the flyer plate repels each other giving rise to the propulsive force that opens the valve.

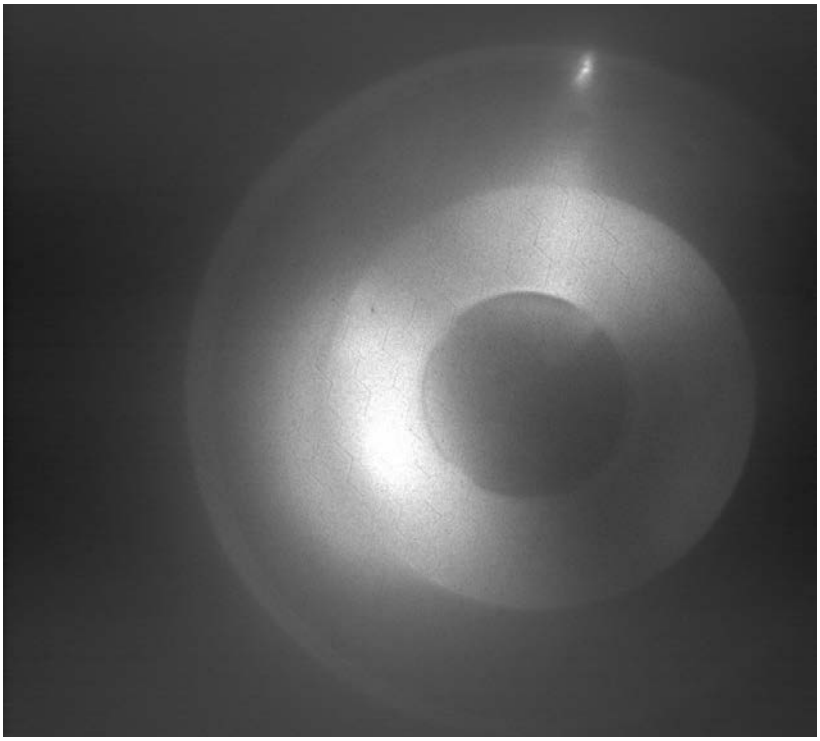
The self-inductance in the drive coil in HJ1 is about 20 times smaller than in Alpha2gun, leading to a 10-fold increase in the electric-to-kinetic efficiency. Consequently, the capacitor bank of about 1 kilo-joule per gas valve that was required to drive the gas valves in Alpha2gun is reduced to only 100 joules, which can be supplied by a capacitor module that can be packed with each individual gun.

The drive coil in HJ1 is a single-plane, axisymmetric coil that can be wound and placed in the gas valve body with a high degree of geometry precision with respect to the flyer plate (Figure 3). The initial gap between the top of the drive coil and the flyer plate is tightly controlled, leading to very little variations in the mutual inductance between the drive coil and the flyer plate from valve to valve. The mutual inductance is the electrical parameter that determines the repulsive force between the drive coil and the flyer plate. Small adjustments to the circuit parameters for the individual coil of each gun will be sufficient to compensate for any electrical and mechanical variations from valve to valve. A dedicated gas-valve test stand to fine tune, calibrate and qualify each gas valve for all the 36 guns have been developed. Improvement in gun-to-gun repeatability of the gas valve is expected.

To prepare the initial neutral gas slab to accept the main current pulse, the



(c)



e drive coil is snugly fitted into the valve body, leaving very little wiggle room. (c) A self-switching glow-like discharge for pre-ionizing the initial gas slab.

gas slab needs to be pre-ionized. In HJ1, we introduce for the first time a new pre-ionization technique for plasma guns based on a self-switching glow-like discharge (Figure 3(c)) [5]. Eliminating the switch simplifies considerably the logistics of implementing the 36-gun plasma liner experiment. Furthermore, the new pre-ionization system is two-fold more efficient energy-wise than that used in Alpha2gun, allowing a smaller capacitor to drive the pre-ionization, small enough for the capacitor to be packed as part of the gun. However, the technique appears to have the tendency to trigger the main current discharge prematurely. We are in the process of troubleshooting the problem.

A new closing switch for the main discharge has been developed that uses a much more efficient triggering mechanism based on the field-distortion configuration. The field-distortion trigger uses only 15 J of energy per gun compared with 250 J of energy per gun in the Alpha2gun. This also eases the logistics burden of fielding the 36-gun plasma liner experiment [5]. Production of the 36 guns is underway.

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Agile software development and the delivery of digital services

Kent J. McDonald, Content Curator at Agile Alliance lifts the lid on Agile software development and the delivery of digital services

Agile software development is an umbrella term for a set of frameworks and practices based on the values and principles expressed in the Manifesto for Agile Software Development and the 12 Principles behind it. Those values and principles emphasise delivering value to your customers, responding to change, and collaboration.

Agile frameworks and practices are particularly helpful if you work in complex or uncertain environments where you know you have a problem to solve, but you're not exactly sure what that problem is and you certainly don't know what the solution is.

Agile frameworks encourage short feedback cycles in the form of frequent deliveries followed by feedback and adjustment. These short feedback cycles help you to validate assumptions, discover the true problem, and identify a proper solution.

When you work on digital services, you interact with people outside your organisation, such as customers, constituents, or suppliers. Those interactions happen on your organisation's website, mobile app, or through software that allows people outside your organisation to self-serve and engage directly with one or more of your processes.

The minute you interact with people outside your organisation, you inherently enter an uncertain and complex domain. You have no control over whether they use your new digital services, so you have to look at those digital services as you would a product. You have to figure out what will encourage use of the services. You have to figure out how those services can add meaningful value to your customers, constituents and suppliers.

You need to learn what customers, constituents, or suppliers find valuable. You need to learn how to apply the values and principles expressed in the Agile Manifesto to provide them with that value. You can do this most effectively by delivering a small piece of your solution and getting feedback. You need to operate in an Agile fashion.

Digital services add value in the private and public sectors

Many organisations view digital transformation as a way to bring efficiency and cost savings to their organisation and its processes. After all, why employ staff to interact with your customers when you can set things up to allow them to self-serve?

This is a short-sighted view that may do harm to those organisations in the long run. Anyone who has fallen into an endless phone tree loop or been lost in a poorly designed online request form can attest to the damage a poorly designed digital service can do to an organisation's reputation in the eyes of its customers.

If you want to adopt digital services your primary focus should be on providing value to your customers. How can you make getting services from your organisation simpler? How can you make your customers want to do business with you? Design those services right, and they will often add an additional way to interact with your organisation rather than replace an existing means. Design those services right, and you will add value for your customer and generate benefits for your organisation at the same time.

The same applies to organisations in the public sector. Replace customers with constituents, and the above still holds true, but perhaps even more so. When you

create a digital service that is easy for citizens to use and allows them to accomplish what they set out to do, your services are more likely to accomplish the outcomes they were established to provide, and your citizens will have more confidence in your organisation.

Becoming an Agile organisation requires change

In order to deliver digital services that truly add value to your constituents, you have to approach delivering those services in an iterative, incremental fashion. You have to be willing to form hypotheses about your constituents and their needs and prove or disprove those ideas with safe-to-fail experiments.

That type of approach will not happen if the only part of the organisation that changes are the people responsible for developing software. Your entire organisation needs to think how to work in a way that delivers value to your constituents, responds to change, and encourages collaboration. This means that bureaucracy, self-serving actions, and empire building cannot have a place in your organisation.

You have to ask on a regular basis: "How might we structure and operate our organisation in a way that allows us to create and respond to change and deal with uncertainty?" You need to follow up on the answers you come up with.

The change is not easy. The change is not quick. But if you're serious about it, the benefits for your constituents and your organisation are well worth it. ■

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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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Canada: Reducing emissions and taking action on climate change

Patricia Fuller, Canada's Ambassador for Climate Change, explains how Canada is taking action to reduce emissions and tackle climate change

In a past edition of Open Access Government, Minister of Environment and Climate Change in Canada, Catherine McKenna detailed the country's plan to reduce carbon emissions and strengthen their clean growth economy. Minister McKenna believes that governments can assist people to thrive in a changing climate. "Governments everywhere want to protect their citizens from climate risks. They want to build resilient communities, protect investments, reduce costs and ensure people thrive in a changing climate", she says.

In March this year, we were very fortunate to enjoy a conversation with Canada's Ambassador for Climate Change, Patricia Fuller, to find out how the Government of Canada is working together with Canadian businesses to grow Canada's clean economy. In this interview, we discover how Canadians coming up with innovative methods to increase energy efficiency and reduce emissions, saving people money and creating good jobs. Looking ahead, we learn about the importance of investing in projects that will help Canada reduce emissions and take action on climate change.

Supporting innovation and the development of clean technologies

We know that there are a wide range of programmes in place to support innovation and the development of clean technologies by the Government of Canada. Innovation is supported from early-stage R&D right through to commercialisation and Patricia notes that in recent federal Budgets, support in this vein was expanded through the Business Development Bank of Canada (BDC) and Export Development Canada (EDC). They have both created special teams focused on financing clean technology companies, but there are also many other forms of support being given, Patricia tells us.

"Another important institution that works within this area is Sustainable Development Technology Canada and they are supporting companies that are looking to develop and demonstrate clean technologies."

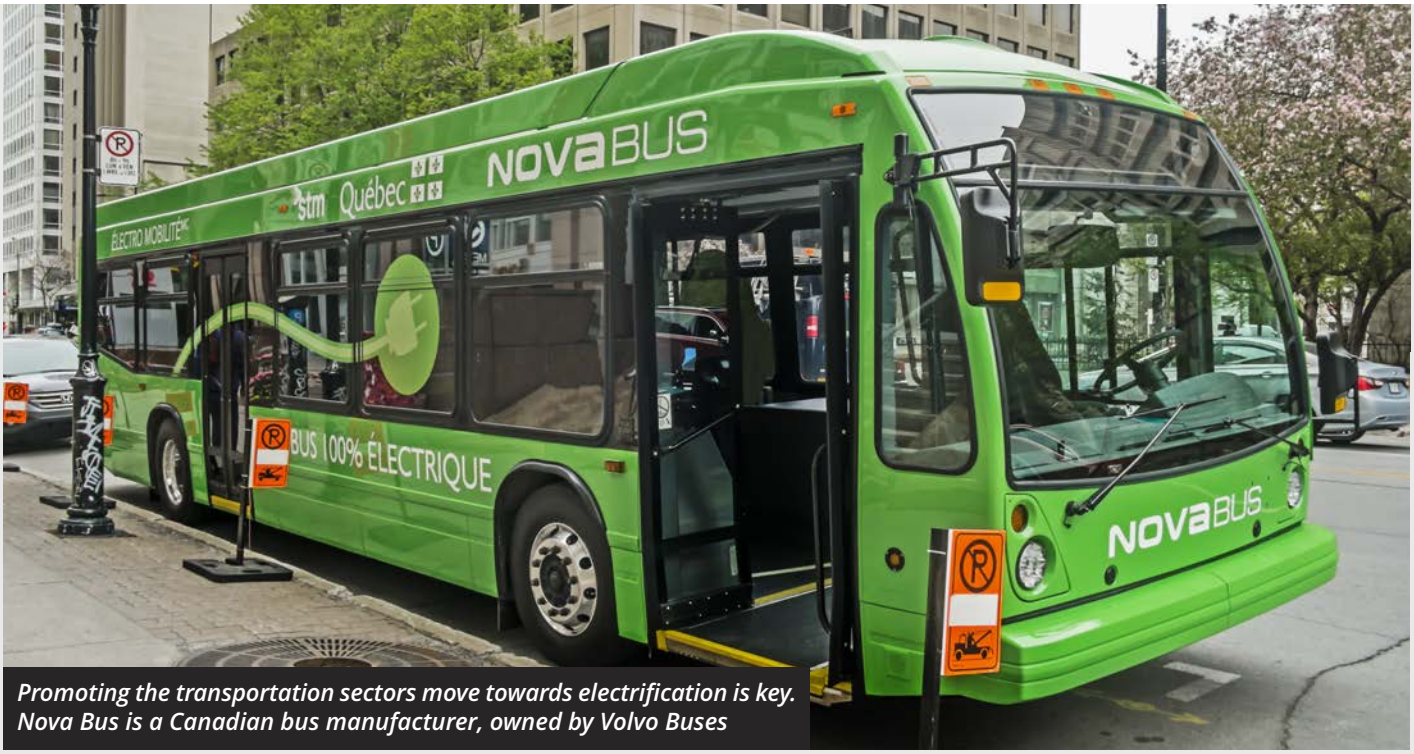
Innovative ways to increase energy efficiency and reduce emissions

The conversation then moves to explain how Canadians coming up with innovative methods to increase energy efficiency and reduce emissions will save people money and create good jobs. Patricia underlines that in Canada today, innovation is being evidenced in all sectors of the economy in light of that fact that both clean technology and clean growth encompass many areas. One example is the industrial sector, where there are innovations around saving companies energy costs through innovation in processes. Patricia then keenly gives additional examples in her own words.

"A whole area of innovation we are seeing a lot of is in the application of IT and the Internet of things (IoT) so that industry can become much more efficient in how they use resources. We are seeing the IT and data analytics space innovating very strongly.

"Also, in the area of electricity generation, we see the application of IT and artificial intelligence (AI) to the management of electricity grids. There is the whole area of smart grid technology and grid modelling, that enables much more use of renewable energy because the electricity grid can become much more decentralised.

"In the area of energy efficiency when it comes to buildings and homes, we have a number of innovations in terms of how to get those projects off the ground. For example, we have seen rapid growth occurring in Toronto over the last 15-20 years in terms of high rise



Promoting the transportation sectors move towards electrification is key. Nova Bus is a Canadian bus manufacturer, owned by Volvo Buses

Image: © Michel Bussieres | Dreamstime.com

buildings while energy demand remains constant, because of improved insulation and lighting, for example, which drives down the use of energy.

"Then, of course, there is the transportation sector where the move towards electrification is key and, we see greater use of electric vehicles and we are supporting charging stations. Canadian companies are also developing electric buses and exporting those internationally, so that is a very exciting area of innovation.

"It's also important to share innovation in the oil and gas sector where companies are investing to drive down the energy-intensity of oil and gas production, as well as developing carbon capture and use technologies. There is the example of a company, Carbon Cure, who puts CO_2 in concrete to make is stronger so that it will create value, and you can see other examples of uses for CO_2 and the potential of a market for that."

Reducing emissions and tackling climate change

As we look to the future, Patricia explains why it is important to invest in projects that will help Canada reduce emissions and to take action on climate change. Investment in these areas creates a "win-win" situation when it comes to Canada reducing their emissions, reaching targets under the Paris Agreement, and helping Canada to be competitive in the global transition towards a low carbon economy.

"We know that all countries are investing in these areas as well and we want to ensure that Canadian industry is positioned to be competitive and to have a leadership role in areas where we have strength. We know that this supports long-term prosperity, as well as the creation of very good jobs today."

Supporting developing countries

From our earlier article by Minister of Environment and Climate Change in Canada, Catherine McKenna, we learn that Canada is assisting developing countries to access clean energy and climate solutions. In 2016, we learn that the Government of Canada committed to contributing $2.65 billion up to 2021 towards the achievement of this goal. Patricia offers her own thoughts on this aspect of policy as the interview draws to a close.

"We are very aware that developed countries need to support developing countries in making the transition and in adapting to the effects of climate change that are already potentially catastrophic for development goals. So, we are investing in programmes that support developing countries to adapt to climate change." ■

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The changing Arctic ice caps

Professor Martin Sharp, University of Alberta, explores the processes, rates and impacts of the changing Arctic ice caps due to global warming

Professor Martin Sharp, University of Alberta

I am a glaciologist with specific interests in the glaciers of the Canadian high Arctic. My work focuses on the rates, processes and impacts of glacier change, glacier hydrology and hydrochemistry, microbial life in glacial environments, and the dynamics of polar glaciers. I am equally interested in communicating about these phenomena, and how they are affected by global climate change, to the broader public, and have been involved in writing several major scientific assessments of Arctic climate change and its impacts. I am also the Director of the Canadian Ice Core Archive at the University of Alberta. This is an ice core research facility that also houses the Canadian national ice core collection.

In the Arctic, semi-permanent ice exists at the Earth's surface in various forms - the seasonal snow cover, as ground ice within permafrost regions, as freshwater ice on lakes and rivers, and as glaciers, ice caps and the continental ice sheet on Greenland. All these forms of ice are susceptible to melting in a warming climate and many of them are already decreasing in extent because the northern high latitudes are among the most rapidly warming regions on Earth.

At present, excluding the Greenland ice sheet, there are estimated to be 64,296 ice caps and glaciers in the Arctic, with a total area of nearly 422,000 km^2. The most heavily glaciated regions are the Canadian Arctic Islands (~146,000 km^2), Alaska (86,725 km^2), Greenland (excluding the Greenland ice sheet, 89,717 km^2), and the Russian Arctic Islands of Novaya Zemlya, Severnaya Zemlya and Franz Josef Land (51,592 km^2). Glaciers cover a further ~ 48,000 km^2 in the Norwegian Arctic (Svalbard and Jan Mayen Island), Iceland, and Northern Scandinavia (Box, Sharp et al., 2017). For the whole Arctic, excluding Greenland, the total volume of glacier ice is estimated to be nearly 115,000 km^3. This volume of ice would be enough to raise the global mean sea level by about 29 cm if all the glaciers melted completely.

Over the period 2003-2009, Arctic ice caps and glaciers were losing mass at a rate of about -176 gigatons (Gt) every year, with the highest rates of total mass loss being estimated for the Canadian Arctic Islands (-60 Gt/yr), Alaska (-50 Gt/yr), and Greenland (excluding the ice sheet, -38 Gt/yr). A further -28 Gt/yr came from glaciers in the Russian Arctic Islands, Svalbard, Jan Mayen Island, Iceland and northern Scandinavia. For reference, one Gt is a billion metric tonnes.

For the longer period 2003-2015, best estimates based on satellite gravity

measurements from the GRACE satellites suggest regional mean rates of -66.8 Gt/yr for Arctic Canada, -42.5 Gt/yr for Alaska, -16.0 Gt/yr for the Russian Arctic, -8.9 Gt/yr for Iceland, and -7.6 Gt/yr for Svalbard (Box, Sharp et al., 2017, following Wouters et al., 2008). Together, these longer-term rates equate to a rate of sea level rise of ~ 3.92 mm/yr. To put these present-day rates of mass loss into some perspective, data derived from analysis of ice cores from the Canadian Arctic ice caps suggest that current rates of melting are the highest in the past 4,000 years, and that they were last exceeded about 9,000 years ago during the Holocene climatic optimum (Fisher et al., 2012).

An increase in global mean sea level is probably the most widely recognised

consequence of melting of glaciers, ice caps and ice sheets, although thermal expansion of ocean waters due to ocean warming also contributes to this. Such sea level rise is a matter of concern because of the high concentrations of human populations, property, and infrastructure at low elevations close to the ocean, where they are potentially vulnerable to coastal inundation driven by rising sea levels.

Large and rapid changes in the rates at which glaciers, ice caps and ice sheets melt can have substantial impacts on the aquatic ecosystems of downstream lakes, rivers, floodplains, and wetlands. These include changes in both mean and extreme water levels, the magnitude and timing of flood events, stream water temperatures, chemistry and sediment loading, and have the potential to impact the full range of organisms that inhabit these environments. Glacial meltwaters can transport large amounts of dissolved and particle-bound nutrients that play an important role in supporting productivity in downstream freshwater and marine environments. For instance, the termini of "tidewater" glaciers that terminate in the ocean are often important feeding grounds for seabirds and marine mammals.

However, higher rates of melt, runoff and sediment transport from glaciers will typically result in more turbid water columns in downstream rivers, lakes, and nearshore marine environments and this can reduce light penetration into the water column and limit photosynthetic activity, primary production, and water temperatures. There are therefore many reasons to be concerned about the consequences of accelerating rates of glacier and ice cap melt in the Arctic as these can be felt well beyond the present-day limits of the ice masses themselves.

Other potential impacts include the release of legacy pollutants that have been deposited on glaciers, ice caps and the Greenland Ice Sheet over time and stored within the upper layers of the snow and firn (snow that is on its way to becoming glacier ice) in high elevation regions where snow typically accumulates year-on-year and is gradually transformed into glacier ice. As atmospheric warming progresses, however, surface melting spreads to higher and higher elevations and eventually mobilises the accumulated reservoir of pollutants and transfers it to downstream aquatic systems, where it may be assimilated into the food chain. As has been demonstrated in the Canadian Rockies, European Alps and Antarctica, this can result in the reappearance in living organisms of pollutants that have been banned and not actively used for decades.

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Reconciliation in a higher education context: Tensions and challenges

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

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

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

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

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

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

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

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

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

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

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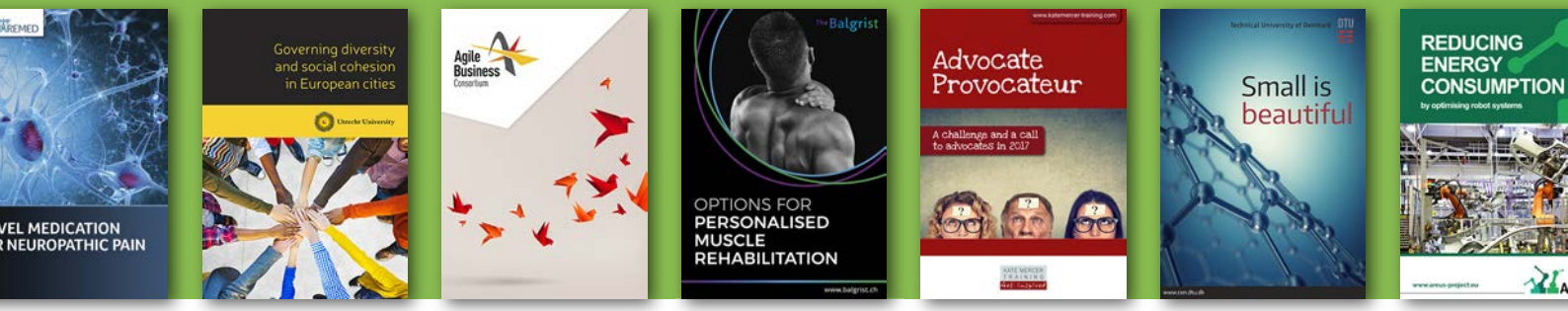

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Gene expression and Huntington's disease

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

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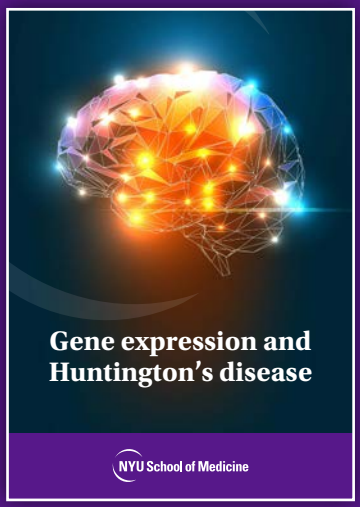
Director, Sackler Institute of Graduate Biomedical Sciences



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