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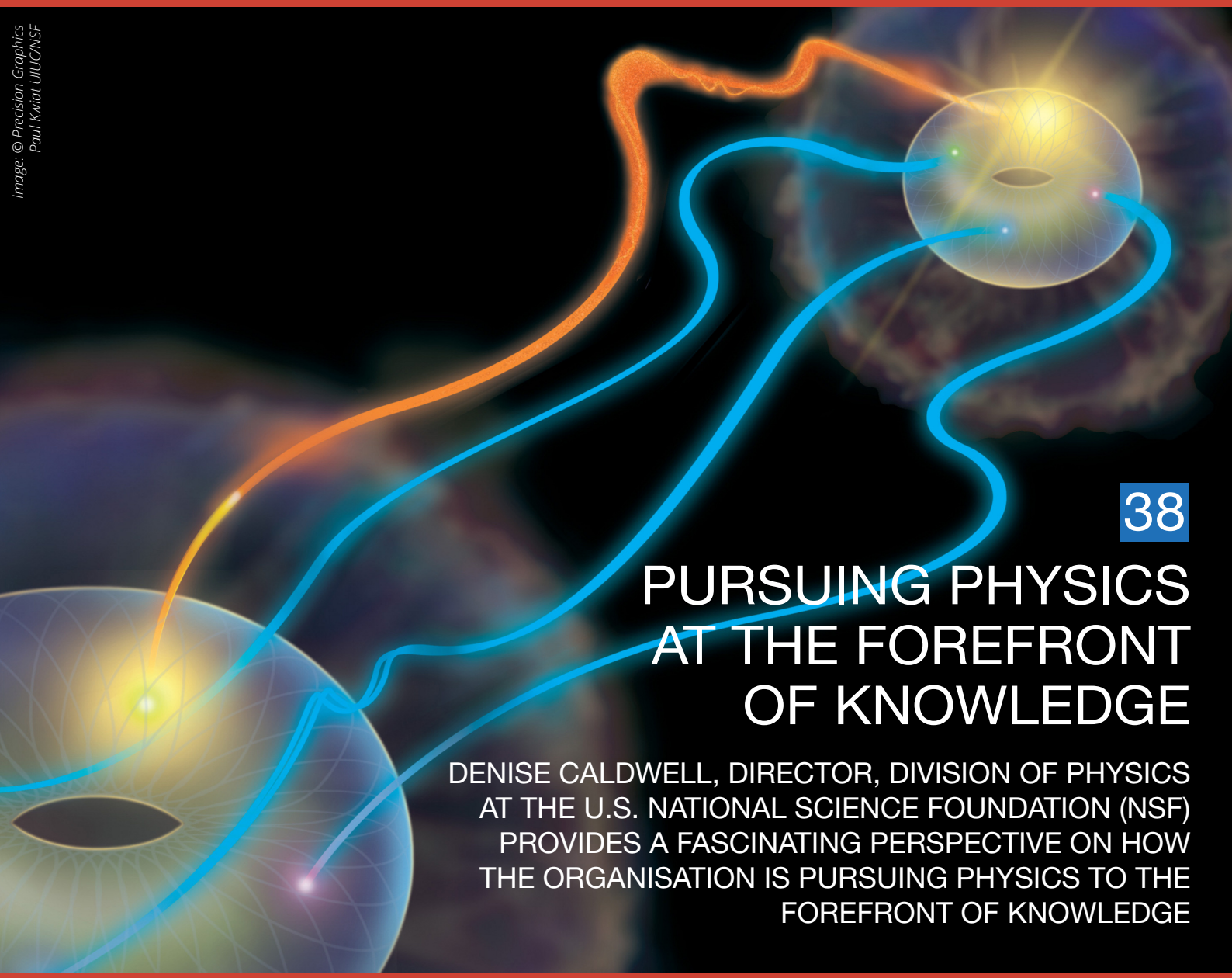
NORTH AMERICA ANALYSIS



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PURSUING PHYSICS AT THE FOREFRONT OF KNOWLEDGE

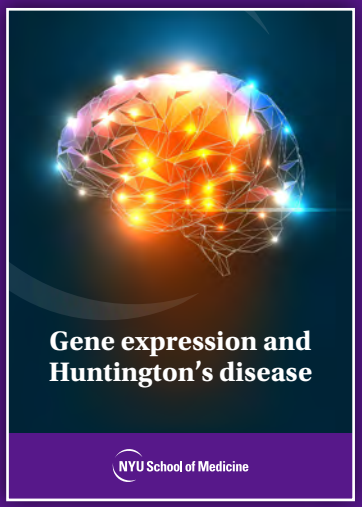
DENISE CALDWELL, DIRECTOR, DIVISION OF PHYSICS AT THE U.S. NATIONAL SCIENCE FOUNDATION (NSF) PROVIDES A FASCINATING PERSPECTIVE ON HOW THE ORGANISATION IS PURSUING PHYSICS TO THE FOREFRONT OF KNOWLEDGE

IN THIS ISSUE

Gene expression and Huntington's disease

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

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



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INTRODUCTION

Welcome to the May 2018 edition of North America Analysis. One of the many highlights of this bumper edition is from Denise Caldwell, Director of the Division of Physics at the U.S. National Science Foundation (NSF). In a compelling opinion article, she shares a fascinating perspective on how the organisation is pursuing physics in America to the forefront of knowledge.

Staying on science, absorbing analysis comes from Sebastien Moranta, coordinator of studies at the European Space Policy Institute (ESPI) who sheds light on Europe's potential to explore the Moon in co-operation with other great world powers, including, of course, America.

One of the highlights of the agriculture section comes from Acting Deputy Under Secretary for Food Safety at the United States Department of Agriculture (USDA), Carmen Rottenberg who explains how the Food Safety and Inspection Service protects Americans from foodborne illness.

We are also delighted to include comment from Greg Rosenthal of the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service who explains how right-sizing regulation can optimise plant protection.

In addition to the many American themed articles here, we also have an interesting Canada section, headed up Minister of Environment and Climate Change, Catherine McKenna, who details the country's plan to reduce carbon emissions and strengthen their clean growth economy.

I would also like to mention an excellent piece from Vice President of the Canadian Society for the Study of Education, Dwayne Donald who gives his expert view on Canadian education and research concerning Indigenous peoples.

I trust that you find this publication both absorbing and insightful. Do feel free to contact me about any suggestions for stimulating content you may have in the future, or perhaps you'd like to just get in touch to provide any remarks on this edition.

Jonathan Miles
Editor

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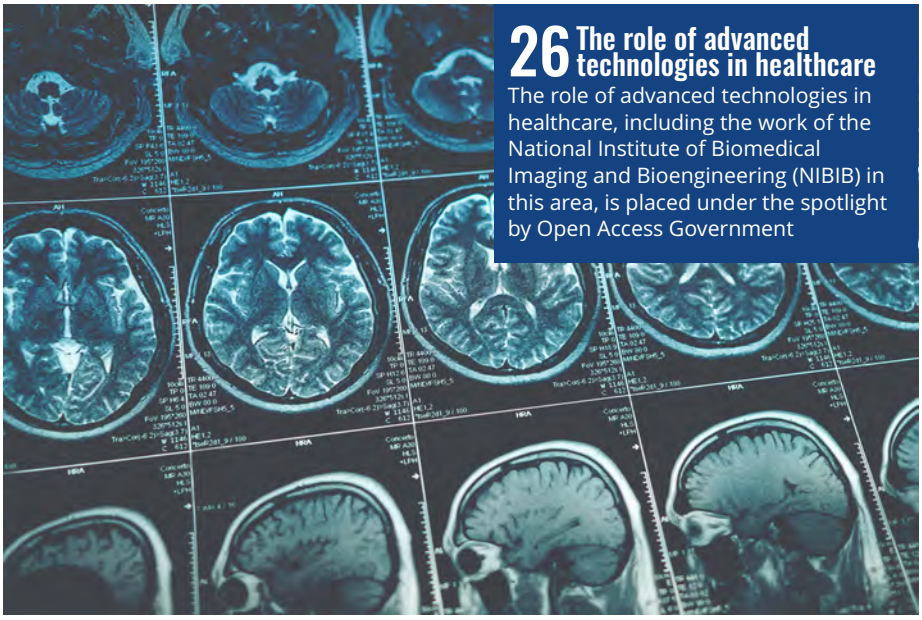

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Dyspnea: Shortness of breath

Donald A. Mahler from the Geisel School of Medicine at Dartmouth and Clinical Resource Center of the Alpha-1 Foundation and Valley Regional Hospital, on behalf of the CHEST Foundation, provides an expert view on shortness of breath (dyspnea)

A healthy person breathes 12-14 times every minute without a thought. Breathing is automatic as the medulla in the brain stem sends electrical signals to the respiratory muscles to control how often and how deep to breathe. Receptors in the respiratory system provide information about how the lungs are working to the brain. Based on a neurobiological model, shortness of breath results from an imbalance or mismatch between the demand to breathe and the ability to breathe.

Dyspnea *(dys – difficult; pnea – breathing)* is the medical word for shortness of breath. The three major qualities are: work/effort of breathing; chest tightness; and unsatisfied inspiration. Those who experience breathing difficulty often report the feeling as, "I am short of breath," or "I feel like I can't get enough air in." These experiences are a warning signal that the interaction between the respiratory system and the brain is not working properly.

Causes of shortness of breath

Shortness of breath is frequently classified by how it develops – acute (sudden onset) and chronic (over weeks to months). The most common causes of acute and/or chronic dyspnea are diseases of the heart (congestive heart failure, valve dysfunction and cardiomyopathy), of the lung [asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease], of the pulmonary blood vessels (pulmonary embolism and pulmonary hypertension) and advanced cancer.

Other possibilities for chronic shortness of breath include anemia, deconditioning ("out of shape") and psychological conditions, such as anxiety or depression. Although a low oxygen level in the body increases

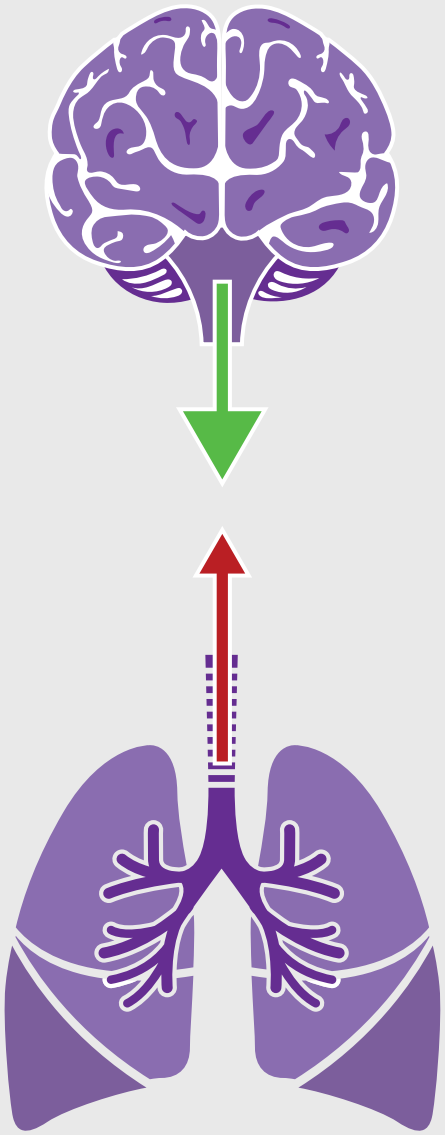


Figure A: simplified model for shortness of breath. The medulla sends an efferent signal (downward arrow) to the respiratory muscles that control breathing. Receptors in airways, lung parenchyma and respiratory muscles send afferent signals (upward arrow) to the brain about rate and depth of breathing.

ventilation and causes shortness of breath, a person may experience breathing difficulty despite a normal oxygen level.

Risk factors for heart disease include smoking, hyperlipidemia, hypertension, diabetes, obesity, physical inactivity and a family history of heart disease at an early age. Risk factors for lung disease are smoking, inhalational exposures both occupational and recreational and a family member with a specific lung condition. Deconditioning is a direct result of reduced physical activities due to a sedentary lifestyle or possibly an illness, injury, or surgery.

The diagnosis

For evaluation of acute shortness of breath, the person typically goes to an emergency department, whereas a complaint of chronic breathing difficulty is usually addressed in an out-patient facility. Assessment by a health-care professional includes a medical history, physical examination and appropriate testing that includes pulse oximetry.

For acute shortness of breath, a chest x-ray and electrocardiogram are essential. Two blood tests can be helpful. Prohormone brain natriuretic peptide (pro-BNP), secreted by the myocardium, is elevated in heart failure; and D-dimer, a product of fibrin degradation in the blood, is elevated with pulmonary embolism. Computed tomography (CT) scanning may be considered for further evaluation.

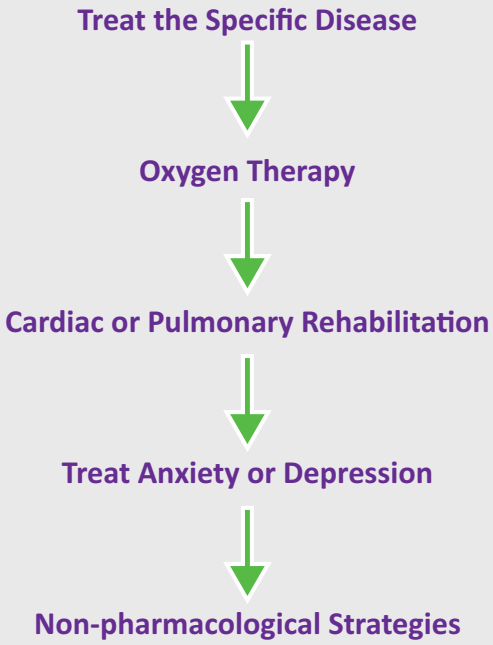
> "Dyspnea *(dys – difficult; pnea – breathing)* is the medical word for shortness of breath. The three major qualities are: work/effort of breathing; chest tightness; and unsatisfied inspiration. Those who experience breathing difficulty often report the feeling as, "I am short of breath," or "I feel like I can't get enough air in." These experiences are a warning signal that the interaction between the respiratory system and the brain is not working properly."

For chronic shortness of breath, pulmonary function testing and a chest x-ray are typically ordered. Other

diagnostic testing may include a complete blood count, an echocardiogram and cardiopulmonary exercise depending on the individual's specific features.

Getting treatment

The following diagram provides a general approach to relieving shortness of breath.



Medications are usually prescribed as treatment for the specific disease that can relieve breathing difficulty. Oxygen therapy is provided if the individual's oxygen saturation is 88% or below. As many individuals with chronic heart or lung diseases are inactive due to their shortness of breath, referral to a cardiac or pulmonary rehabilitation program is important.

Studies show that supervised exercise training will relieve shortness of breath, improve quality of life and enhance functional ability. Anxiety and/or depression should be treated to improve an individual's mental health which may also alleviate breathing difficulty.

Non-pharmacological strategies for relief of dyspnea include a fan blowing air on the face, pursed lips-breathing (puckering the lips during exhaling in those with asthma and COPD), the leaning forward position with forearms resting on the thighs or hands on a shopping cart, listening to music, meditation, mindful breathing (an awareness of each breath so that the focus is on the present and breathing becomes relaxed) and yoga.

The priorities for future research

The following recommendations are proposed to advance the treatment of shortness of breath.

- Educate the public about the importance of shortness of breath as a symptom of heart and lung disease. It should not be considered a consequence of aging.

- Develop a new scale or instrument for individuals to rate shortness of breath related to daily and recreational activities. An ideal scale would be valid, reliable and responsive to treatments, would be used in clinical practice and would be accepted by regulatory agencies for approval of new therapies.

- Provide research support to develop new treatments. Possibilities include acupuncture, chest wall vibration and a custom engineered opioid that does not depress the respiratory drive to breathe. ■

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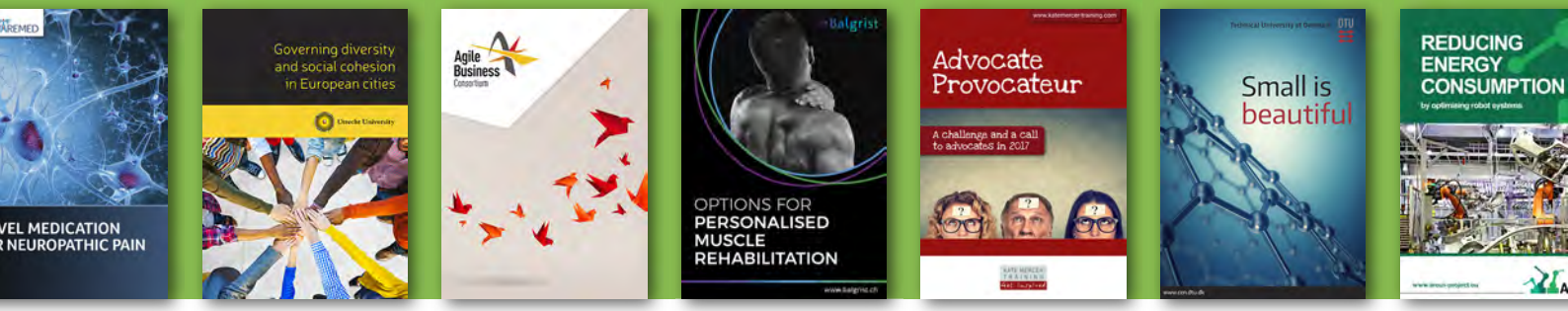

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Understanding the process of intravenous access

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

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

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

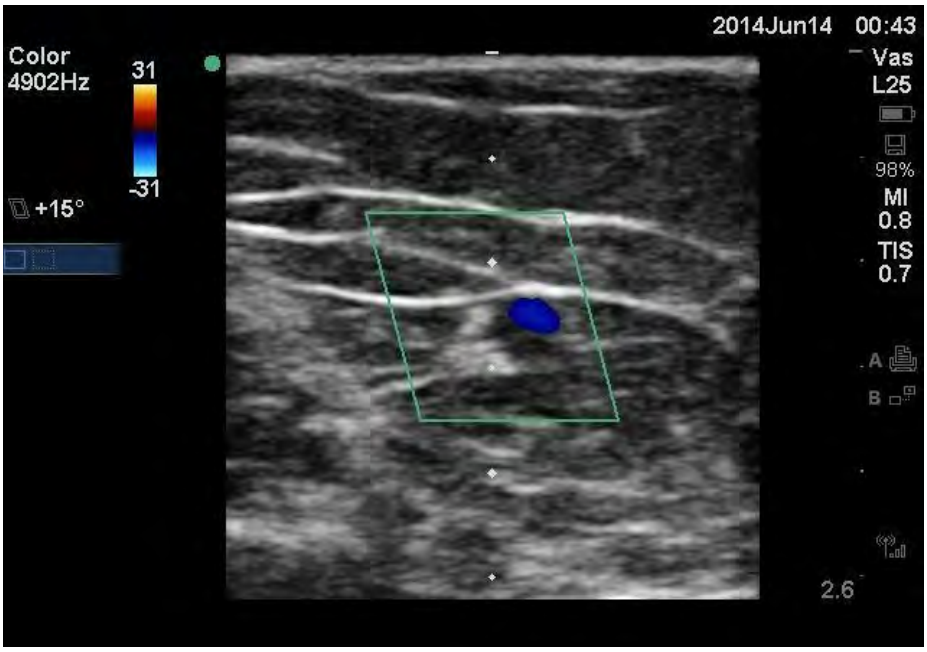

Figure 1: Short axis view of a peripheral vessel visualised with Colour Doppler (blue). The scale on the right of the screen demonstrates a total depth of 2.6 cm. A guide (white dots) in the centre of the screen marks each 0.5cm of depth. Therefore the depth of the vessel is between 1-1.5cm deep to the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

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

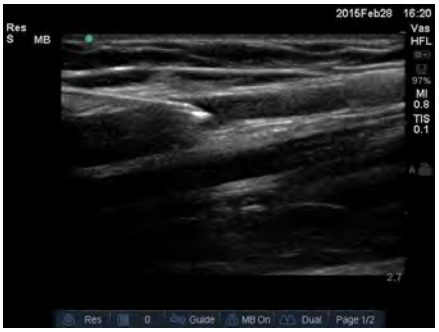

Figure 2: Long axis view of a peripheral vessel. The hyperechoic needle is visualized approaching from the top left of the screen into the vessel lumen.

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

Identify the vein: remember the two C's

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

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

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

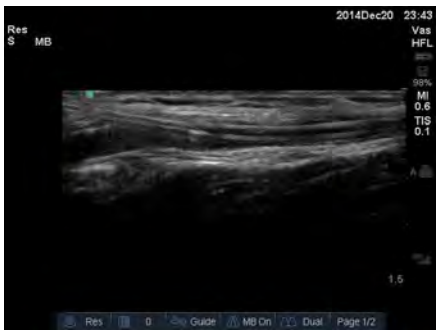

Figure 3: In this long axis view of a peripheral vessel the catheter has been threaded and is seen within the lumen of the vessel.

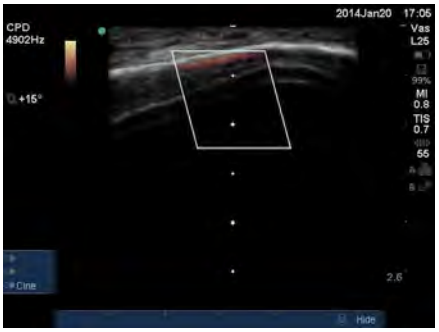

Figure 4: Power Doppler (orange) confirms placement of an intraosseus line within the distal tibia. The bright white line of the tibia cortex (in long axis view) is visualised at the top of the screen, with flow confirmation from a 10cc saline flush immediately distal (below) to the hyperechoic cortex.

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

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Huntington's disease – accessing hope

Sorcha McPhillips, Chief Executive of the Huntington's disease (HD) Association for Northern Ireland, raises awareness of HD and discusses the impact of hope on the community in the face of new treatments

Huntington's disease (HD) is described as a 'neuro-degenerative' disorder as it damages or kills the neurons in the brain. It is a genetic disease affecting males and female equally. Every child of an affected parent has a 50% chance of inheriting the gene mutation which causes the disease. A simple blood test indicates whether a person has tested positive or negative for the gene mutation. If tested positive, the individual will develop the disease at some point in their lifespan.

HD affects approximately 1 in 10,000 individuals in Europe and is sometimes referred to as a 'rare' or 'orphan' disease, although a recent statistical report from 2016 indicates that the prevalence of HD in the UK has been severely underestimated and that for every person with the faulty gene there are as many as 5 people at risk of inheritance.[1]

HD usually affects adults between the ages of 30-50 and is often described as an "adult-onset disease". Although it can occur anywhere from age 2-70, it is less common in children and older people. It is said that those who develop HD earlier in life may find their illness progresses at a faster rate.

- Life expectancy from the onset is approximately 15-20 years.
- HD causes progressive deterioration – physically, cognitively and emotionally until the individual becomes dependent on the help of others.
- No two patients' condition progress in exactly the same way.
- Symptoms can vary widely, and the rate of progression is difficult to predict with any real accuracy.
- HD is referred to as a 'disease of families' where several family members from different generations may be symptomatic at the same time.

As a 'disease of families' no family member is left untouched because if they do not have symptoms themselves or have tested negative they are still affected by the emotional and practical implications of the disease on the family with many people having a caring role to play.

Most of the, approximately 200, HD sufferers in Northern Ireland are cared for at home by family members although many will require the assistance of home care workers, respite in care homes and eventually nursing home care. It is essential for carers, both family and professionals, to develop an understanding of the complexities of HD and how it can impact on all members of the family.

There is no known cure for HD, however, this is an unprecedented time for Huntington's disease families. HD is among the 25% of rare diseases with a known genetic cause and so to some extent, those with HD are among the lucky ones. They can access a diagnosis by blood test and since the cause is known, treatments are possible. The first-ever human trial is underway of a drug that aims to reduce the brain's production of the mutant protein HTT – the known cause of HD. Phase 1/2 of this Ionis/Roche trial has just concluded with 46 patents across nine global sites with participants shown to tolerate increasing doses of a drug delivered by a monthly lumbar puncture.

The results are incredibly positive with significant dose-dependent reductions in the level of the mutant protein – basically the higher the dose administered, the lower the level of protein detected. This trial will

Sorcha McPhillips, Chief Executive

now expand to include more participants to monitor the effect on a larger patient group for a longer period. The hope is that this drug could delay or even prevent the onset of HD symptoms. Several other drugs to do the same thing by different approaches are under development and expected to reach trials soon. There are currently 15 clinical trials of different treatments currently underway so there is real hope for a cure.[2]

These developments bring real hope to families currently living with the symptoms or the future threat of this devastating disease. However, in Northern Ireland, they also bring questions, anxiety and frustration. Participants for clinical trials are usually recruited through Enroll HD study sites. Enroll HD is an innovative way of gathering data on HD patients and their family members, including biological samples, which are then coded and uploaded anonymously on to a global research database which is freely accessible to anyone working on HD research.[3]

There is an Enroll HD site in Ireland and 28 sites across Scotland, England and Wales, but not a single site in Northern Ireland. Although we have some limited neurological, psychiatric, nursing and genetic expertise in Huntington's disease locally, they do not have the capacity or the administrative support to establish a site here. Families are asking, and rightly so, how can we access these clinical trials before it's too late for us? The postcode lottery is something many are sadly all too aware of as in Northern Ireland only those living within two of the five healthcare Trusts can access a specialist HD nurse. This is an issue which HDANI continues to lobby for but when you have no functioning government where do you lobby? There has been no Minister for Health in Northern Ireland since January 2017 and with that a vacuum against which to push for an end to the inequality of care which exists and the need to promote access to HD research and clinical trials. It truly is a time of hope for Huntington's Disease families around the globe and hope can do exceptional things to the human body and spirit but for families living in Northern Ireland, it seems like hope is just beyond their grasp. ■

To learn more about HD in Northern Ireland watch our video https://tinyurl.com/y7dudr7m

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2 For up to date information on HD drug and treatment developments see https://en.hdbuzz.net/

3 https://www.enroll-hd.org/

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

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

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

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

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

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

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

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

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

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

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

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

Mutant RNA binding proteins, however, show altered biophysical properties. They have increased propensity to interact with one another and affect the formation and function of granules. There is increasing evidence that over time mutant RNA binding proteins in these granules steadily accumulate and become converted to irreversible aggregates that are toxic to cells. Neurons are vulnerable to aberrant proteins that accumulate because neurons do not divide. Ultimately the machinery in the cell fails to remove toxic proteins, causing cell death.

Since the functions of normal HTT and the mechanisms by which its mutant counterpart contributes to HD remain unclear, my lab began investigating the role of HTT in RNA metabolism. New imaging techniques have helped us determine the location of the normal HTT protein inside neurons.

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

New experiments in HTT

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

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

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

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

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Cancer research and training in the United States

The work of the National Cancer Institute (NCI), the federal government's principal agency for cancer research and training in the United States, is profiled here by Open Access Government

The National Cancer Institute (NCI) is the federal government's principal agency for cancer research and training in the United States today. Their impressively sized team of around 3,500 people is part of the National Institutes of Health (NIH), one of 11 agencies that make up the Department of Health and Human Services (HHS) in the United States. In particular, NCI has two broad roles: cancer research plus training and support for cancer researchers.

NCI's mission statement is as follows: "NCI leads, conducts and supports cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives." (1)

NCI is a leader of the cancer research enterprise, collectively known as the National Cancer Program and is the largest funder of cancer research in the whole world. It's true to say that NCI manages a vast array of research, training and information dissemination activities that reach across the entire United States, meeting the needs of all demographics – urban and rural, rich and poor, urban and rural and all ethnic-racial/populations.

When it comes to funding, NCI receives its funds from Congress. The bulk of NCI's budget supports extramural grants and cooperative agreements to facilitate research taking place at universities, hospitals, medical schools, cancer centres, research laboratories and private firms in the United States and further afield.

On the impact that NCI's investments have had, we know that this has led to declines in the rates of new cancer cases and cancer deaths as a whole in the United States over the last few decades. In keeping with this impressive improvement, the number of cancer survivors in the country has more than doubled from 7 million in 1992 to more than 15 million in 2016 and unfortunately, it is predicted to rise to more no less than 26 million by 2040. These trends reflect advances in the detection of cancer detection, diagnosis and patient care which have led to people living longer and healthier lives than has been known previously.

The PanCancer Atlas

One example of research taking place, that is funded by the National Institutes of Health concerns the completion of a detailed genomic analysis, known as the PanCancer Atlas, on a data set of molecular and clinical information from over 10,000 tumours – that represent 33 types of cancer.

"This project is the culmination of more than a decade of ground-breaking work," says NIH Director Francis S. Collins, M.D., Ph.D. "This analysis provides cancer researchers with an unprecedented understanding of how, where and why tumours arise in humans, enabling better-informed clinical trials and future treatments", she adds.

"TCGA was the first project of its scale to characterise – at the molecular level – cancer across a breadth of cancer types", adds Carolyn Hutter, Ph.D., director of NHGRI's Division of Genome Sciences and the NHGRI team lead for TCGA. "At the project's infancy 10 years ago, it wasn't even possible, much less on such a scale, to do the types of characterisation and analysis that were being proposed. It was a hugely ambitious project."

The project focuses on cancer genome sequencing and on different types of data analyses, for example, investigating gene and protein expression profiles, as well as associating them with clinical and imaging data.(2)

Sorafenib improves progression-free survival for patients with rare sarcomas

In other news, interim results from a randomised clinical trial for patients with desmoid tumours or aggressive fibromatosis (DT/DF) show that the drug sorafenib tosylate (Nexavar) extended progression-free survival, compared with a placebo. The trial was sponsored by the National Cancer Institute (NCI), designed and conducted by researchers with the Alliance for Clinical Trials in Oncology (Alliance) and supported by Bayer HealthCare AG, which provided the study drug.

"Sorafenib is a novel way of treating this rare cancer," comments lead investigator and study chair Mrinal M. Gounder, M.D., sarcoma medical oncologist at Memorial Sloan Kettering Cancer Center in New York City. "The promising results of this phase 3 trial represent a paradigm shift in the approach to treatment of patients with desmoid tumours."

"Currently, there is no standard treatment for this rare disease and the effectiveness of the treatments that are used for it – for example, surgery, radiation and chemotherapy – is generally limited," adds Jeff Abrams, M.D., clinical director of NCI's Division of Cancer Treatment and Diagnosis. "But the interim results of this trial are promising and may offer a new treatment alternative." [3]

The development of vaccines for the human papillomavirus (HPV)

In other noteworthy news, Douglas R. Lowy, M.D. and John T. Schiller, Ph.D., of the Center for Cancer Research at the NC) were recognised for their contributions toward the development of vaccines for the human papillomavirus (HPV) in February.

On winning the 2018 Szent-Györgyi Prize for Progress in Cancer Research, Sujuan Ba, Ph.D., co-chair of the 2018 prize selection committee and president of the National Foundation for Cancer Research (NFCR), which awards the annual prize, said that Drs Schiller and Lowy: "have made monumental impacts in the field of cancer sciences and could not be more deserving of this award."

NCI Director Ned Sharpless, M.D. adds: "We at NCI are very proud to see Dr Lowy and Dr Schiller awarded this prestigious prize for their important work in cancer research. Their receipt of the Szent-Györgyi Prize for their extraordinary research recognises how important discoveries come from building on earlier work and how those efforts can lead to major breakthroughs in public health." [4]

Looking ahead

Looking to the future, everybody at some point in their lives has been touched by cancer, perhaps through a loved one dealing with it by the experience of a personal diagnosis. While incredible strides have been made in advancing scientific knowledge of the disease, there remains a great deal more to be done. In this vein, NCI will always support the most innovative laboratory research and clinical trials to transform the data we have today into tomorrow's most revolutionary clinical discoveries.

The last word goes to NCI who explain in their own words how they are leading the way in understanding, preventing and treating cancer: "From basic science to clinical science, from implementation science to cancer care delivery and from advanced technology development to data-sharing and analysis systems, NCI is leading the way in how we understand, prevent and treat cancer." ■

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Sunlight-induced carcinogenesis: Angiogenesis in skin cancer progression

Dr Olga V Volpert's work on sunlight-induced carcinogenesis at the MD Anderson Cancer Center is explored here, including why angiogenesis is critically important in skin cancer progression

Sunlight-induced carcinogenesis has become a concern since the 1980s when the depletion of the ozone layer was first noticed. Long-term exposure to ultraviolet B (UVB) component of sunlight is a risk factor for both non-melanoma and melanoma skin cancers. The incidence of skin cancers is increasing, with 2-3 million non-melanoma skin cancers and 132,000 melanoma cases occurring globally each year. Skin is sensitive to photodamage even after short-term exposures to UVB.

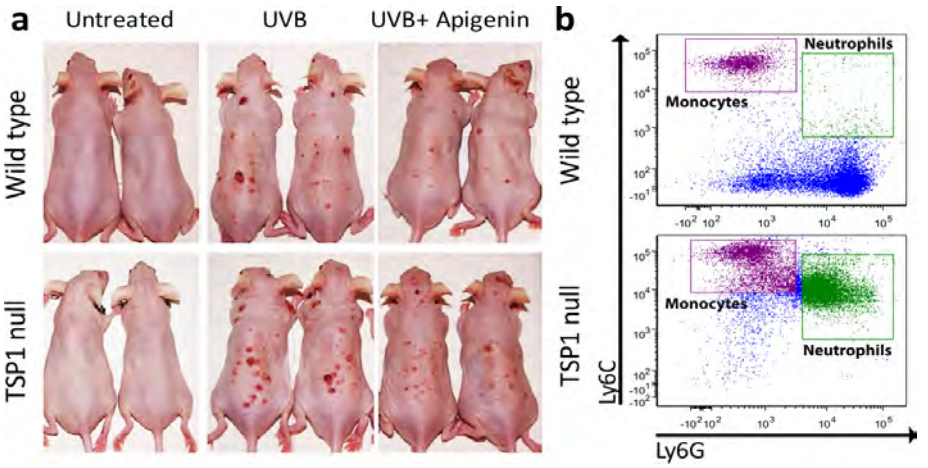

Figure 1. Loss of TSP1 blunts the anti-cancer effects of apigenin. (a) Wild type and TSP1 null mice were treated as indicated at the top of the panel for 22 weeks. TSP1 null mice develop multiple skin tumors despite apigenin treatment. (b) Bone marrow of wild type and TSP1 null mice treated with UVB and apigenin was analyzed by flow cytometry, to measure the neutrophil (Ly6G-high, green) and monocytes (Ly6C-high, purple) cells. In TSP1 null mice apigenin does not block mobilisation of inflammatory cells.

As with other cancers, angiogenesis is critically important in skin cancer progression and UVB-induced vascular changes in the skin have been attributed to increased production of pro-angiogenic cytokines and chemokines, such as vascular endothelial growth factor (VEGF), cyclooxygenase (Cox)-2, basic fibroblast growth factor (bFGF) and interleukin-8 (IL-8).

Thrombospondin-1 (TSP1), a large glycoprotein abundant in healthy adult tissues is a major inhibitor of angiogenesis. Loss of TSP1 has been implicated in the progression of many cancers including breast and colon carcinomas and skin cancers. In the skin, TSP1 produced by keratinocytes in the epidermis acts as a gatekeeper of the vascular changes associated with and required for cancer progression.

Therefore, TSP1 seems an obvious candidate for prevention or treatment of cancer. However, a very large protein with complex functions is difficult to manufacture for clinical purposes. What if there was a compound that impedes subcutaneous angiogenesis by keeping normal, high TSP1 levels in the skin? There may be such a compound coming from a medicinal or culinary plant, chamomile or parsley.

Chamomile flowers are known since antiquity, for their healing properties. Apigenin, an active ingredient found in chamomile, has potent chemopreventive properties against UVB-induced skin cancer. In addition to its cytotoxic effects, potentially useful for arresting the growth of rapidly multiplying tumour cells, apigenin inhibits angiogenesis.

Using cultures of human and mouse keratinocytes, as well as mouse models, Dr Volpert and colleagues carried out studies confirming the anti-angiogenic effects of apigenin and showed that it can reverse TSP1 loss in the UVB-exposed skin. This is the first known report of apigenin directly controlling endogenous anti-angiogenic protein. Treatment with apigenin, before or after UVB irradiation, restored TSP1 levels in cultured cells and in the skin.

They also found that, like apigenin, an active TSP1 peptide inhibited the production of Cox-2 and VEGF and reduced UVB-induced cancer-related vascular effects, angiogenesis and epidermal thickening. These studies strongly suggest the benefits of apigenin for therapy or prevention of skin cancer and provide mechanistic insights into its protective action.

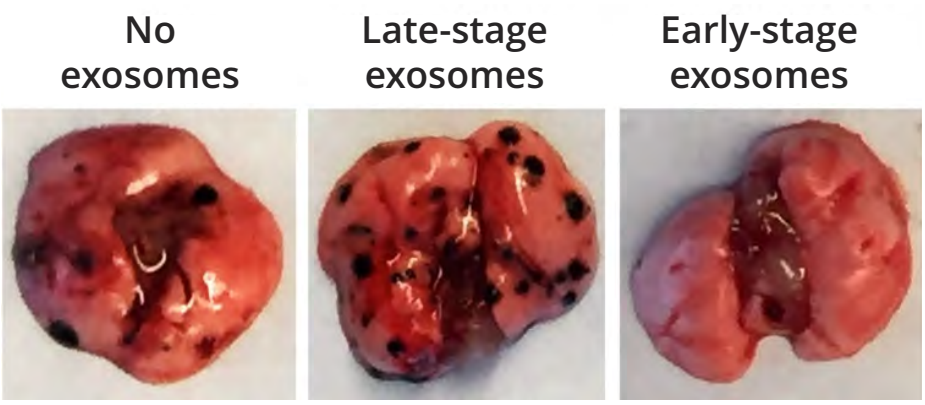

Figure 2. Early stage (PEDF-positive) exosomes block melanoma metastasis to the lung. Mice were treated as indicated at the top of the panel and melanoma cells injected in the bloodstream. Two weeks later, lungs were examined for metastasis (B16F10 pigmented melanoma can be visualized due its dark coloring).

Angiogenesis inhibitor alters the immune landscape in skin

Further studies by the Volpert group, indeed, showed that apigenin efficiently inhibits the UVB-induced skin carcinogenesis in wild-type mice but loses its anti-cancer effect, in which TSP1 gene is disrupted (TSP1 null) (Fig. 1a). Surprisingly, the most dramatic change in TSP1 null mice is in the inflammatory component of a tumour. It appears that TSP1 interferes with the UVB-induced production of inflammatory cytokines IL-6 and IL-12 and that in mice null for TSP1 far more inflammatory cells – neutrophils and inflammatory monocytes are recruited from bone marrow to skin where they produce growth factors to support cancer progression (Fig. 1b).

Angiogenesis Inhibitor is transferred by exosomes to bolster innate immune surveillance

Exosomes are tiny physiological vesicles (50-150 nanometres in diameter) formed through the endosomal pathway and released by all cells in the body. Exosomes and carried in biological fluids, like serum and urine. Studies of the past decade have identified exosomes as natural vehicles assisting communications between cells and distant tissues.

These natural nanovesicles bioactive molecules to the recipient cells and change their properties or behaviour. Most studies show that exosomes released by cancer cells promote metastasis by creating permissive environments at the sites of their arrival (metastatic niches).

One of the major effects of cancer exosomes is immunosuppression. By transferring immunosuppressive cytokines and immune checkpoint inhibitors, cancer exosomes can incapacitate natural killer and cytotoxic T cells. This deficient host immune response serves to protect disseminating cancer cells and facilitate metastasis.

In a recent study, Dr Volpert and colleagues determined that cancer cells can also activate early immune surveillance. Working with melanoma as a model, they have demonstrated that at an early stage, melanoma cells alert the immune system of the host to the presence of metastasis by sending out exosomes, which activate highly specialised cells called patrolling monocytes.

In the absence of cancer, patrolling monocytes constantly scan the blood vessel to seek out and eliminate damaged or dying cells. In case of metastatic cancer, the patrolling monocytes can detect and destroy lurking cancer cells. The Volpert group showed that one of such exosome-associated activators of patrolling monocytes is a known angiogenesis inhibitor, pigment epithelium-derived factor (PEDF).

Once activated with PEDF-containing exosomes, patrolling monocytes kill and engulf cancer cells on their own or recruit other cancer-killing immune cells, called natural killer cells. This is yet another case where anti-angiogenic protein 'doubles' as an activator of immune response and stops the spreading of cancer cells to the distant organs (Fig. 2).

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Non-invasive radiofrequency hyperthermia

Steven Curley from the Michael E. DeBakey Department of Surgery, Baylor College of Medicine and a group of experts from Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center share their expertise on non-invasive radiofrequency hyperthermia (NiRFH)

Non-invasive radiofrequency hyperthermia (NiRFH), is an oncologic intervention that is being used as an adjunct to cytotoxic chemotherapy or ionising radiation [1]. It involves the application of high-frequency electromagnetic fields to produce mild hyperthermia (39-45°C) in malignant tumours.

While NiRFH has been extensively investigated clinically for several tumours (e.g. central nervous system, lungs, breast), clinical studies of NiRFH for hepatic malignancies remain elusive [2]. This is primarily due to technical challenges associated with the anatomic location of the liver and the high energy cost of transmitting the electromagnetic field through adipose tissue, which often leads to insufficient heating of the liver, overheating of subcutaneous fat and chest wall structures and skin burns.

In our own work, we have demonstrated significant problems and highly variable results when attempting to produce low-level hyperthermia in normal liver in a porcine model using a single capacitive end-fire antenna and receiving plate [2]. The skin and subcutaneous tissue experienced rapid heating and clinically relevant hyperthermia in the liver was attained in less than 40% of the animals tested.

We hypothesise that the currently available NiRFH field equipment is inadequate to heat tumour tissues in liver reliably and reproducibly. We have developed a mechanistic mathematical model of NiRFH treatment for primary hepatic tumours and liver metastases. The model, built on basic principles of physics, takes into account the narrow therapeutic index of hyperthermia, i.e., the constraints of the maximum tolerated dose by the fat and minimum effective dose for a tumour.

Using known human tissue frequency-dependent specific absorption rates (SAR) of RF energy, we produced a novel closed-form solution (Equation 1) of the heat equation describing the energy transfer in tissue and then tested the model to evaluate variables including frequency, increasing subcutaneous fat thickness and differential electrical properties of liver and malignant liver tumours. The model indicates that clinically effective temperature increases in liver (to 43-45°C) are *physically unattainable* due to the excessive heating of fat tissue at all frequencies and powers currently used.

The model demonstrates that, while it is possible to limit temperature increases in the fat by acting on a number of variables, including cross-section of the beam, power, time duration of the RF treatment and frequency, the relative increase in temperature in the liver is always a fraction of the corresponding temperature increase in the fat at all frequencies. The model solution for the change in temperature (ΔT) with ΔT_{L} for liver and ΔT_{F} for fat is:

$$\frac{\Delta T_{\mathrm{L}}}{\Delta T_{\mathrm{F}}} = \frac{c_{\mathrm{F}}}{c_{\mathrm{L}}}\left(1-\frac{x_{\mathrm{F}}}{L_{\mathrm{F}}}\right)\frac{SAR_{\mathrm{L}}}{SAR_{\mathrm{F}}} \quad (1)$$

where c_i represents the specific heat in fat ($i = \mathrm{F}$) and liver ($i = \mathrm{L}$), x_{F} is the thickness of fat tissue and L_{F} is a characteristic length scale of the tissue, which depends on the relative SAR therein. It is found that the ratio of length scales $\frac{x_{\mathrm{F}}}{L_{\mathrm{F}}} \ll 1$ under all conditions. Since the ratio in SAR ($\frac{SAR_{\mathrm{L}}}{SAR_{\mathrm{F}}}$) is approximately 1/10 at all frequencies (Figure 1, adopted from Ho *et al*. [2]) and the ratio in specific heats ($\frac{c_{\mathrm{F}}}{c_{\mathrm{L}}}$) is approximately 1/2, it follows that a number of converging beams of the order of $n > 24$ is predicted to be necessary just to achieve equal temperature increases in the fat and liver.

This does not take into account the further penalty of significant heat dissipation coming from the vascular heat sink effect due to the high blood flow rate in the liver (17 ml/min/kg = 1,190 ml/min flow rate in a 70 kg human) [3], or even higher flow rates in a hypervascular liver cancer (shown to be higher than normal liver due to

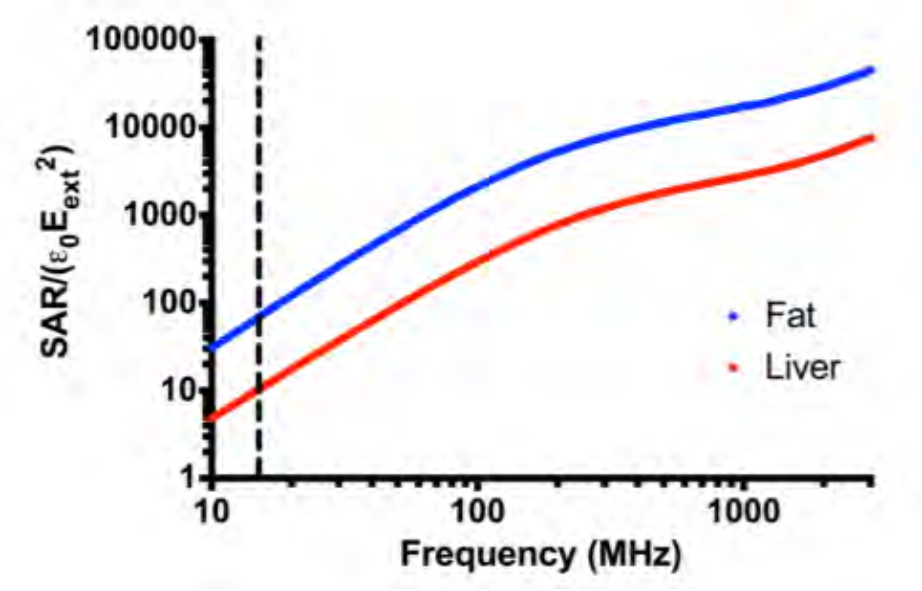

Figure 1. Relative SAR for subcutaneous fat and liver from 10 MHz to 3 GHz as measured with direct permittivity probes placed into tissue during variable frequency RF treatments in a large animal (pig) model. Adopted from Ho et al. [2] with permission

increased hepatic arterial flow rates in hepatocellular carcinoma) [4].

To develop a model for predicting RF therapy efficacy, we will integrate our energy transfer model with a spatio-temporal tumour response model [5], which has been used to understand and predict tumour response to chemotherapeutic drugs in patients. The energy transfer model will solve for energy deposition into the tumour tissue and feed this information into the tumour response model, which will then predict the extent of tumour kill by solving a system of differential equations with tissue- and treatment-specific parameters. The resulting integrative model, based on a combination of physical transport and electromagnetic theories (accounting for tissue heating for different tissue types), will be calibrated and validated with patient data and then prospectively used to optimise RF treatment for individual patients.

We recommend, based on our preliminary analysis, that a large number of multiphase array variable frequency (patient-specific) RF beams be used clinically. Precision cancer care based on patient-specific genetic, proteomic and metabolomic analyses will become the standard of care; NiRFH should also be designed to meet a patient's cancer-specific and body mass-related electrical properties using mathematically determined frequency, power and treatment duration parameters.

Another possible approach to overcome the high adipose tissue SAR of RF (while avoiding heating and injury to fat-bearing tissues or adjacent organs) is to use nuclear magnetic resonance (NMR) Fourier decomposition techniques to focus the intensity of the RF at a desired depth in a liver tumour, thus bypassing the fat [4]. Finally, the use of RF-absorbing metallic-nanoparticle-based sensitisers that specifically localise in liver malignancies and are shielded from ionic charge buffering offers another possible means to achieve targeted hyperthermia [6].

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Acute myeloid leukaemia (AML) research and application

The current state of metabolomics research and application in Acute Myeloid Leukaemia is placed under the spotlight by Bradley Stockard and Jatinder Lamba from Department of Pharmacotherapy and Translational Research, University of Florida

Acute myeloid leukaemia (AML) represents 1.3% of all new cancer cases, with 21,380 new cases anticipated in the United States in 2017[1]. AML is a clinically challenging and heterogeneous disease that can become rapidly fatal if untreated. Despite continuing advances in treatment options, global 5-year survival rates are approximately 27% for adult patients and 60% for paediatric AML patients[2].

The heterogeneous nature of AML is characterised by the presence of numerous genetic lesions and chromosomal abnormalities present in its many subtypes. Although the most common mutations in AML have been defined, there is still a gap in our understanding of the molecular mechanisms underlying the variation in survival outcomes.

Due to these challenges, there is an ongoing search for molecular markers that can improve prognosis assignment and prediction of treatment and survival outcomes in AML patients. For the most part, studies conducted to identify these predictive markers have been focused on genomics and epigenomics based methods. However, the growing field of metabolomics has shown significant results in many forms of cancer and haematological malignancies. In the case of AML, metabolomics research has been very limited, but the results have been promising. This article reviews the literature currently available for AML metabolomics.

In vitro metabolomics of drug response

One of the earliest studies in AML metabolomics, was an *in vitro* metabolomics study conducted on AML cell lines[3]. The objective of this study was to use nuclear magnetic resonance (NMR) metabolomic profiling to study the effect of bezafibrate (BEZ) and medroxyprogesterone acetate (MPA) on AML cell lines and provide evidence for the underlying mechanism of action of BEZ and MPA. The cell lines showed significant changes to tricarboxylic acid (TCA) cycle intermediates following exposure to BEZ and MPA in the form of an increased conversion of alpha-ketoglutarate to succinate. This study shows the potential benefit of conducting *in vitro* metabolomics studies to explore the impact of drug treatment in AML cell lines. Specifically, these results highlight the importance of energy production pathways for AML cells, an ongoing area of focus in AML metabolism studies.

Application of glucose targeted metabolomics in AML prognosis

Rapid cellular proliferation is a major feature of many forms of cancer, including AML. This feature of elevated proliferation requires AML cells to upregulate multiple metabolic pathways involved in energy production, such as glycolysis and the TCA cycle[4]. A particular feature of TCA cycle reprogramming in AML involves mutations in the gene encoding for isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). IDH isoforms normally catalyse the decarboxylation of isocitrate to form α-ketoglutarate, an essential step in the TCA cycle. However, mutant forms of IDH gain an additional function of catalysing the conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG). These changes to glucose metabolism have been of particular interest in AML metabolomics studies.

Recently, two major metabolomics studies have been conducted for adult AML patients, targeting glucose related metabolites for investigation. In the first study, patients were enrolled in a clinical trial to evaluate the prognostic value of serum 2-HG levels in AML patients[5]. Results showed that 2-HG could be used effectively as a prognostic factor in patients that were positive for IDH1/2 mutation.

A follow up study was conducted by the same group to evaluate the prognostic value of 10 different metabolites related to glucose metabolism in adult AML patients[6]. The investigators determined that increased abundance of five of these glucose metabolites, including lactate, 2-oxoglutarate, pyruvate, 2-hydroxyglutarate and glycerol-3-phosphate, were significantly associated with worsened survival

outcomes. The investigators used these metabolites to develop a prognosis risk score for each study patient. Ultimately, the results showed that prognosis risk scoring was able to predict poor survival outcomes in low scoring patients without the use of other prognostic factors. Together, these studies have helped confirm the importance of altered glucose metabolism in AML and they support the potential clinical relevance of metabolomics for AML patients.

Global metabolic profiling in AML

While the exploration of altered glucose metabolism in AML continues to yield significant results, the changes to many other metabolic pathways are not as well understood. To address this, multiple studies have taken a more untargeted approach to AML metabolic profiling to evaluate global changes to metabolism. A study by Wang, Y et al. using ^{1}H NMR spectroscopy found significant differences in multiple metabolic pathways between healthy controls and AML patients, including glycolysis, TCA cycle, protein and lipoprotein biosynthesis, fatty acid metabolism and cell membrane component metabolism[7].

Another study by Musharraf et al. involved the global metabolic profiling of AML patients, as well as acute lymphoblastic leukaemia and aplastic anaemia patients. 27 metabolites were found to be significantly different between leukaemia patients and healthy controls[8]. Related metabolic pathways included fatty acid and ketone body metabolism and steroid hormone biosynthesis.

Finally, a more recent study conducted by Tan et al. focused on differentiating metabolic profiles of AML patients who achieved complete remission with cytarabine and anthracycline chemotherapeutic regimens as compared to those who were non-responders[9]. The study identified two differential metabolites of interest, dodecanamide and leukotriene B4 dimethylamide, which the investigators were able to use to differentiate patients according to clinical response successfully. Ultimately, global metabolomics studies of AML have helped reinforce the role of glucose metabolism in AML disease progression and establish the importance of other metabolic pathways associated with AML, such as fatty acid metabolism.

Conclusion and future directions

Overall, the current body of research for AML metabolomics shows that this type of study can be successfully applied to improve our understanding of AML disease progression and characteristics, as well as the significant variation in clinical outcomes between AML patients. Many of these studies have identified glucose metabolism and fatty acid metabolism as metabolic pathways significantly associated with AML. However, there have been relatively few AML metabolomics studies published, even compared to many other cancer types.

Additional research is needed to further elucidate the metabolic pathways linked to the AML disease state. Ideally, metabolomics data can be integrated with additional 'omics' data to fully explain the path from gene to phenotype and help contribute to personalising AML evaluation and treatment for the individual patient. The current contributions of metabolomics to understanding AML are promising and its potential continues to be realised with growing interest in the field.

Acknowledgements

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The illusion of cancer and death: Illusion of the self

Sumith A Kularatne, PhD, discusses his thoughts on the illusion of cancer and death

The moment we hear the word cancer, the thought that immediately crosses anyone's mind is death. So, everyone collapses both physically and mentally. If we learn to drop this inner conflict and accept the reality, we can experience and adore the life without fear. Moreover, we will learn that there is no difference between a so-called healthy person and a cancer patient.

As humans, we all are immersed in our circadian lives to feed our personal egos and desires like machines. As in the movie The Matrix, most of us may not be able to perceive this dual nature of the mind while living in the matrix and feeding illusory dreams. According to Vedic teaching, this state of mind is called "the divine game of Lila." We were all born into this world with personal identity or "self" (a physical body and a soul). We have not only forgotten that cancer conquered the soul well before it attacked the body, but also life and death are inseparable. So, every living being including cancer patients is barcoded with an expiration date.

According to the American Cancer Society, ~1,400,000 Americans were diagnosed with cancer during 2008, leading to ~560,000 deaths. On the other hand, about 1,735,350 Americans will be diagnosed with cancer in 2018 and ~610,000 will die. If modern science and technology can cure cancer, what is the rationale for increasing number of cancer incidence in each year? Whilst the immune system is supposed to eliminate cancer cells within the body, it is not able to differentiate cancer cells from normal healthy cells. As healthy cells, cancer cells also express receptors that signal immune cells to prevent an attack or to keep the immune system in check.

While the treatment of invasive or metastatic cancer is often limited to chemotherapy, scientific ingenuity has created novel therapeutic agents only to find cancer has evolved to develop drug resistance. Cancer may have started from a singularity and spiralled out as "the primordial Om" or may have evolved from a single cancer stem cell as Darwin's theory and then metastasize to distant organs. While curing metastatic disease may be elusive, we may able to use the idea of the fractal to explain metastatic patterns as Benoit Mandelbrot used it to describe geometrical patterns in nature.

Moreover, no matter what treatment is used for the cancer patient, cancer recurs at any time without a warning. In Greek mythology, the gods commanded Sisyphus to infinitely push a boulder up a mountain, only to have it roll down. So, are we futilely rolling a boulder uphill by searching impermanent solutions for a permanent problem?

J. Krishnamurti has famously said that "it is no measure of [one's] health to be well-adjusted to a profoundly sick society." So, a drug's mechanism of action may be the least to worry. As Kohlberg pointed out in "the Heinz dilemma," we must evaluate the value of human life over the pharma-companies' greed for money. According to the Heinz dilemma, a woman who was in near death from a special kind of cancer was prescribed a new drug that the doctors thought might save her. While the drug was expensive to synthesize, the druggist was charging ten times what the drug cost him to make. Left with no other option, the sick woman's husband, Heinz, stole the drug for his wife.

Although Kohlberg developed the Heinz dilemma to evaluate moral ethics, cancer drugs are extremely expensive when compared to the production cost. On the other hand, most of the drugs are discovered in sweatshops using scientists. As we learned from the Stanford prison experiment, management always likes to have more control, more power, more recognition, more money, and more of everything. Plato's Chariot analogy, as well as Freud's model, explains the nature of these human behaviours.

In Plato's Chariot analogy, a chariot (one's soul) is driven by two powerful winged horses whereas, in Freud's structural model, the soul is driven by

consciousness and unconsciousness. One horse is noble, rational and moral in nature (mirroring consciousness) while the other horse is wild in character (mirroring unconsciousness) and driven by basic instinct such as aggressiveness, sexuality and control.

In today's world, there are many people seeking spiritual enrichment by engaging in religious activities such as rituals, chanting, praying, singing, etc. However, most of those can be seen as human performing some conditioned activities rather than searching for one's self. As humans, while following religious habits on Sundays, we ride the wild horse comfortably during the rest of the week. We are waiting for The Second Coming of the saviour; however, no one willing to get up on the cross except partaking in the sacrament.

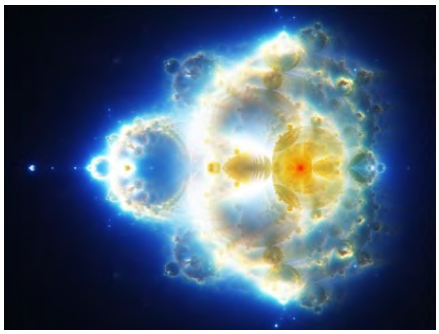
As Ludwig Feuerbach depicted, we may have already realised that "we create God in our own image by unconsciously projecting our idealised perfection as a divine being." On the other hand, Gaunilo's may have convinced us of the non-existence of God by his "Lost Island" analogy. In contrary, how are we going to explain the existence of evilness, discrimination, abuse, natural calamities, death from cancer, etc. In the allegory of the cave by Plato, three prisoners lived chained in a cave from their birth. The only thing they could see were shadows cast on a blank wall by the objects passing on a raised walkway behind them.

Plato showed the misconceptions about knowledge and wisdom, such as restored organised religions through false prophets, using the prisoners' guessing game from the shadows. He made the story more intriguing by allowing the escape of one prisoner into the real world, represents a philosopher who searches for wisdom, who ultimately comes back to the cave to relay the reality to remaining two. However, the two prisoners not only disbelieved him, but also threatened anyone who tried to free them from the cave. Although Plato wrote the allegory of the cave in ~400BC, it looks like; humanity is still searching the path to escape from the cave.

Although Rene Descartes, the father of modern philosophy, developed a "method of doubt" to objectively evaluate all that he believed to be true, he is famous for the saying "Cogito Ergo Sum" (English: "One thing I know for sure, I exist") without a doubt. He was a devout dualist in the sense that the self consists of an immaterial soul that is absolutely distinct from a finite, material body.

On the other hand, David Hume, a devout empiricist, claimed there is no self. Most of us may have never realised the no-self (minimal self), or what the Buddha called anatta. It goes beyond the body and the soul. Based on Buddhist philosophy, self can be defined as an impermanent (anicca) flow of energy (desire) through the continual interaction of five aggregates (i.e. physical form, sensation, conceptualisation, disposition to act and consciousness) with right assembly that brings continual suffering (dukkha). We were named by the parents and told who we are by the society. If there is a self, we should have control over of sickness, ageing, death, social impacts, authoritative influences and natural calamity.

Once we realise the true nature of life and death and at the same time, the reality of self, we all will learn to die before we die. We will learn to let go of our ego construct by identifying the root for suffering. The intention of this article is not to make cancer patients walk away from medicine or their religious beliefs, but to inspire them to find the middle path (according to Buddha) or the golden mean (according to Aristotle). Simultaneous treatment of both soul and body may give a better outcome for the therapy and your soul will remain cancer free.



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The role of advanced technologies in healthcare

The role of advanced technologies in healthcare, including the work of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) in this area, is placed under the spotlight by Open Access Government

On the website of, National Institutes of Health (NIH), we learn that for most of the history of medicine, doctors have relied on their senses – that is vision, hearing and touch – to diagnose illness and monitor a patient's condition.

However, NIH's investment in research over the period of a whole century has helped to completely change medical diagnostics. The new technologies of today allow doctors to find out an increasing amount of detailed information about both the progression and treatment of disease and can even offer personalised treatment based on a patient's genes, we discover.

In addition, NIH-funded scientists have helped to pioneer the development of magnetic resonance imaging (MRI), but they have also made important strides toward uncovering the medical potential of stem cells and as such, they have developed new tools for genome sequencing. With these advanced technologies in place, scientists are finding out how genes affect human health and how a genetic approach can help doctors tailor treatments and prevention strategies for each patient. Certainly, millions of individuals have already been touched by the exciting era of personalised medicine that has grown directly from this research, we learn. [1]

Advances in medical imaging

One area that concerns the NIH is medical imaging, an area they are thoroughly committed to. Indeed, they have an entire institute, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), who seek to improve health by leading the development, acceleration and application of biomedical technologies.

NIBIB is devoted to integrating the physical and engineering sciences, with the life sciences, to further basic research and medical care. This ambitious aim is achieved through:

- Research and development of new biomedical imaging and bioengineering techniques and devices to improve the prevention, detection and treatment of disease;
- Furthering present imaging and bioengineering modalities;

- Supporting relevant research in the physical and mathematical sciences;
- Encouraging research and development in multidisciplinary areas;
- Supporting studies to assess the effectiveness and outcomes of new biologics, processes, materials, devices and procedures;
- Developing technologies for the early detection and assessment of health status where diseases are concerned and;
- Developing advanced imaging and engineering techniques for carrying out biomedical research at multiple scales. [2]

Below, we explore just two examples of the excellent research NIBIB is supporting, where medical technologies are concerned.

Thermo-chemotherapy combo eradicates primary and metastatic tumours in mice

In recent news, we find out that bioengineers at NIBIB developed a smart anti-cancer nanoparticle with precisely targeted tumour-killing activity, which was found to be superior to the previously available technologies.

We are told that state-of-the-art nanoparticle features a very sturdy shell, which is capable of carrying large loads of chemotherapeutic drugs through the circulatory system to a tumour – that is without the leakage that can damage healthy tissue. The nanomedicine is photothermal-responsive, so the cancer-killing load of the particle is released only when it enters the tumour cells and is activated by laser light, we discover.

Reported in the February issue of Nature Communications, this cancer-killing technology is the latest and most effective created by members of the Laboratory of Molecular Imaging and Nanomedicine (LOMIN) at NIBIB, which is led by Xiaoyuan (Shawn) Chen, Senior Investigator.

Fluorescent nanoparticles track cancer metastasis to multiple organs

Researchers funded by the NIBIB have developed fluorescent nanoparticles that light up to track the progress of breast cancer metastasis, we find out. They are currently testing the particles in mice, with the hope of one day using them in humans, we are told.

Prabhas Moghe, Ph.D., professor of Biomedical Engineering and Chemical and Biochemical Engineering at Rutgers University and his team are developing nanoparticles that can help identify and track cancer metastasis early on, even when a tumour is really small.

"There are still significant hurdles to be overcome before this imaging technique could be used in humans, but it is an important step in moving optical imaging cancer diagnosis forward," says Behrouz Shabestari, Ph.D., director of the NIBIB Program in Optical Imaging and Spectroscopy. "It has the potential to help doctors to identify tiny cancer cells and track their spread more effectively, leading to early detection and potentially improved treatment planning."

As well as tracking the spread of cancer, the nanoparticles could potentially be used to differentiate cancer tissue from healthy tissue for surgeons who are removing tumours. Moghe and his team are hopeful that the technology could be positioned for use in humans within the next 10 years. [3]

Final thoughts

You can find many more examples of how NIBIB is improving human health, by leading the development and accelerating the application of biomedical technologies in the US today, which this article provides a flavour of. ■

For more information, please visit www.nih.gov .

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

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

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

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

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

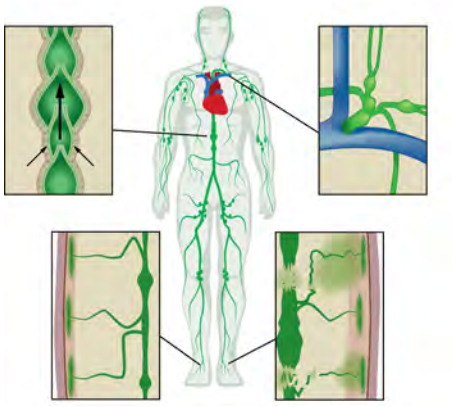

Figure 1: A schematic of the open and unidirectional lymphatic system which begins at the initial lymphatics (lower left panel) that line all organs and carries lymph through lymph nodes and the thoracic duct before emptying into the supraclavicular vein (upper right panel). The system includes series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

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

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

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

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

returns to the blood vasculature (Figure 1).

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

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

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

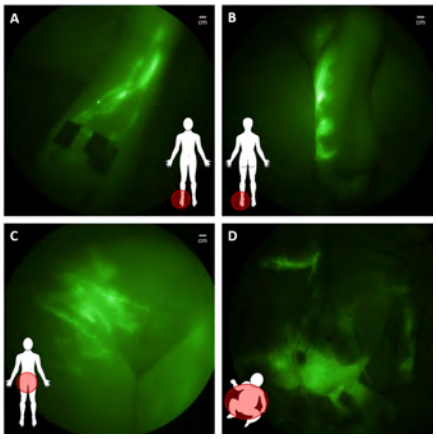

Figure 2: Conducting lymphatics on the top (A) of the right foot and (B) abnormal drainage on the bottom of the left foot of a 17-year girl with congenital lymphedema; Lymphatic congestion in the pelvis of (C) a 16-year girl with congenital lymphedema and (D) a 23-day old male infant with surgery-induced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

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

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

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

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

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Cloud computing in medical imaging: Not a matter of if, but when

Nadim Michel Daher, industry principal at Frost & Sullivan reveals his views on the vital role of Cloud computing in medical imaging

In the minds of healthcare IT decision-makers, as several surveys have shown, Cloud-based solutions have long been associated with data security and data ownership concerns. The apprehension does have a strong rationale: Why would anybody move confidential patient data off-premises and willingly become dependent on the network or on a vendor to be able to access and utilise data they own?

While this perception has caused lasting resistance to Cloud adoption in healthcare, especially in the government hospital segment, it has been changing gradually over the last few years. Years that also happened to be punctuated by regular Cloud outages and cybersecurity attack horror stories.

Recognising the Cloud's benefits

The benefits of Cloud solutions, such as their cost-effectiveness and predictability, unlimited scalability and deployment flexibility, have started to outweigh the perceived risks. Cloud proponents even go as far as to admit that vendors are in a better position than their own IT organisations, to proactively protect data while leveraging the latest data security advances. They realise that there are waste and inefficiency inherent to the conventional siloed on-premises IT models and that they could use freed-up time to focus on higher-value enterprise initiatives. Therefore, as they contemplate the second or third generation of various health IT solutions, the standard model of buying, operating and maintaining that in-house is naturally coming into question.

Medical imaging, a precursor

This is especially true in medical imaging, where the unending growth in image data volumes, coupled with long-term data retention policies in place, makes traditional storage upgrade and scale-up mechanisms clearly unsustainable over the long run. This is why, since the early 2000s, Cloud-based solutions have provided a viable alternative to tape- and truck-based solutions for the long-term archival of medical image studies. While this early adoption has enabled many providers to get their feet wet with Cloud solutions, there is actually so much more today to Cloud use than mere back-office data storage support.

Cloud storage is only the beginning, Cloud computing is next

Two simultaneous and complementary market trends are advancing Cloud-based imaging informatics into new use cases: the continuous expansion of medical imaging applications into niche subspecialty clinical areas and the ongoing diversification in the points of care where medical multimedia content is produced and consumed by various enterprise imaging stakeholders. This is driving the development of the following four core application areas:

- Cloud-based image archiving, which has been advancing beyond "deep" archival towards real-time online accessibility.
- Cloud-based image distribution (for inter- and cross-enterprise image exchange, image-enabled electronic health records (EHRs), patient portals and healthcare information exchanges (HIEs)).
- Cloud-based image diagnosis (RIS, PACS, Teleradiology, Reporting), which can complement or completely replace on-premises image management solutions.
- Cloud-based imaging analytics, with various types of applications that can be delivered on-demand as software-as-a-service (SaaS) or on a subscription basis as part of Cloud-based ecosystems or marketplaces.

A fast-developing but fragmented market

On the vendor front, the industry players can be categorised into three groups as follows:

- The speciality early-movers, who have embraced the Cloud early-on as the core enabling platform for their solutions, built some of their own data centres and who can be credited for the inception of this emerging market.

- The large cross-industry Cloud infrastructure vendors (led by Amazon, Microsoft and Google), who are now fully proactive in developing their industry partnerships as well as native solutions in healthcare, including in imaging.

- The established imaging IT vendors, many of which have been fairly conservative in transitioning their customers to Cloud solutions, but some of which are preparing a major realignment around Cloud-based models.

Double-digit growth rate projections

Cloud-based imaging informatics still represents a relatively small market, totalling $285.4 million in revenue in 2016 globally. It accounts for 8.5% of the total Cloud-based health IT market and to 3.8% of the total imaging IT market. However, while fairly niche, the market is expected to remain on a very strong growth trajectory over the next few years, growing to $830.5 million in 2021, or an impressive compound annual growth rate of 23.8%.

New dimensions via enablement and synergies

Transitioning to a Cloud-based imaging IT model is no easy shift, whether for healthcare providers or for vendors. Both have to align with the new purchasing, business, management and governance models that this shift entails and to be able to absorb its unconventional operational, security and financial risk profiles. Yet, as we have moved past the innovator stage and well into the early adopter phase of the Cloud in imaging, now is the time for Cloud solutions to unleash their untapped potential.

For their greatest value is fact not in Cloud technology per se, but in its synergies with the field's most impactful developments: by enabling greater data usability for advanced imaging analytics (big data, radiomics and machine learning), accelerating interoperability imaging research initiatives, or converging with healthcare blockchains, the Cloud will be, without a doubt, a pervasive actor in the ongoing transformation of the medical imaging value chain. ■

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Arthritis, musculoskeletal and skin diseases including muscular dystrophy

The work of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, including muscular dystrophy (MD), is placed under the spotlight by Open Access Government

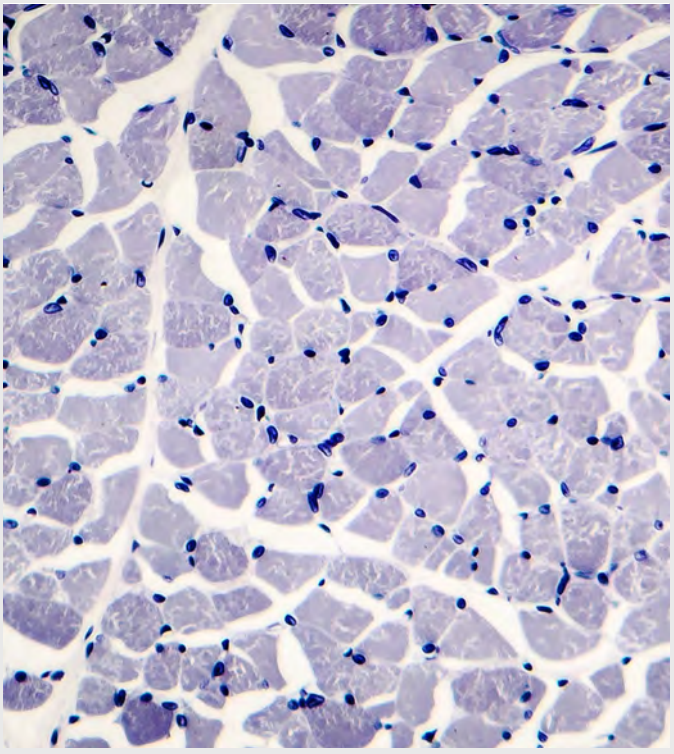
The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is one of 27 institutes and centres at the National Institutes of Health (NIH) in America today.

By way of background, NIAMS started in 1986 and strongly supports research into the causes, treatment and prevention of arthritis and musculoskeletal and skin diseases; as well as the training of basic and clinical scientists to undertake such research; plus, the dissemination of information on how research on these diseases is progressing.

NIAMS underlines that most households in America are affected by diseases of the bones, joints, muscles and skin. Indeed, these common and rare diseases impact on people of all ages, racial and ethnic populations and economic status. Unfortunately, many of these conditions affect women and minorities disproportionately and as such, NIAMS is committed to uncovering the reasons for these disparities and therefore coming up with effective strategies to treat and even prevent them.

Also, NIAMS works to understand and treat a vast array of diseases and conditions, such as:

- Autoinflammatory diseases;
- Back pain;
- Connective tissue diseases, such as Marfan syndrome;
- Fibromyalgia;
- Hair loss disorders, such as alopecia areata;
- Lupus;
- Muscular dystrophy (MD);
- Osteoarthritis;
- Osteoporosis;
- Rheumatoid arthritis;
- Scleroderma and;
- Skin diseases, such as psoriasis, eczema and acne.



Human skeletal muscle

Muscular dystrophy (MD)

Another branch of the National Institutes of Health, The National Institute of Neurological Disorders and Stroke (NINDS) provides further details about one of the above-mentioned areas, muscular dystrophy (MD). Before we look at this, however, it's important to consider the wider work of NINDS.

In summary, we know that the NINDS supports a broad programme of research studies on MD. The goals of these studies are to gain an understanding of MD and to develop techniques to diagnose, treat, prevent, and ultimately cure the disorder. It's also worth highlighting that NINDS is a member of the Muscular Dystrophy Coordinating Committee (MDCC).

We know that the muscular dystrophies (MD) are a group of more than 30 genetic diseases characterised by progressive weakness and degeneration of the skeletal muscles that control our movement. Some forms of MD are evidenced in infancy or childhood, while others may not appear until middle age or later. The disorders vary in terms of the distribution and extent of muscle weakness (some forms of MD also affect cardiac muscle), the age of onset, the rate of progression and the pattern of inheritance.

The most common form of MD that primarily affects boys is known as Duchenne MD. It is caused by the absence of dystrophin, a protein involved in maintaining muscle integrity. The onset of Duchenne MD is between 3 and 5 years old and the disorder, unfortunately, progresses rapidly. Most boys cannot walk by age 12 and at a later stage, they require a respirator to breathe. Girls in these families have a 50% chance of inheriting and passing on the defective gene to their offspring. Boys with Becker MD, which incidentally is very similar than Duchenne MD, but is less severe have faulty or not enough dystrophin.

"We know that the muscular dystrophies (MD) are a group of more than 30 genetic diseases characterised by progressive weakness and degeneration of the skeletal muscles that control our movement."

The website of NINDS also informs us about Facioscapulohumeral MD, which normally begins during the teenage years. It causes progressive weakness in muscles of the face, arms, legs and around the shoulders and chest area. While it progresses slowly, it can vary in symptoms from mild to disabling.

The most common of the disorder in adult form is known as Myotonic MD, which is typified by prolonged muscle spasms, cardiac abnormalities cataracts and endocrine disturbances. Individuals with myotonic MD can be described as having long, thin faces, drooping eyelids and a swan-like neck.

Treatment

At the time of writing, there is, unfortunately, no specific treatment to stop or reverse any form of MD. However, current treatments for MD may include respiratory therapy, physical therapy, speech therapy, orthopaedic appliances used for support, as well as corrective orthopaedic surgery.

Drug therapy is also used to treat MD and includes:

- Antibiotics to fight respiratory infections;
- Anticonvulsants to control seizures and some muscle activity;
- Corticosteroids to slow muscle degeneration and;
- Immunosuppressants to delay some damage to dying muscle cells.

Also, some individuals may benefit from occupational therapy, as well as assistive technology. Some patients may need assisted ventilation to treat respiratory muscle weakness and a perhaps pacemaker for cardiac abnormalities.

Prognosis

In closing, it's worth highlighting that the prognosis for people with MD varies according to both the type and progression of the disorder. Some cases can be mild and progress very slowly over a normal lifespan, while others produce functional disability, severe muscle weakness and loss of the ability to even walk. While some children with MD die in infancy, others live into adulthood with only a moderate disability. ■

For additional information on the issues discussed here, please visit https://mdcc.nih.gov/ and www.niams.nih.gov.

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Duchenne muscular dystrophy (DMD)

Associate Professor and Director of Medical School Curriculum at the University of Illinois, Dr Ahlke Heydemann underlines Duchenne muscular dystrophy (DMD) – a debilitating, progressive muscle weakening disease

Duchenne muscular dystrophy (DMD) is a debilitating, progressive muscle weakening disease. Currently, there are no cures and no effective treatments for muscular dystrophy (MD). However, there are multiple highly promising therapeutics in the pipeline that should give patients and their families' significant hope. One exciting avenue of research is identifying novel methods of immune inhibition.

Immune inhibition is a promising therapeutic avenue because of the large body of data (from both lab animals and patients) that indicates reducing the chronic inflammation that always accompanies DMD is significantly beneficial (reviewed Evans 2009 and Tidball 2005). In MD mice, various scientists depleted CD8+ T-cells, or CD4+ T-cells, or macrophages, or neutrophils and have demonstrated significant improvement of pathology (reviewed in Evans). Now, researchers must achieve these immune-cell reductions in humans and without side effects.

MD pathobiology initiates with muscle cell membrane permeability, immune infiltrate, myofibre loss and fibrosis. Despite the complicated characteristics of the immune system, its role in acute muscle wounds and MD pathology can be described. In muscle wounds, the immune system is responsible to clean the wound, create scar tissue to halt bleeding, remodel the scar tissue and then terminate the immune system response. Neutrophils and type 1 macrophages initiate the immune infiltration followed by eosinophils and T-cells.

The type 1 macrophages then transition to the anti-inflammatory type 2 macrophages. The disease is so devastating because of the chronic, ongoing nature of the membrane damage and the resultant asynchronised healing response. One cell may be at the correct stage to repair its membrane and is secreting appropriate anti-inflammatory cytokines, while a neighbouring cell is secreting cytokines to attract macrophages and T-cells and thereby inhibit the first cell's repair process. Interesting data even indicates that the immune cell infiltrate precedes disease histopathology (Spencer 2001), providing more impetus for inhibition of the immune system to treat MD.

In fact, the current standard of care – corticosteroids – is beneficial because it inhibits the immune response. Steroid therapies postpone the patient's need for a wheelchair. However, the steroids cause significant side-effects and other therapeutics must be identified. Among the latest, clinically-relevant, immune inhibition therapeutics are:

1) Antibodies against NFκb;

2) All-trans retinoic acid;

3) TGFβ inhibition;

4) IL-10 injections;

5) Identifying the best dose and schedule for corticosteroid régime; and

6) Fingolimod.

Each of these compounds has a strong scientific rationale for its inclusion in trials against MD. However, my real optimism for these treatments to be effective against MD is that they can be combined with each other and therapeutics that target other MD molecular mechanisms. Thereby, clinicians can tailor-make therapies for each patient and minimise the doses to avoid patient-specific side effects, while still achieving maximum benefits.

MD research has been made possible and greatly accelerated due to the availability of many mouse models. The most commonly used mouse is the naturally occurring dystrophin deficient mdx mouse (muscular dystrophy on the X-chromosome). In addition, the individual sarcoglycans have been genetically mutated to make the range of sarcoglycanopathies, including the gamma-sarcoglycan

mutations (Sgcg-/-). Both of these models, the mdx and the Sgcg-/-, have been breed onto the highly fibrotic DBA/2J mouse strain. Through this breeding, the mice closely resemble the pathology seen in patients.

My lab has focused on immune inhibition strategies because of the strong benefits are seen by this strategy. The mechanism my lab has focused upon is the use of the FDA approved sphingosine-1-phosphate receptor modulator Fingolimod. Fingolimod is FDA approved to treat relapsing multiple sclerosis (MS) and has proven very effective for these patients. MS is an auto-immune disease in which the bodies' antibodies attack and often destroy the myelin sheaths surrounding the nerves. This causes profound muscle weakness and lesions in the brain. Many MS patients have been taking Fingolimod (Gilenya, Novartis) for six years, with few side effects. Fingolimod's mechanism of action sequesters immune cells in the peripheral lymph tissue and thereby inhibits further damage.

This mechanism is very different from the immune inhibition provided by the steroids, thereby allowing the possibilities of co-therapy combining these two strategies. The most important, although rare side effects of Fingolimod are transient bradycardia after the first dose and lymphopenia after prolonged use. The lymphopenia is reversed with treatment discontinuation. Although MD is not a true auto-immune disease, the chronic immune response is pathogenic and must, therefore, be reduced. In addition to its immune inhibition, we have demonstrated that sphingosine-1-phosphate receptor modulation with Fingolimod provides additional benefits against MD.

In both the Sgcg-/- DBA/2J and the mdx DBA/2J mouse strains my lab has identified that Fingolimod has pleiotropic beneficial effects upon MD disease progression and even initiation. We have demonstrated that a three-week treatment course administered to young animals reduced the disease-proximal membrane permeability, reduced the immune infiltrate, reduced the resulting fibrosis and increased some of the respiratory functional parameters (Heydemann 2017).

Based on published research studies, our initial hypothesis was that Fingolimod would inhibit the pathogenic immune response and thereby reduce the necrosis-induced fibrosis. We had hoped that a slight improvement of membrane strength would also be achieved because of the reduction in cytokines. However, we were very surprised at the data demonstrating such a large reduction in membrane permeability. The treatment reduced the membrane permeability to not significantly different from wildtype levels.

As with most research studies, this study produced more questions than answers. Our current experiments are designed to answer the most important of these questions. Therefore, we are examining how Fingolimod strengthens the muscle membrane. In this pursuit, we have preliminary data that indicates that treatment with Fingolimod re-establishes the remaining – non-mutated – members of the dystrophin glycoprotein complex. We will now establish if this is through increases in transcription, translation, protein stability or complex stability. We are also conducting additional preclinical trials, such as dose-response curves, longer treatment times, prevention and reversal strategies and co-therapy trials.

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Nanomaterials in the healthcare sector: The navigation paradox applied to healthcare

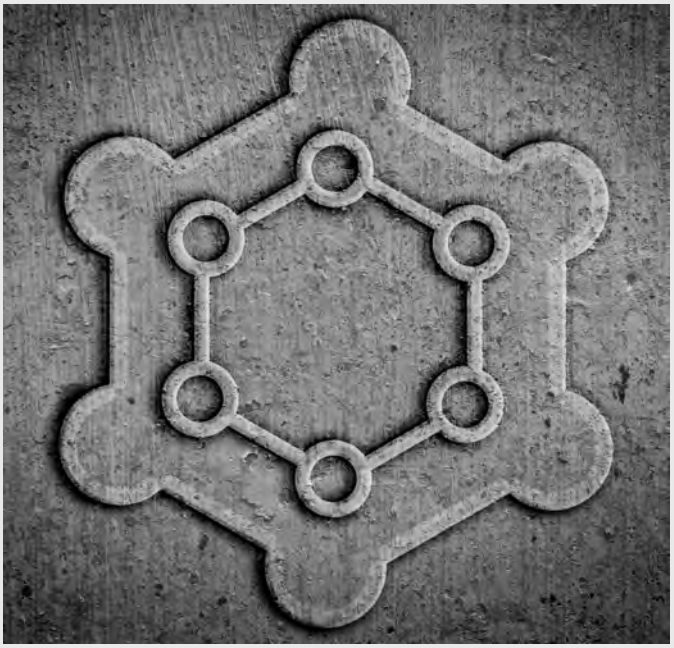
Cecilia Van Cauwenberghe from Frost & Sullivan shares her expertise on nanomaterials in today's healthcare sector, including therapeutic precision versus nanotoxicology risk

The navigation paradox affirms that increased navigational precision may result in increased collision risk. In fact, improved positioning systems have gained significant precision at the expense of a greater probability of occupying the same space on the shortest distance line between two navigational points. According to Drlickova et al., 2017, although nanomedicines potential has revolutionised precision medicine approaches, the unique properties of nanoparticles capable of penetrating inscrutable biological barriers can induce unintended adverse effects on human health and environment, thereby adding some complexity to the balance between therapeutic efficacy due to impressive technological advances and safety due to nanotoxicity issues. Gkika et al., 2018, also depict the conflict between science advocating for the use of high-risk, potentially toxic nanomaterials due to their higher therapeutic target precision and being society reticent to the utilisation of certain nanotechnologies.

Risk assessment and decision-making tools

Chemical and biological risk evaluation, life cycle assessment, safety-by-design, stakeholder engagement and risk governance, among many additional criteria, constitute key items in an effort to address the needs of emerging technologies such as nanomaterials.

The design of new decision support frameworks to assist the solution of the aforementioned paradox has been analysed by Rycroft et al., 2018. The researchers intend to derive a complete characterisation of the risks and benefits that a given nanomaterial may proffer within a specific nanomedical application, based on multicriteria decision analysis. Conscious of the double-edged sword of risks and benefits of nanomedicines, the authors analysed the risks and benefits of a whole decade of nanomedicines development in order to build a valuable, knowledge-based framework focused on



nanotoxicology and risk assessment interventions. This tool not only enriches multicriteria decision analysis approaches but also introduces risk-based decision-making and alternatives-based governance criteria for emerging technologies beyond nanomedicines.

The road ahead: Introducing more science

Occupational exposure limits

Specific occupational recommended exposure limits (REL) for nanomaterials are limited. The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) recommend to workers do not exceed the exposure to 1.0 micrograms per cubic meter ($\mu g/m^3$) as an 8-hour time-weighted average to respirable carbon nanotubes and carbon nanofibres, as an example.

Workplace design optimisation

The NIOSH advice companies for controlling possible exposure of their workers to nanomaterials in the work-

place through a series of new workplace design solution documents. These four deliverables strategically help optimise the workplace design to guarantee workers' safety during nanomaterials handling.

Bioprotective complexes administration

According to a recent publication authored by Leso et al., 2017, challenges faced during nanotechnology translation to the healthcare industry are numerous. The researchers highlight the high level of uncertainty related to the physicochemical properties of nanomaterials regarding potential toxicity, the difficulty in extrapolating dose-response correlations and the complexity in measuring nanomaterial exposure.

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However, Privalova et al., 2017, demonstrated that highly adverse effects of metallic nanoparticles at organ-systemic level can be manifestly mitigated by background administration of suitable combinations of bioactive agents in innocuous doses aiming for improving the body's resistance to the adverse effects of nanoparticles. These bio-protectors principally consist of pectin, vitamins, glutamate, glycine, N-acetylcysteine, omega-3 PUFA and different essential trace elements. They are suggested by the authors as an efficient auxiliary instrument of health risk management, according to the beneficial results exhibiting interference with toxicokinetics and toxicodynamics of metal nanoparticles.

Artificial intelligent solutions

Ponce and Krop, 2018, illustrate the launch of the EU Observatory for Nanomaterials as a form of impact assessment. The broad goal is to build a framework to trace where nanomaterials are being produced and how they are used and how they are disposed of. With the advent of digital technologies, artificial intelligence, robots, new materials and new processes, nanomedicines are supposed to lead significant progress in the industry. Therefore, artificial intelligent and smart healthcare solutions must serve to regulate and provide transparency at all levels of nanomaterials manipulation in order to shape the future of technology synergy over solid health and safety bases.

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Pursuing physics at the forefront of knowledge

Denise Caldwell, Director, Division of Physics at the U.S. National Science Foundation (NSF) provides a fascinating perspective on how the organisation is pursuing physics to the forefront of knowledge

On September 14th, 2015, the twin detectors of the National Science Foundation's (NSF) Laser Interferometer Gravitational-Wave Observatory (LIGO) registered a gravitational wave as it passed through the Earth. The distortion of space-time – predicted by Albert Einstein one hundred years earlier – was generated as two black holes merged into one, releasing the energy of three suns in the process.

The LIGO observation marked the first time scientists had ever directly observed a gravitational wave, an achievement that even Einstein himself did not believe possible. LIGO's success is the result of a high-risk, high-impact investment made over four decades by NSF through its Physics Division, a commitment to build what is arguably the most sensitive detection instrument ever constructed.

Since that first observation, LIGO has witnessed four additional black-hole mergers, followed in August of last year by the first gravitational wave detection of paired neutron stars. That detection was immediately followed by observations from 70 telescopes around the world, providing new insight into the collision from visible light, ultraviolet light, radio waves, x-rays and gamma rays.

The complementary observations brought together two of the three elements in multi-messenger astrophysics: explore the cosmos through observations of gravitational waves, while collecting radiation across the entire electromagnetic spectrum. The third element, an observation that combines data from elementary particles such as neutrinos with electromagnetic data, is on the horizon. As the elements of multi-messenger astronomy are united, humanity will have an unprecedented, comprehensive view of the most powerful events in the universe.

Searching for answers to some of science's most challenging questions is a core goal for the NSF Physics Division. The study of physics as an intellectual pursuit underpins all the other physical sciences and increasingly, the life sciences as well, as physicists and biologists increasingly cooperate to address problems covering a range of scales, from molecule to organism.

Since 1975, scientists supported by the NSF Physics Division have made seminal contributions to advancing the frontiers of the field, from the vast reaches of the universe to the tiniest particles of matter, helping secure U.S. leadership across science.

We support scientists working at the ATLAS and CMS detectors, part of the Large Hadron Collider at the CERN laboratory in Switzerland, where three years prior to the LIGO discovery, scientists participated in the discovery of the Higgs boson, the last remaining elementary particle needed to complete the Standard Model of particle physics. Our division also supports the National Superconducting Cyclotron Laboratory at Michigan State University and IceCube, an NSF-funded neutrino detector located at the South Pole.

Those efforts are complemented by our support of NSF Physics Frontiers Centers, which focus on addressing the most compelling frontier science questions. In that setting, research progresses through the concerted efforts of large, often interdisciplinary, groups working together.

While large facilities are important for discovery, our division's primary mechanism of support is to individual researchers and small groups. Our funding almost exclusively supports faculty research programmes housed at universities and in this way, we foster scientific progress while ensuring the propagation of ideas

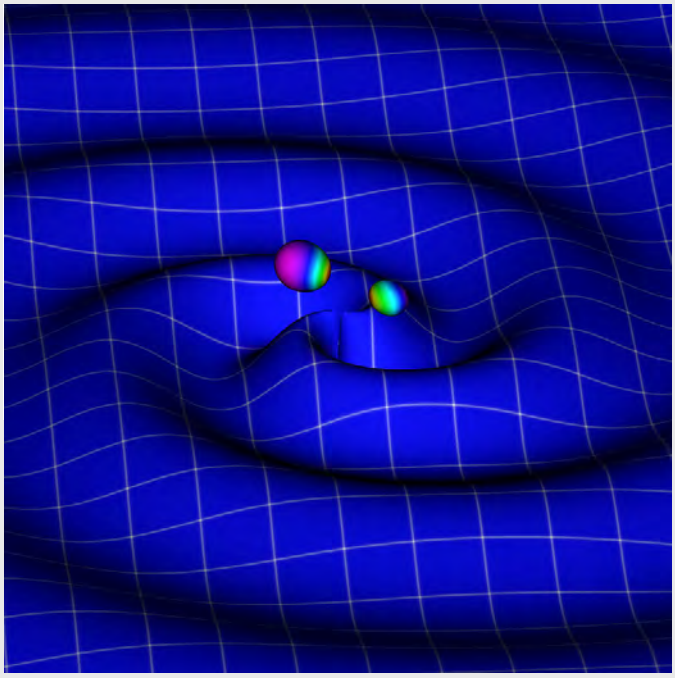

Image: NCSA Gravity Group

Gravitational waves

to students and early career faculty, the next generation of researchers. Significant support for students and junior scientists is inherent to our portfolio, as it is critical to prepare the next generation of researchers for advanced, high-tech work and innovative new technologies that arise in the quest to answer some of the hardest questions that nature can pose.

Through our portfolio of awards, NSF's Physics Division pursues its primary goal "to promote the progress of science", as expressed in the legislation that founded our agency, the National Science Foundation Act of 1950. The awards support research necessary to address scientific questions at the frontier of current knowledge, while at the same time extending and redefining that frontier.

For example, crucial discoveries made by NSF grantees helped launch and lay the groundwork for quantum information science. That effort continues and contributes to current, rapid progress toward 21st Century quantum-based breakthroughs, from quantum computers to high-resolution sensors that could revolutionise measurement technology.

Across NSF there are examples of investment that begin with new ideas generated by the physics community. Those are further informed through workshops, input from advisory committees, proposal reviews and the scientific expertise of a group of top-flight programme directors, each a scientist in his or her own right. NSF relies on these community-based resources to decide where to direct our physics investment.

The breadth of investments is extensive. Through the Physics of Living Systems program, the division has helped establish and grow a community of physicists who look at the living world as a laboratory through which to learn new physics while at the same time informing breakthroughs in biological understanding. For example, a study of sand lizards moving through sand served as a paradigm for motion in granular media in general, an important concept for the design of robots for exploration.

Through the Nuclear Physics program, scientists are enhancing our understanding of the forces that drive the formation of the elements in the universe. And most recently, a telegram from the NSF IceCube Neutrino Observatory (supported both by the Physics Division and the NSF Office of Polar Programs) announced the detection of a high-energy extragalactic neutrino. That detection was quickly followed by observations from a suite of telescopes across the globe, which reported high-energy electromagnetic radiation from the same location as the neutrino, yet another breakthrough in multi-messenger astrophysics.

As such science progresses – whether it be neutrinos, cold atoms, Bose-Einstein Condensates, astrophysical plasmas, or the origin of the elements in the universe – the Physics Division has had and continues to have, a major role to play in driving scientific knowledge. ■

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Physics: Understanding the elusive dark matter

Richard G. Milner from the Department of Physics and Laboratory for Nuclear Science at Massachusetts Institute of Technology provides an absorbing insight into the search for an understanding of the elusive dark matter, one of the great scientific quests of our age

The search for an understanding of the elusive dark matter is one of the great scientific quests of our age. In the 1930s, astronomers first made determinations of the gravitational mass of galaxies that were significantly larger than expected from the observed luminosities and wrote of dunkle Materie[1]. Almost 90 years later, there is collective evidence that is substantial and consistent across seven orders of magnitude in distance scale[2], that an unknown substance (dark matter) shapes the large-scale structure of the universe.

We believe that dark matter interacts gravitationally and that its non-gravitational coupling is of order the weak interaction[3], or less. We expect that there must be some new interaction via a mediator between dark matter and atomic nuclei for dark matter to be in equilibrium with other matter in the early universe. We know the approximate density and velocity of dark matter in our galaxy. Dark matter does not form tightly bound systems larger than about 1,000 solar masses, but it appears to account for about 25% of the mass of the universe, that is about five times larger than the matter we can see.

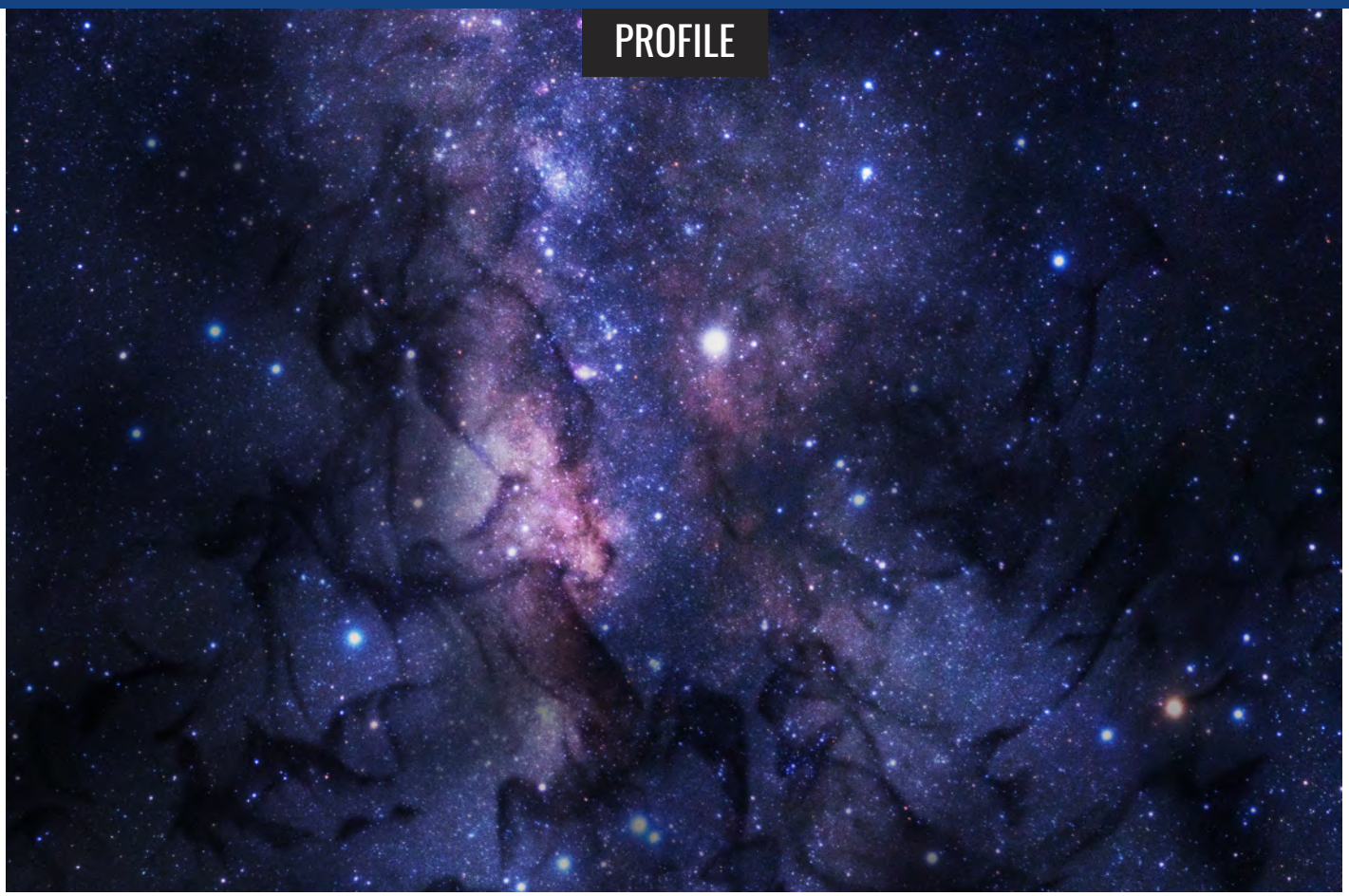
The known, uncharged particles, for example, the neutron or neutrino, cannot account for dark matter. The focus over several decades has been to look for a weakly interacting massive particle (WIMP) via a rare scattering from an atom in a large detector, typically located deep underground to minimise the rate of background events. The recoil atom's energy is detected. Thus far, no conclusive evidence for WIMPs has been found. The present experiments set the WIMP-atom interaction limit lower than the rate of a low-energy[4] neutrino interacting with atoms[5]. Searches for WIMPS will continue for at least another decade. However, there is a fundamental limit to this approach due to the inability to distinguish between a neutrino-atom interaction and a WIMP-atom interaction. The WIMP mass region explored by the underground experiments typically ranges from about three proton masses to about 10,000 of the same.

A complementary experimental thrust in the quest to understand dark matter, is to search for evidence of the mediator of a new interaction between our visible world, successfully described in terms of four forces (gravity, electricity and magnetism, nuclear force and weak force) and the world of dark matter. This new interaction would constitute the fifth force.

The simplest mediator widely considered is a dark photon that couples to the known particles via their electric charges. The searches involve experiments using particle beams delivered by accelerators to produce the mediator. The mediator decays either into (a) known, detectable particles that are sought (visible decays) or (b) into the dark sector, which are undetectable, but whose presence is deduced by observation of a large missing energy and momentum in the final-state (invisible decays). The results of the searches are usually summarised in terms of their ability to constrain the mediator-to-known-matter coupling strength and the mediator mass. At the Large Hadron Collider at CERN, Geneva, Switzerland, searching for evidence of dark matter is a major activity at the three principal experiments[6].

Recently, there has been a focus on searching for a mediator with a mass lower than the proton mass. Astrophysical observations and observed anomalies in measurements involving the muon and nuclear transitions hint at this possibility. Existing experiments, primarily using the decay of the neutral pion, have searched inconclusively for evidence of a dark photon. However, a more general fifth force, where the couplings are no longer simply the charges, remains a viable possibility.

Our MIT group is focused on searching for evidence of a fifth-force, with a mediator of mass less than about 10% of the proton's mass. In collaboration with colleagues, we have proposed the DarkLight experiment[7] at Jefferson Laboratory[8], Newport News, Virginia,



USA to produce the mediator in electron-nucleus scattering and searching for visible decays into a positron and electron. DarkLight requires an intense, bright and halo-free electron beam possible only with a new accelerator technology, called an Energy-Recovery Linac (ERL).

A phase-1 DarkLight experiment has been funded and a search, focused in a specific mediator mass region suggested by a reported anomaly, is in preparation. Jefferson Laboratory pioneered the development of ERLs using superconducting accelerator technology and next-generation ERLs are at present under construction at Cornell University, USA[9] and at Mainz University, Germany[10]. Searches for evidence of dark matter via low-energy signals in electron scattering are being planned at both machines.

In summary, the search for evidence and understanding of dark matter is an intensive, worldwide research endeavour by physicists using state-of-the-art accelerator and detector technology on, above[11] and beneath the Earth. Calculations by theoretical physicists are essential for the design of experiments with maximum sensitivity to uncovering new physics. This research drives technology development in high-intensity accelerators, detectors and high-rate data acquisition.

There are major new initiatives underway worldwide and this area will continue to be a forefront activity for the foreseeable future, attracting some of the best and brightest young minds. This curiosity-driven, fundamental research into understanding our universe is made possible by the generosity of the taxpayer via government support of fundamental research[12].

1 F. Zwicky, Helvetica Physica Acta, 6, 110 (1933)

2 From 1 kpc to 10 Gpc: 1 pc = 3.26 light years = 3.1 x 10^{16} m.

3 The weak interaction initiates the fusion process in the sun and drives beta-decay.

4 10 keV.

5 Present best cross-section limit is about 10^{-46} cm^2 at a WIMP mass of about 50 proton masses.

6 ATLAS, CMS and LHC: home.cern.

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12 The author gratefully acknowledges the support of both the Office of Nuclear Physics of the Department of Energy and the National Science Foundation of the United States.

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Next steps to the Moon: What role for Europe?

Sebastien Moranta, coordinator of studies at the European Space Policy Institute (ESPI) sheds light on Europe's potential to explore the Moon in co-operation with other great world powers

With an extension of operations beyond 2024 under discussion and promising opportunities of partnership with the private industry under development, the long-term future of the International Space Station (ISS) is not yet written.

Notwithstanding, the preparation of the post-ISS era is a central topic for the partners (U.S., Russia, Europe, Japan and Canada) who, despite multiple exchanges of ideas, declarations and precursor programmes, had been, so far, struggling to build a steady, robust and commonly-shared vision for the future of human spaceflight and space exploration. Recent events and announcements suggest, however, that the state of affairs is now progressing as agencies seem to be converging toward a shared enthusiasm for the Moon and moving ahead with preliminary steps.

In ESPI Brief n°12 "Making Exploration Great Again", ESPI highlighted the important step forward made by the American administration in the field of space exploration with the signature of NASA's Transition Authorization Act by President Donald Trump in March 2017. The document underlined a strong willingness of the U.S. to engage more actively in human space exploration with the development of a Deep Space Gateway (DSG) in cis-lunar orbit as the next programmatic step to prepare the journey to Mars.

Although building on past projects (e.g. the Space

Launch System and Orion capsule), U.S. plans marked a turn from the Obama administration's "Low Earth Orbit-Asteroid-Mars" path and a come back to the former "Low Earth Orbit-Moon-Mars" Constellation programme, supported by the Bush administration. Two major announcements recently highlighted a solidification of this renewed U.S. posture and confirmed the emergence of an international cooperation dimension.

Firstly, during the meeting of the re-established U.S. National Space Council on 5 October 2017, Vice-President Mike Pence delivered an engaging speech calling for a return to the Moon in cooperation with international and commercial partners under American leadership. The Council directed NASA to develop a plan within 45 days to carry out that revised policy. This presidential declaration and the development of a plan by NASA further consolidate both political support and programmatic implementation of the rehabilitated U.S. strategy.

Secondly and perhaps more importantly, the DSG gained an official international dimension with the signature of a joint statement by Roscosmos and NASA on 27 September 2017 at the 68th International Astronautical Congress in Adelaide, Australia. Although NASA had already been discussing technical options for the DSG concept with ISS partners through the ISS Exploration Capabilities Study Team (IECST) and International Spacecraft Working Group (ISWG) during meetings in Japan, Canada and Europe in 2017, the joint statement, focusing at the moment on preliminary studies, marks a noticeable milestone in the development of an international cooperation structure around the DSG project.

Regardless of the U.S.'s considerable financial and technical resources, international cooperation will be critical to achieving ambitious objectives, to secure programme stability and to consolidate U.S. leadership on the global scene. From this perspective, the acceleration observed recently suggests that the DSG provides a more fertile environment for international partners to contemplate a financially and technically conceivable contribution to the programme, than previous plans developed under the Obama administration did.

This being said, it is important to recall at this stage that, despite a strong political support, the programme still has to face major hurdles before becoming a reality. This includes the definition of an architecture meeting various objectives from different partners, the allocation of an appropriate budget (which may be challenged by the willingness to also expand ISS operations) and eventually an official endorsement by U.S. and international partners' establishments.

Nevertheless, partners can now build on an existing and robust multinational cooperation framework, such as the one of the ISS, which will undoubtedly simplify future political and programmatic progress. Overall,

in a context where drivers seem to outweigh barriers, the DSG seems particularly close to becoming the next stage of international cooperation in space exploration.

Another interesting factor that will certainly have to be closely looked into is the role that China may play in the future. As of today, with the Chinese programme ramping up toward the Moon and multiple legal and political constraints for NASA to engage in cooperation with China, the situation suggests that, following Cold War competitive era and ISS cooperation era, the third era of space exploration will very likely give way to a mix of cooperation and competition for leadership.

Regardless of the U.S's considerable financial and technical resources, international cooperation will be critical to achieving ambitious objectives, to secure programme stability and to consolidate U.S. leadership on the global scene.

What role for Europe?

Europe is already engaged, through ESA (The European Space Agency) and at a national level, in technical discussions with NASA and other partners and organised various consultations about the DSG. Maintaining such active dialogue will be essential to get an informed understanding of the evolution of the project and of European industrial and scientific communities' interest and to secure an active participation in the concept definition. Assuming that Europe intends to play a prominent role in the DSG, as it did for the ISS, the acceleration of the project on both the American and international scene now requires Europe to bring the topic to a higher level and to reach a political momentum.

As a partner, European decision-making process obviously depends on the progress of programme approval by U.S. institutions; yet, reaching a shared European position will require a preliminary effort to build a political consensus, if not unanimity, among the Member States. Achieving this consensus shortly is a necessary condition to secure Europe capacity to react timely to future evolutions on the American and international scene and to already position Europe as a key partner.

When looking at the rehabilitated Moon objective and taking into account that current DSG plans foresee robotic and human Moon landings, one cannot overlook the renewed light that is shed on ESA Director General's Moon Village vision. Indeed, the current dynamic of the international space exploration scene could offer an interesting springboard for Europe to implement, at least partially, this ambitious vision.

With the declared objective to prepare a journey to Mars, the deployment of a Moon Base as a potentially European-led component of an international DSG programme would certainly offer a relevant test bed for the development and validation of key capabilities for future Mars mission such as in-situ resource utilisation, robotic-human cooperative operations or ground base assembly among many others. In general, the role that Europe will hold within the next international partnership framework will be first and foremost framed by the financial and technical resources it is ready to commit. ■

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Space: Reaching out to new heights to benefit mankind

Open Access Government reveals the exciting mission of the National Aeronautics and Space Administration (NASA) and how the United States aims to reach out to new heights to benefit mankind when it comes to exploring space and beyond

The National Aeronautics and Space Administration (NASA) prides itself in the collaboration of technology, science and unique global Earth observations to provide societal benefits and strengthen the United States. NASA's succinct vision for the past and present has always remained the same. "We reach for new heights and reveal the unknown for the benefit of humankind." (1)

Leading the way back to the Moon

In February 2018, NASA Administrator Robert Lightfoot spoke about the Fiscal Year 2019 agency budget proposal and remarked how it reflects the US administration's confidence that through the leadership of NASA, America will lead the way back to the Moon and take the next giant leap from where they made that first small step almost 50 years ago. Firstly, he explained how the budget focuses NASA on its core mission and how it will help to place a renewed focus on the U.S.'s human spaceflight activities.

"This budget focuses NASA on its core exploration mission and reinforces the many ways that we return value to the U.S. through knowledge and discoveries, strengthening our economy and security, deepening partnerships with other nations, providing solutions to tough problems and inspiring the next generation. It places NASA and the U.S. once again at the forefront of leading a global effort to advance humanity's future in space and draws on our nation's great industrial base and capacity for innovation and exploration.

"This proposal provides a renewed focus on our human spaceflight activities and expands our commercial and international partnerships, while also continuing our pursuit of cutting-edge science and aeronautics breakthroughs at the core of our mission."

Lightfoot then went on to explain how the United States is once again on the path to return to the Moon, also with an eye towards Mars. He said that NASA is called to refocus existing activities towards exploration, by redirecting funding to innovative new programmes, as well as support for new public-private initiatives. Here, he expands on these ambitious goals in his own words, as well as explaining how the International Space Station (ISS) will be the cornerstone for pushing human presence further into space.

> "Webb is the highest priority project for the agency's Science Mission Directorate and the largest international space science project in U.S. history. All the observatory's flight hardware is now complete, however, the issues brought to light with the spacecraft element are prompting us to take the necessary steps to refocus our efforts on the completion of this ambitious and complex observatory."

"We are leveraging multiple partners both here at home and internationally in developing a sustainable approach where the Moon is simply one step on our truly ambitious long-term journey to reach out farther into the solar system to reap the economic, societal and expanding knowledge benefits such an endeavour will bring.

"We've used the International Space Station (ISS) as the cornerstone for pushing human presence farther into space, with a horizon goal of humans to Mars. This includes learning about the human physiology of spaceflight and enabling new industry partners to bring to bear their capabilities and emerge as leaders... to help us on this journey. The commercial cargo and crew work continues through the life of the International Space Station in the budget." (2)

Lightfoot adds that while the Fiscal Year 2019 agency budget proposal does not provide funding for an Office of Education, NASA's mission successes will nevertheless continue to inspire the next generation to take up studies in science, technology, engineering and mathematics. Lightfoot believes that the next generation will become the diverse workforce of the future, where aerospace careers are concerned. He went on to develop this point, adding that NASA will help the United States lead the way in the space sector, despite the hard choices that have had to be made.

"We will use every opportunity to engage learners in our work and the many ways it encourages educators, students and the public to continue making their own discoveries.

"We can't do everything and as always, we've had to make hard choices, but we will continue to forge new paths and partnerships that strengthen our industrial base and our engagement with other nations to achieve challenging goals that advance our capabilities and increase our security and economic strength. NASA will continue to deliver on the promise of U.S. ingenuity and proven leadership in space."

In other interesting news, we also find out that NASA's James Webb Space Telescope is undergoing final integration and test phases that will require more time to ensure a successful mission. Following an independent assessment of remaining tasks for the highly complex space observatory, the launch is now targeted for around May 2020.

Lightfoot comments more on this ambitious aspect of NASA's work: "Webb is the highest priority project for the agency's Science Mission Directorate and the largest international space science project in U.S. history. All the observatory's flight hardware is now complete, however, the issues brought to light with the spacecraft element are prompting us to take the necessary steps to refocus our efforts on the completion of this ambitious and complex observatory."

Also, worth noting is that Webb has already completed extensive tests to make sure it reaches its orbit safely, at almost one million miles from Earth. As with all NASA projects, rigorous testing takes time, which of course, increases the likelihood of the mission being successful. Thomas Zurbuchen, an associate administrator for NASA's Science Mission Directorate, comments on this point: "Considering the investment NASA and our international partners have made, we want to proceed systematically through these last tests, with the additional time necessary, to be ready for a May 2020 launch." [3]

NASA believes that the James Webb Space Telescope will be the world's premier infrared space observatory and the biggest astronomical space science telescope ever built, complementing the scientific discoveries of NASA's exciting missions, such as the Hubble Space Telescope. Webb will explain the mysteries of the solar system, look beyond to distant worlds around other stars probe the mysterious origins and structures of the universe, as well as our place in it. This fits in perfectly with NASA's mission to: "reach for new heights and reveal the unknown for the benefit of humankind." ■

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Developmental biology: Fulfilling the promise of Organoids

Professor of Developmental Mechanics at the Department of Genetics, University of Cambridge, Alfonso Martinez Arias shares his expert view on Organoids, within the field of developmental biology

A few years ago, a headline and a picture captured the imagination of the world: scientists had been able to grow a miniature version of a human brain in a dish in the lab. Understandably, such a feat unleashed the imagination and the hope of people, particularly those with disease. It did not matter that similar findings had been made and reported with the mouse before, the adjective 'human' always has an impact on anything science related. Soon the word was out that this would revolutionise the study of mental health, pave the way to cure disease and, of course, there were the inevitable claims to the cure of cancer.

These 'mini brains were part of a menagerie of counterfeits of human organs and tissues grown in the lab including disembodied eyes, livers, intestines and pancreas that came to light with this finding. How was it possible? What does it mean? It is sometimes difficult to disentangle hype and hope in scientific research but, in this area, one needs to, as the potential gains are enormous but only if they are built on sound foundations and not on false expectations. For the moment, understanding mental health with mini brains is not on the cards, though understanding something about how cells make brains is. If you want to build tall edifices you need good foundations.

What are Organoids?

The structures reportedly grown in the lab are known as 'organoids', because they are imperfect replicas of real organs. They result from remarkable and still little understood, abilities of special cells, stem cells. Cells do not live forever, and most tissues of our body require a constant replenishment. This is what stem cells do. They manage to keep themselves going, while providing a constant stream of material to repair damage and keep organs functioning.

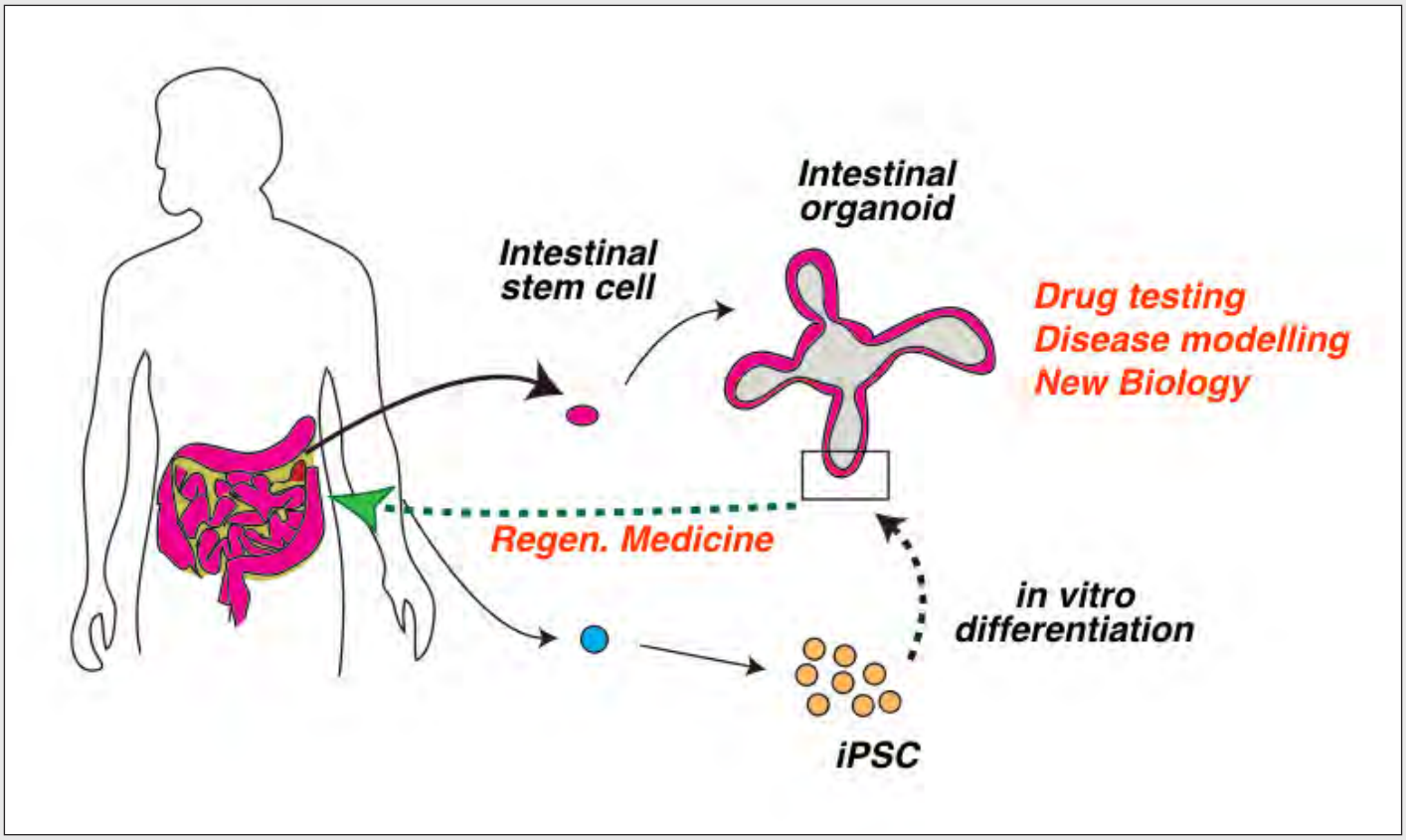
For example, every day your body produces 200 trillion red blood cells to keep you fit and stem cells in your intestine 30 billion cells to deal with your digestion; this is the awesome power of these cells. The ultimate stem cells are embryonic stem cells (ESCs), derived from very young embryos they can be grown almost indefinitely in culture and, at any time, any single one of them can generate a whole organism.

Organoids are the result of the potential of stem cells. It is not yet possible to grow blood in the laboratory, but intestinal and embryonic stem cells are paving the way for much of what we shall be able to do in the future. A single intestinal stem cell can produce a rough copy of the adult intestine, an intestinal organoid, *in vitro* and steering ESCs in defined environments with specific chemicals, can produce rudimentary kidneys and lungs. It is these ESCs that were used to build mini brains. However, for now, we cannot control these processes just watch them unravel.

The promise

It is early days. Organoids are, in most instances, too imperfect to be of use but the goal is to use these cellular contraptions to understand the disease, test drugs and even one day, create replacements for some tissues and organs.

One of the main problems of regenerative medicine, in which we can replace a damaged organ or tissue for a healthy one, is the matching of tissues between a donor and a patient. The work with organoids promises to solve this problem with the use of so-called induced pluripotent stem cells (iPSCs): ESCs generated by converting adult cells from an individual into ESCs which then, in principle, can be transformed into any tissue and organ.



Thus, iPSCs allow generating tissue matches for the patient as the donor is genetically the same. There is little question that this will happen in the future, but it will not happen faster because of ill-founded claims that it can happen, and we should avoid listening to siren chants that are so frequent in this field.

One of the roadblocks to progress is 'reproducibility'. In biology, when something works it is capable of making many good copies of itself; behold embryos building organisms. Unfortunately, most organoids now are low frequency, heterogeneous and not functional. To break this impasse, we need more basic research. Two fields will have an impact in progress: developmental biology – that teaches us how animals develop – and engineering – that tells us how to control processes and make them efficient.

The way to the promise

For now, however, while we realise the promise of iPSCs, intestinal organoids, probably the most advanced and reproducible in the field of human organoids, are providing a reference for some of the work that can be done. In a recent landmark study, scientists made intestinal organoids from cancer patients that were undergoing treatment and observed that the *in vitro* avatars responded to the treatments as the individuals did. This opens enormous possibilities for the use of these organoids to rapidly test drugs and treatments highlighting the potential that lies ahead.

The emerging organoid field at the crossroads of stem cell, developmental biology and engineering will transform our understanding of how cells build organs and tissues and in doing so will pave way for significant applications in biomedical research. For this to fulfil its potential we should resist the allure of statements that promise much in a short-term present and investing in solid knowledge for a long-term future. ■

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Electrical activity as a regulator of induction and the maintenance of specialised tissues

Intro: The electrical activity as a regulator of induction and the maintenance of specialised tissues is placed under the spotlight by Graciela A. Unguez at the Department of Biology, New Mexico State University in the United States

It is increasingly clear that electrical impulses – action potentials – have profound effects on virtually all organs regulated through neurons that communicate through such impulses. One such target organ that is regulated by nerve-dependent electrical impulses is the skeletal muscle in vertebrate animals. In fact, the induction and maintenance of many properties of skeletal muscle are evident by the dramatic wasting and debilitating conditions that result in humans affected by genetic and degenerative diseases, trauma, injury and the ageing of the neuromuscular system[1].

Conversely, we know that the application of neuromuscular electrical stimulation evokes involuntary muscle contractions and supports muscle mass maintenance in conditions of muscle disuse[2]. To date, research from many labs continues to uncover ways by which the phenotypic and functional properties of skeletal muscle respond to changes in innervation – under different environmental conditions from early development to ageing.

One fundamental question that remains largely unanswered is how do the amounts or patterns of electrical activation regulate the diversity of the many muscle fibre types? Specifically, how is neural input, coupled to the regulation of transcriptional and post-transcriptional changes of muscle genes that affect metabolism, morphology and contractility is unknown?

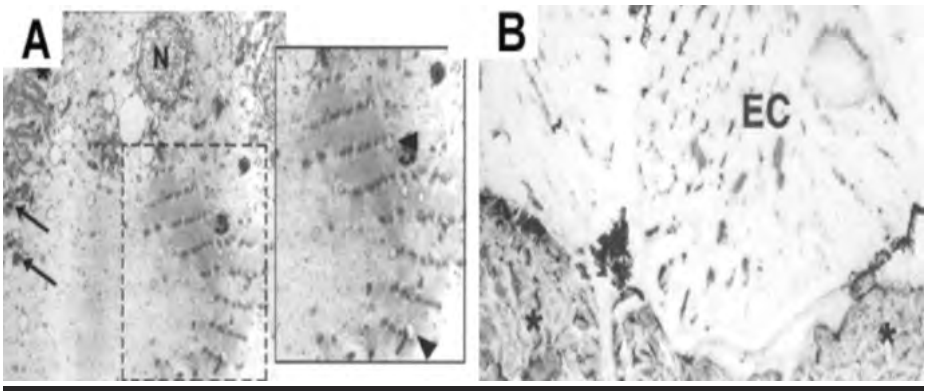

Figure 1. Electrically inactive electrocytes make new sarcomeres. A: Electron micrograph shows a sarcomere bundle in the electrocyte after spinal transection (see cartoon depicting inactivation of EMNs and SMNs). N, nucleus. B: Clustered anti-MHC labelling pattern inside electocyte (EC), a pattern corresponding to sarcomeric clusters shown in electron micrographs. Mitochondria (arrows) are located peripherally near the cell membrane. (Unguez and Zakon, 1998b).

Moreover, the role that electrical activity patterns may plan in the extreme transformation of skeletal muscle from a force-generating tissue to a specialised energy-producing, but not force-generating, tissue has only recently been addressed. Here, an evolutionary myogenic "novelty" is highlighted to raise interest in phenotypic outcomes of distinct nerve-myogenic tissue systems maintained by unique electrical impulse patterns.

In the electric fish Sternopygus macrurus, some skeletal muscle fibres exhibit an extreme phenotypic plasticity by losing their contractility during normal development to give rise to electrocytes (ECs), the specialised cells that generate electricity and make up the electric organ (EO)[3]. ECs are also unique in that they are electrically driven by a population of spinal motoneurons called electromotoneurons (EMNs)[4] at a continuous rate of 50-200 Hz[5].

By comparison, somatomotoneurons (SMNs) in teleost fish innervate muscle fibres that are driven intermittently and at frequencies lower than 8 Hz[6]. We tested the idea that differences in activation patterns between SMNs and EMNs account for the differences in muscle and EO phenotypes in the adult[7], by eliminating all motoneuronal activity to the muscle and EO tissues in adult fish.

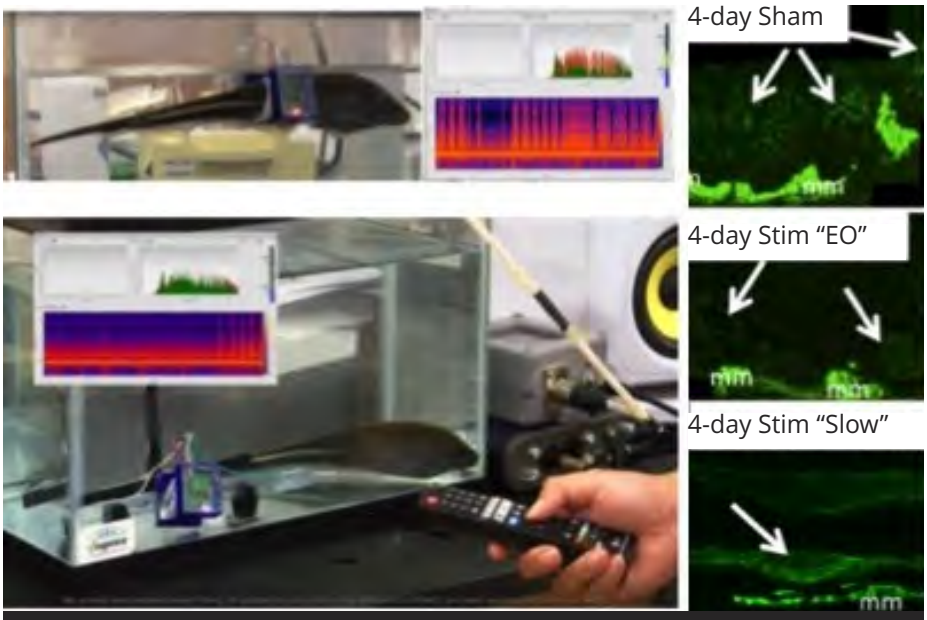

Figure 2. Wearable 3D printed backpack by free-swimming fish with remote controlled stimulation. Top left: Fish wearing a backpack. Bottom left: Real-time recorded electric field in real-time when changing stimulation patterns and testing remote control of stimulator. Right panel: Immunolabeling for sarcomeric myosin (arrows) in sham and tails electrically stimulated with an electric organ-like (EO) or a slow-twitch muscle like (Slow) pattern. mm, muscle.

Interestingly, this treatment resulted in the re-expression of sarcomeric contractile proteins and formation of sarcomeres de novo within mature electrocytes (Fig 1). Furthermore, in the absence of neural input the muscle-to-electrocyte conversion does not take place[8].

To directly test the role of electrical activity on EC and its myogenic properties, we have pioneered a 3D-printed wearable backpack system that allows underwater chronic in vivo electrical stimulation (Fig 2)[9]. The stimulation pattern can be remotely controlled using infrared light with a TV remote controller. The stimulation pattern is adjustable by programming a microcontroller. The stimulator circuit is placed on a printed circuit board, which is placed in a waterproof circuit case attached to the backpack[9].

Immunolabeling experiments of tails receiving different activity patterns suggest an upregulation of sarcomeric myosin heavy chain in ECs in sham controls (spinal transected only; Fig 2) and stimulated (spinal transected and stimulated; Fig 2) tails. The ability to impose a wide range of electrical activation patterns will further our knowledge of how specific features of electrical stimulation may affect differentiation, maintenance and transdifferentiation of the skeletal muscle program.

Other myogenically derived tissues with unique non-force producing functions such as the heater organ in billfishes[10] and sound organ in toadfish[11] also receive neural input, that is different from that of skeletal muscle fibres. Whether specific electrical impulse patterns induce and maintain the muscle-to-heater cell and muscle-to-sonic muscle cell phenotypes in these tissues will be interesting with respect not only the degree of plasticity of the skeletal muscle phenotype, but also the evolution of "novel" vertebrate tissues. Learning more about the electrical activity patterns in a wide range of nerve-target organ phenotypes is particularly relevant in the current interest in the development and use of electroceuticals – the use of electrical impulses to modulate the function and repair of body tissues[12].

Funding source

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Biology: Enabling discoveries for understanding life

The mission of the Directorate for Biological Sciences (BIO) at the U.S. National Science Foundation (NSF), is to enable discoveries for understanding life, as Open Access Government discovers

The clear mission of the Directorate for Biological Sciences (BIO) at the U.S. National Science Foundation (NSF) is to enable discoveries for understanding life. BIO-supported research furthers the frontiers of biological knowledge, increases our understanding of complex systems and provides a theoretical basis for original research in various scientific disciplines.

BIO supports research to advance our understanding of the principles and mechanisms that govern life itself. The research studies of BIO extend across systems that encompass biological molecules, cells, communities, tissues, organs, organisms, populations and ecosystems up to and including, the global biosphere. In addition, it is worth noting that BIO is divided into five divisions, which are:

- The Division of Biological Infrastructure (DBI);
- The Division of Environmental Biology (DEB);
- The Division of Integrative Organismal Systems (IOS);
- The Division of Molecular and Cellular Biosciences (MCB) and;
- The Emerging Frontiers (EF) Division.

To deal with ecological questions that cannot be resolved with short-term observations or experiments, NSF established the Long Term Ecological Research Program (LTER) way back in 1980. This research is located at specific sites chosen to represent major ecosystem types or natural biomes. It places focus on the study of ecological phenomena over long periods of time. According to the NSF, long-term studies are crucial to arrive at an integrated understanding of how populations, communities and other components of ecosystems interact, as well as to test ecological theory.

One recent example of LTER's work can be found concerning scientists at the National Science Foundation (NSF) Bonanza Creek Long-Term Ecological Research (LTER) site in Alaska, one of 28 such LTER sites. Here, they are working to understand interactions between changing tree lines and plant-eating animals, like the snowshoe hare.

"This study is a reminder that there will be winners and losers as climate changes and that species' interactions with their environments will play a critical role in how the landscape changes," said Colette St. Mary, an NSF LTER programme director.[1]

Another example of LTER's research is when scientists wanted to find out where the greatest risk of a mosquito bite is if you live in Baltimore, Maryland. Studying in Baltimore neighbourhoods where residents have low, median or high incomes, the scientists concluded that people are most at risk in areas with median incomes.

Providing insight into this fascinating area of research, Doug Levey, a director of the National Science Foundation's (NSF) Long-Term Ecological Research (LTER) program says: "Nature is all around us, including in downtown Baltimore. In this case, urban landscapes provide excellent habitat for rats and mosquitoes. Understanding how they live can help protect us from diseases."

Shannon LaDeau, a scientist at the Cary Institute of Ecosystem Studies in Millbrook, New York and co-author of the paper, explains that: "Mosquitoes are a global threat to public health. We're interested in knowing how

urban landscape features and social patterns influence mosquito biting behaviour."

"Our findings suggest that median-income areas are where people are most at risk of being bitten," adds LaDeau. "There are plenty of people for mosquitoes to bite and residents may be more likely to spend time in community gardens and shared green spaces, which makes them available to mosquitoes."[2]

Staying on the subject of ecology, it's worth looking at another example of NSF's Long-Term Ecological Research (LTER) Program's recent research. It concerns a study which ties phosphorus loading in lakes to extreme precipitation events. Going into more detail, the study shows that April showers contribute to toxic algae blooms, dead zones and declining water quality in U.S. coastal waters, reservoirs and lakes.

"This is an important example of how changes in one aspect of the environment, in this case, precipitation, can lead to changes in other aspects, such as phosphorus load," says Tom Torgersen, director of the National Science Foundation's (NSF) Water, Sustainability and Climate program, which, along with NSF's Long-Term Ecological Research (LTER) program, funds the research.

David Garrison, chair of NSF's LTER Working Group, comments: "This study's findings, which depend on long-term data, are important to maintaining water quality not only today, but into the future."[3]

The above examples tell us about the guiding principles of LTER, in that long-term studies are vital to gain an integrated understanding of how populations, communities and other components of ecosystems interact. They also bring us back to the fundamental point that BIO research always aims to increase our understanding of the principles and mechanisms that govern life on earth. ■

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The amazing spiny mouse, the champion of mammalian regeneration

Malcolm Maden, Department of Biology & UF Genetics Institute, Gainesville, Florida, USA shares his expert opinion on the amazing spiny mouse, the champion of mammalian regeneration

If you ask most people whether mammals can regenerate or not they would surely answer no. After all, many people have scars on their skin from wounds, burns or surgery, amputated limbs do not regenerate, tumour removal leaves large tissue defects and many people die from the fibrosis resulting from a heart attack. But if you scour the scientific literature for regenerative ability in mammals there seems to be quite a number of diverse reports. The annual replacement of deer antlers is surely one of the most conspicuous examples of regeneration and shows many features typical of complex tissue regeneration, such as limbs in lower vertebrates including the formation of a blastema (see The Champion of Regenerative medicine – the Axolotl).

The digit tips of children, mice, rats and monkeys also regenerate by the formation of a blastema. Holes punched through the ears of rabbits, cows, pigs, chinchillas, pikas, hares and bats are said to regenerate so this includes cartilage in the middle of the ear and skin over the top. Most impressively for a mammal, new-born mice can regenerate cardiomyocytes following a myocardial infarction, although this ability is lost by seven days after birth.

And of course, the mammalian liver regenerates (as the ancient Greeks in the legend of Prometheus knew), not by the formation of a blastema, but by a process known as compensatory hypertrophy, such that if a lobe of the liver is removed the remaining liver lobes grow and expand to replace the lost function. This process involves the coordinated up-regulation of cytokine, growth factor and metabolic networks resembling true regeneration. Similarly, the lung can undergo compensatory hypertrophy after the removal of one or more of the lobes, in exactly the same manner as the liver.

Although tantalising, these regenerative abilities are too sporadic to provide us with a new model of mammalian regeneration which we clearly need for regeneration studies so that direct comparisons between the damaged organs (e.g. the skin or the heart) of an adult regenerating mammal and an adult non-regenerating organ (e.g. the lab mouse or human) can be made. We need these directly equivalent comparisons to eliminate differences due to developmental age or evolutionary distance to identify the molecules that are causing scarring and fibrosis in the typical mammal and may not be present in a regenerating mammal. We would then want to counteract these fibrotic molecules in a human with the intention of inducing regeneration and/or preventing scarring.

Excitingly, it now appears that we may have discovered an adult mammal which can regenerate many organs, namely the spiny mouse of the genus Acomys (Fig. 1A). There are several species of these mice which inhabit desert areas in North Africa, the eastern Mediterranean and southwards into Kenya. Along with several colleagues (Ashley Seifert, Megan Seifert, Jake Goheen) we found that these species could frequently be trapped with large segments of skin missing from their backs and when these animals were kept the wounds regenerated perfectly and replaced the hairs, sebaceous glands, erector pili muscles of the hairs and the dermis without scarring (Fig. 1B).

"Excitingly, it now appears that we may have discovered an adult mammal which can regenerate many organs, namely the spiny mouse of the genus Acomys."

In contrast, a similar wound in the lab mouse produces a scar covered by a hairless, glassy wound epithelium (Fig. 1C) just as humans do. In further skin experiments using full thickness thermal injuries rather than a physical wound, the Acomys skin regenerates perfectly with a full complement of hairs and no scar (Fig. 1D), whereas the lab mouse produces a hairless scar (Fig. 1E). Histologically these repairing skin tissues look remarkably similar in terms of the dermis. A section of Mus dermis four weeks after a burn injury is shown in Fig. 1F covered by a uniform epithelium.

In contrast, a regenerated Acomys burn injury at the same time point is

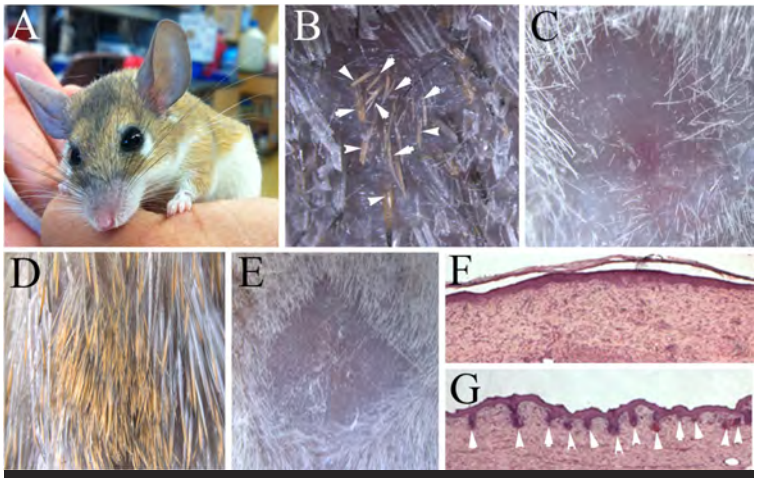

Figure 1

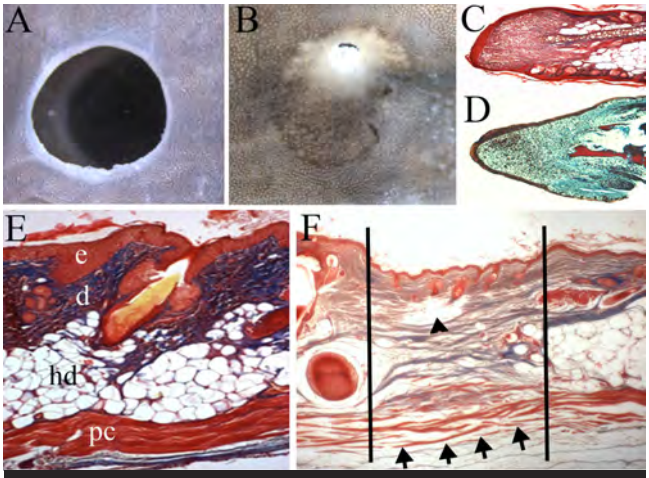

Figure 2

shown in Fig. 1G and many regenerating hair follicles spread across the wound epithelium can be clearly seen. However, there are molecular differences in the dermis of the regenerating and scarring dermis in terms of the collagens and other extracellular matrix molecules that are deposited, which may play an important role.

In the same series of experiments, we also showed that large 4mm holes punched through the Acomys ear could regenerate completely, replacing not only the skin but also the cartilage in the middle of the ear (Fig. 2A, B). This process of ear punch regeneration involves the formation of a blastema (Fig. 2C) which shows a remarkable similarity to the blastema of the regenerating amphibian limb (Fig. 2D and The Champion of Regenerative medicine – the Axolotl). This shows the truly epimorphic nature of this mammalian regenerative event.

An even more surprising result was seen in these skin regeneration studies because unlike the human skin, the rodent skin has a layer of skeletal muscle at the base called the panniculus carnosus (Fig. 2E). Normally, skeletal muscle cannot regenerate in mammals when a hole is made through the tissue. This is known as a volumetric muscle loss and frequently occurs after injuries such as gunshot wounds. But when the spiny mouse skin regenerates the missing segment of the panniculus carnosus regenerates as well (Fig. 2F). This is a very exciting result and may lead to discoveries in how to regenerate missing muscle segments in humans.

In addition to the skin, the ear and skeletal muscle the Acomys heart also shows regenerative properties. In the lab mouse and humans after a myocardial infarction the damage immediately causes a huge drop in the ability of the ventricle to pump blood, known as the ejection fraction from which it does not recover. Heart cells at the site of the ischemia die and local fibroblasts proliferate and lay down a scar.

The reduced ejection fraction induces the ventricle to pump more blood and as a result, the ventricle wall thins dramatically. In adult Acomys, however, the immediately decreased ejection fraction caused by the myocardial infarction recovers over a period of 14 days to return to pre-MI levels. The missing capillaries are regenerated and there is a vastly reduced level of scarring. Future studies will be aimed at determining whether heart cells can divide and replace the ischemic tissue.

Our studies to date on the regenerative properties of the adult Acomys skin, skeletal muscle, ear and heart have revealed a striking lack of fibrosis in each tissue at the site of damage and this allows the natural regenerative abilities of cells and tissues to take place unhindered. We suggest that Acomys is a great candidate for an adult mammalian regeneration model for use in regenerative medicine with the ultimate aim of discovering why this genus can regenerate and extrapolating this knowledge to generate therapies for the benefit of humans.

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The health effects of exposure to chemicals and other substances

Open Access Government details the work of the National Toxicology Program, a world leader in providing scientific information to help evaluate and better understand the potential health effects of exposure to chemicals and other substances

The National Toxicology Program is a world leader in providing scientific information to help evaluate and better understand the potential health effects of exposure to chemicals and other substances.

The National Toxicology Program (NTP) was established in 1978 to strengthen the science base in toxicology, support the development of improved testing methods and provide information about potentially toxic chemicals to health and research agencies, scientific and medical professionals and the public.

Based at the National Institute of Environmental Health Sciences (NIEHS) in North Carolina, the NTP coordinates toxicology and testing across the US Department of Health and Human Services.

Over the years, it has become a world leader in the development of techniques and testing regimes to evaluate the health-related effects of environmental and occupational substances. This includes short and long-term toxicology/carcinogenicity studies to address the gap in knowledge concerning the toxicity of substances in the environment, along with chemical disposition and toxicokinetic studies, which assess the absorption, distribution, metabolism and excretion of substances in laboratory animals.

The long-term goal of these studies is to gather data to better assess the structure-activity relationships that determine chemical disposition in the test subjects and, ultimately, better interpret the significance of this data to humans.

The NTP has also developed a range of genetic toxicology testing regimes to evaluate the potential of environmental and occupational substances to damage DNA, as well as toxicogenomic studies to examine how chemicals can change the expression of genes, proteins and metabolites in living cells. Measuring genome-wide changes in affected tissues can help to identify markers of toxicity or disease and improve understanding how genetic variations between individuals can influence their sensitivity to substances.

In addition, the NTP has established techniques for testing the potential of substances to affect the development of and cause damage to, reproductive organ systems and tests to determine the toxic effects of exposure on the immune and nervous systems.

In recent years, a key focus for the NTP has been the development of new, alternative methods of toxicology research that will reduce, replace or refine the use of laboratory animals. Systems currently under development include computer-based predictive toxicology models, genetically engineered in vitro cell systems, microchip array technology, non-mammalian species and transgenic species.

In March, at the Society of Toxicology's 57th Annual Meeting and ToxExpo in San Antonio, Texas, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), a committee under the NTP Interagency Centre for the Evaluation of Alternative Toxicological Methods (NICEATM), continued the rollout of a strategic roadmap for establishing new methods to evaluate the safety of medical and chemical products while reducing or eliminating the need for animal testing.

The roadmap, which was drawn up with input from 16 federal agencies, multiple interagency work groups and the public, aims to create a framework to support

the development of, foster confidence in and ensure the adoption of these new approach methodologies (NAMs). The implementation of the roadmap is currently focused on three areas: acute systemic toxicity; eye and skin irritation; and skin sensitisation.

Temporary, ad hoc work groups are playing a key role in implementation by undertaking specific tasks identified by the ICCVAM as being important for the development or validation of NAMs.

Chairs representing agencies that use or require data from an area of interest set their group's scope and charge. Once approved by the ICCVAM, member agencies and partners from the International Cooperation on Alternative Test Methods (the European Union Reference Laboratory for Alternatives to Animal Testing, the Japanese Centre for the Evaluation of Alternative Methods, the Korean Centre for the Evaluation of Alternative Methods and Health Canada) are invited to participate.

The work groups will develop detailed implementation plans to meet the roadmap's goals based on four key elements: definition of testing needs; identification of any available alternative tests and computer models; a plan to develop integrated approaches to testing and assessment and defined approaches for interpreting data; and a plan to address both scientific and non-scientific challenges, including regulatory issues such as international harmonisation.

"This roadmap represents a coordinated effort by federal government agencies to proactively develop and adopt new approaches to toxicity testing, rather than having changes driven by external influences", says Warren Casey, PhD, director of the NTP Interagency Centre for the Evaluation of Alternative Toxicological Methods.

"If actionable progress in this area is going to happen, the agencies need to take the lead and that is exactly what they are doing with this roadmap." ■

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The potential long-term environmental health consequences of urban wildfire debris

Birgit Puschner and Pamela Lein from the University of California, Davis share their expert views on the impacts of urban wildfire on chemical contamination in small backyard agriculture

Worldwide, the frequency and severity of wildfires are increasing due to changes in temperature and precipitation patterns consistent with climate change and changes in land use, particularly at the rural-urban interface. The fire problem is particularly acute in Northern California, which has experienced a significant increase in wildfire frequency over the past few decades. In addition to the risk of injury, loss of life and destruction of property, there is increasing appreciation that wildfires pose significant environmental health threats.

Much of the research on adverse health impacts of wildfires has focused on wildfire smoke and recent reviews of this scientific literature conclude there is strong evidence that wildfire smoke exacerbates respiratory ailments, including asthma and chronic obstructive pulmonary disease and contributes to cardiovascular disease. What is less well understood, however, is the potential impacts of wildfire debris on human, animal and ecosystem health.

Debris from urban wildfires is particularly worrying because these fires involve the combustion of building materials, electronic equipment, chemicals and industrial equipment that contain toxic chemicals such as metals, pesticides and persistent organic pollutants (POPs).

POPs of concern include the polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs). PCBs are man-made chemicals that were widely produced for diverse industrial applications beginning in the 1930s until their production was banned in 1979 because of their carcinogenic potential and developmental neurotoxicity.

PCBs are found in older electrical transformers, capacitors and light ballasts still in use today and in caulking material, paints and sealants used to construct municipal buildings and homes prior to the 1979 ban. PBDEs are also man-made chemicals that were widely used as flame retardants in various consumer products including foam, plastics and textiles.

Due to health concerns, the state of California began prohibiting the manufacture, distribution and processing of flame-retardant products containing penta- and octa BDEs in 2006. However, human exposure continues because many households have products produced prior to the ban. Moreover, PBDEs are not chemically bound to materials and therefore, leach out of household products into the environment. Like PCBs, PBDEs persist in the environment and biomagnify up the food chain.

Pyrolysis results in the release of PCBs and PBDEs into the environment. Increased PCB concentrations have been documented in air masses associated with fires. The ash from the September 11th 2001 World Trade Center fire in New York City was found to contain excessive PBDE levels. The combustion of man-made materials, particularly electronic equipment, is also associated with the mobilisation of metals. For example, ash debris from the California wildfires from 2007 contained toxic metals, specifically, arsenic, cadmium, copper and lead, at levels associated with long-term health effects in animals and humans.

Urban wildfires not only release toxic chemicals, but also generate hazardous compounds, such as dioxins and dibenzofurans, which are formed by the combustion of organic matter, such as paper and wood. Once the burning has stopped, re-volatilised chemicals distribute out of the atmosphere onto soils, vegetation and surface water, while non-volatile chemicals are deposited as ash. The increased environmental availability of these chemicals increases the risk of groundwater contamination, the uptake by plants and ingestion by animals, culminating in increased risk of human exposure for months to years. Thus, a question of growing concern is whether urban wildfires pose a significant long-term environmental health risk via chemical contamination of home-grown produce or animal-derived foods.

Wildfire aftermath on Cobb Mountain during the Valley fire in northern California

This concern is heightened by lay articles in the New York Times and San Francisco Chronicle and peer-reviewed publications reporting increased human exposure to lead (Pb) through consumption of eggs produced by backyard chickens. Eggs and eggs products are one of the most consumed foods worldwide. In the United States, individuals consume an average of 24 grammes of eggs per day. Backyard chicken ownership has grown in the United States in part because the eggs from backyard hens are perceived to be healthier than commercially produced eggs.

However, recent studies have identified concerning levels of Pb in eggs produced by chickens raised in areas with significant Pb contamination of the soil, usually as the result of the weathering of older buildings with Pb-based paints. The consumption of one average size 50-60 gramme egg from Pb-contaminated environment can exceed the safe threshold dose of 6µg of Pb per day from all combined dietary sources. What about PCBs and PBDEs? These are very fat-soluble chemicals and egg yolk is rich in lipids resulting in an average fat content in an egg of 10%. Thus, the potential for significant contamination of eggs in regions with increased soil levels of these POPs is not unreasonable, as suggested by recent data reporting the detection of PCBs and PBDEs in milk from dairy cows of California.

The overwhelming majority of food safety research associated with backyard poultry and other home-produced food products has largely focused on microbial contamination. Human illness from most foodborne pathogens is limited to transient gastrointestinal symptoms; in contrast, human exposure to unsafe levels of PCBs, PBDEs or metals has the potential to cause long-term adverse health effects. Currently, urban and backyard farmers have no way of knowing whether eggs or other home-grown food products are contaminated with toxic chemicals unless they are lab tested. There is, therefore, an urgent need to study environmental chemicals in home-produced food in geographic regions that have experienced urban wildfires to assess the potential food safety risk and to generate information needed to inform rational risk management.

In conclusion, the increase in wildfires has potentially serious long-term health consequences for communities and ecosystems. One important concern is the generation or release of chemicals into the soil and water environment and the risk for chemical contamination of home-grown produce, eggs and other animal-derived food products. To more accurately predict the risk to humans, it will be necessary to obtain data regarding the actual levels of toxic chemicals of concern in the environment before and after urban wildfires and to model the transfer of these contaminants through the food chain.

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Specific Language Impairment (SLI) versus Speech Sound Disorders (SSD)

The important differences between Specific Language Impairment (SLI) in children and Speech Sound Disorders (SSD) in children are placed under the spotlight by Mabel L. Rice, Fred & Virginia Merrill Distinguished Professor of Advanced Studies at the University of Kansas

Around the world young children are expected to learn the language they overhear in conversations around them. This is a robust, spontaneous ability of humans, unlike, for example, reading, which must be explicitly taught. One prominent scholar of children's language acquisition once put it this way: "... there is virtually no way to prevent it from happening short of raising a child in a barrel."[1]

Although true of most children, children with Specific Language Impairment (SLI) are the exceptions to this assumption. These are children who do not have overt neurodevelopmental disorders, hearing impairments, or other obvious causes of developmental disorders and who live in ordinary families. Yet they are later than other children in learning a language and are at risk for persistent low language abilities into adulthood. The best estimates for the prevalence of SLI are 7-10% of children at school entry (5-6 years).[2,3]

SLI is often confused with Speech Sound Disorders (SSD) in children. Between one and five years of age children are learning two distinctly different parts of the human language capacity. One is the production of speech sounds needed in their native language. In the beginning, children can produce more sounds than they need for the language or languages they are hearing. Their first job is to refine them to match the ones they need and to drop the ones that may not matter and to develop the motor control needed to do that.

Humans at birth are equipped with motor movements for breathing, sucking and swallowing (basic functions for survival), along with a wide range of sounds. Some vocalisations serve communicative purposes, and some are biological (such as burps or coughs). Between one and two years of age, babies master more refined tongue, lips and palatal movements needed for speaking the words and sentences of a language. This requires a fine-tuned synchrony of muscles, sound perception and the cognitive centres of the brain. The output is a sequenced speech pattern, such as what we hear in a phone conversation.

The second part of the human language capacity is more covert, a matter of cognitive processes in the brain that do not require a speech production system. For example, deaf children can acquire a language system that can be expressed in physical signs of the hands, face and body postures. Language emerges in young children first in short utterances that lengthen with age. In English, language emerges as one or two words at a time, which relatively quickly expand to phrases or sentences.

SSD can be obvious to adult listeners of young children. Young children's attempts to talk can be unintelligible, especially when they are very young. If unintelligibility persists as children age, it becomes noticeable and a matter of concern because it is not "typical." Some mispronunciations are understandable but regarded as immature, such as "wabbit" for "rabbit", "thoup" for "soup", or "bawoon" for "balloon." Scholars have tracked the order in which children learn their speech sounds and have developed age norms for evaluating whether a child meets age expectations[4]. The prevalence of SSD in 4-6-year-old children in population-based cohorts is approximately 3-6%[5] and the condition appears to resolve in 75% of children by age 6[6].

People often assume SSD is the same as SLI, such that children's speech abilities reflect their underlying language abilities or vice versa. This is not true. In the most precise study of a population-based sample of 5-year-old children, the co-occurrence of speech and language impairments, once adjusting for age expectations, was estimated at less than 2%[5]. For the children with SLI, speech impairment was evident in approximately 5-8% of the children. The authors concluded that SSD and SLI are independent; they are not likely to co-occur. Thus, SSD is not a diagnostic marker of SLI and presumably, the two condi-

tions do not share a common causal pathway.

The non-overlap of SLI and SSD carries implications for public health services and for scientific studies of the nature and origins of SLI and SSD.

- A big issue for public health services is that children with SLI are likely to be overlooked as needing language intervention services, perhaps in part because of the fact that SSD may be obvious to adults/caregivers, but SLI is not[7].

- SSD is likely to resolve with age (children are likely to "outgrow" it) whereas SLI is likely to persist into adulthood[7].

- At school entry, SLI predicts later reading impairments[8] whereas SSD predicts weakly, if at all, once adjusted for co-occurring language impairments.[9,10]

- Scientific studies of children's communication problems in medical conditions should differentiate between SLI and SSD. A recent study of children exposed to Human Immunodeficiency Virus (HIV) is the first report of SSD outcomes compared to primary language impairments (i.e., without other developmental disorders). The risk for language impairments in the children was higher than population norms but the risk for SSD was not elevated.[11]

Examples of how children talk can illustrate the differences between SLI and SSD. Consider two 5-year-old boys. They are talking about a picture of red rabbits. One, dressed in purple, has an SSD, apparent in his mispronunciations of the speech sounds needed to say "why are the rabbits red." Within his speech system, he says "why ah de wabbits wed?" The substitution of w/r in "rabbit" and "red", along with the omission of the final /r/ in the word "are," are not unusual speech errors in the speech of young boys.

Such errors are quite noticeable although they often do not interfere with adults' understanding of the intended meanings. The other boy, dressed in green, asks a question formulated in the adult grammar as: "why is/are that rabbit/those rabbits red?" The boy says "Why that red?", a sentence consistent with the grammar rules for children this age with SLI[7]. He demonstrates a deficiency in sentence structure, with the omission of the obligatory copula form of BE ("is'" or "are") and the substitution of a pronoun ("that") for the common noun "rabbit." Furthermore, the specification of singular versus plural for the noun phrase is vague because the noun information is underspecified. His articulation of speech sounds is at adult levels and his meaning is effectively conveyed.

Although the speech sound errors of the child with SSD are likely to be noticed and to generate attempts by adults to correct the problem, the grammar errors of the child with SLI are less likely to be noticed or understood as flags for concern. Yet it is the child in green who is at higher risk of adverse developmental outcomes than the child in purple, who is more likely to "outgrow" the SSD and less likely to encounter problems with literacy, school achievement, or long-term persistence of subtle but very important elements of grammar and vocabulary. Our research and our service systems will be improved by increased recognition of the important differences between SLI and SSD.

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How right-sizing regulation can optimise plant protection

Greg Rosenthal of the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service explains how right-sizing regulation can optimise plant protection

The idea of right-sizing regulation is a guiding force for USDA's Animal and Plant Health Inspection Service (APHIS). Part of our mission is safeguarding U.S agriculture and natural resources against invasive pests and diseases and facilitating the safe trade of agricultural products. The scale and complexity of this work is vast. In 2017, APHIS helped safeguard more than $98 billion worth of U.S. agriculture production and facilitate agricultural exports valued at over $138 billion.

The role of regulations

APHIS' regulations are a crucial tool for mission success. Our regulations prevent devastating foreign pests and diseases from entering the United States on imported agricultural products. Should a pest or disease enter our country, regulations or other regulatory means allow us to take decisive action to prevent its spread.

The balance: most effective, least restrictive

Of course, there is another side to regulations. Some regulatory actions can create burdens on producers and the industries they supply. That is why we constantly seek the most effective – and least restrictive – approach possible.

To make sure we are hitting the mark, APHIS officials meet yearly with representatives from various commodity sectors to discuss the opportunities and challenges they face. We also reduce burdens by constantly applying cutting-edge science, technology and data analysis to streamline inspection methods, commodity treatments, pest detection, pest management and export certification. In addition, APHIS uses existing regulatory flexibilities and non-regulatory solutions to right-size regulation.

Inspectors with USDA's Animal and Plant Health Inspection Service ensure that imported plant parts comply with science- and risk-based regulations that are designed to keep invasive pests and diseases out of the United States.

Regulatory flexibility

The status of plant and animal pest and disease conditions worldwide constantly changes and import requirements must keep up. That can be challenging, however, when each change requires a time-consuming rulemaking process. To respond faster, APHIS has begun moving specific import requirements for certain commodities out of the Code of Federal Regulations (CFR) and into online regulatory manuals. More general import requirements remain in the CFR and the CFR

Image: USDA Photo by R. Anson Eaglin

Invasive pests can infest the millions of sea containers that carry agricultural commodities around the world. USDA, working with our Canadian partners and the maritime industry, have formed the North American Sea Container Initiative to develop and promote the use of voluntary guidelines for effectively cleaning and disinfecting sea containers to reduce this risk.

refers to the manuals for specific requirements. That allows us to change these requirements when needed through a much faster notice-based process, which includes a public comment period.

Non-regulatory solutions

We are eager to look beyond rulemaking to solve plant and animal health problems through other means whenever possible, using solid science and industry best practices. In 2016, we used this approach when we confirmed that bacterial leaf streak, a disease affecting corn plant leaves, was present in several states throughout the U.S. Corn Belt. We knew that regulating the disease would be neither practical nor possible.

Instead, APHIS worked with our partners to identify best management practices to effectively control the disease. At the same time, APHIS gathered scientific evidence on this little-known pathogen to help build a strong case for the safety of U.S. corn, protecting $6.3 billion in U.S. corn exports from trade disruption.

We also collaborate with industry, states, academia and others to promote voluntary programmes that protect U.S. agriculture. For example, APHIS and the seed industry are developing a Seed Health Regulatory Framework. It will make international seed movement safer by promoting the worldwide use of consistent and equivalent requirements that reduce pest risk.

Through our Offshore Certification Programs, we verify that overseas nurseries and other facilities that export large-volume, high-demand plants, cuttings, seeds and other products to the United States meet minimum production and sanitation standards. This offshore work is an effective way to prevent harmful plant pests and diseases from entering our country.

Everyone wins

APHIS constantly strikes that critical balance of taking the most effective and least restrictive approach. This allows us to regulate at the speed of commerce and relieve industry burdens wherever possible – without compromising our mission. ■

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Biological pesticides and the future of sustainable agriculture

Cooperative Extension Specialist at the Department of Botany and Plant Sciences, University of California Riverside, Dr Philippe E. Rolshausen shares his thoughts on biological pesticides and the future of sustainable agriculture

Crop yield and quality of marketable fruit are corner stones of any farmers' business model. To that end, chemicals have been widely deployed in agriculture to fertilise soils and plants or to kill pests and pathogens that are limiting factors to optimum productivity.

However, the 20th century dogma that chemicals could be used blindly without restrictions has found its limits in today's era. Concerns about their excessive use on human health and environmental pollution have shifted the farming philosophy to a more sustainable approach. Here, we will review some of the key discoveries that have advanced the field of biological pesticides and discuss how new technologies could shape the future of sustainable agriculture.

Synthetic agrochemical products have been successful for decades to manage pests and pathogens. An agrochemical is categorised by its active ingredient and metabolic target. One the major negative side effect of over-using chemicals with a similar mode of actions is the selection of resistant strains within microbial populations. Examples of resistance to fungicides and bactericides in fungal and bacterial pathogen populations are well documented, but often growers manage the problem by rotating their chemistries, adopting disease forecast models to reduce chemical input and adapting their management practices to minimise disease pressure.

However, in extreme events, farmers have no chemical alternatives to manage a disease. For example, resistance to the neonicotinoid insecticide in psyllid populations has been clearly established in the United States and it no longer suppresses populations of psyllids below desirable levels. This has become a major threat to the citrus and potato industries because this insect feeds on plants and transmits bacterial pathogens (Candidatus liberibacter species) that cause diseases known as Huanglongbing and Zebra Chip, respectively.

In recent years, there has been a shift in consumer mentality, with an increased demand for organic food and food products. US farms produced and sold $7.6 billion (up 23% from 2015) in certified organic commodities, according to the U.S. Department of Agriculture's National Agricultural Statistics Service. As a result, there has been an increase of organic farms (over 14,000; up 11% from 2015) and a total acreage (5 million acres, up 15% from 2015).

Conventional farms also tend to be more mindful of their farming practices. To that end, biological pesticide application, which consists of using beneficial microbes or microbial products to control disease, improves soil and crop health and has been deployed in a broader capacity because of their low environmental

impact. For example, one of the many benefits is that resistance cannot develop against microbes.

The first biological control ever discovered in the early 20th century was the bacterium Bacillus thuringiensis. Some strains produce toxins that are lethal to insect pests and those have been commercialised, as either a biological insecticide or an insect-resistant genetically modified crops. Because of the toxin host-specificity, it is regarded as environmentally friendly.

Another key example of biological pesticide is Agrobacterium radiobacter strain K84 registered in the late 20th century as a biological control agent of grown gall caused by Agrobacterium tumefasciens, a soil-borne pathogen that affects a broad spectrum of crops. A. radiobacter strain K84 releases a toxin that alters the ability of the pathogen to reproduce.

Despite those key scientific discoveries that became commercial successes, biological pesticides only remained adopted in niche markets where synthetic chemicals were not registered, not effective, or not economical. Thus, the discovery of new biological pesticides remained marginal because of the widespread adoption of cost-effective synthetic chemicals. Nowadays, this trend is reversed. The commercialisation of chemical pesticides is declining whereas biopesticide has become a booming market.

One of the major game changers for biological pesticides discoveries was the advent of 'Omics' technologies. The traditional microbiological techniques that were utilised in the 20th century did not allow for a high throughput screening of organisms. In addition, most organisms are not culturable, so the microbial techniques only recovered a small range of the plant-associated microbes and most bacteria and fungi were overlooked. Plants host an infinite number of microorganisms and looking for the 'good ones' at the time was comparable to finding a needle in a haystack.

> "In recent years, there has been a shift in consumer mentality, with an increased demand for organic food and food products. US farms produced and sold $7.6 billion (up 23% from 2015) in certified organic commodities, according to the U.S. Department of Agriculture's National Agricultural Statistics Service."

In today's era, 'Omics' technologies have allowed us to profile the microbial communities living inside and outside of plants and better understand the complex plant-microbe and microbe-microbe interactions and their biological functions. These new technologies can reveal in a high throughput capacity taxa, genes, metabolites or proteins that have potential antimicrobial attributes.

In my laboratory, we are using these technologies to identify solutions to two important bacterial diseases of grapes and citrus, namely Pierce's Disease and Huanglongbing, respectively. Those global emerging diseases are huge threats to crop production because they can rapidly kill a vine or tree. We have been exploiting a natural phenomenon occurring in vineyards and orchards whereby some vines or trees under high disease pressure are not symptomatic.

Because plants are of the same genetic make-up (same variety grafted on the same rootstock) we hypothesise that the residing microbial communities cause the disease tolerance that we observe. Our approach is to collect plant tissue samples from both symptomatic and asymptomatic plants and deploy a culture-dependent approach with traditional microbial techniques and culture-independent approach using a next generation sequencing-based platform, so we capture all the organisms associated with those plants.

The computational analyses of the DNA-database provide the seeds for obtaining a greater understanding of the factors that shape the plant microbiome, as well as identifying the microbes that potentially play a role in plant health and disease suppression or exacerbation. Those potential beneficial microbes can be cross-referenced in our culture collection and recovered for downstream evaluation in in vitro and in planta bioassays. This approach provides opportunities for the patenting of novel technologies and for the development and commercialisation of new science-based bioproducts.

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USDA: Protecting Americans from foodborne illness

Acting Deputy Under Secretary for Food Safety at the United States Department of Agriculture (USDA), Carmen Rottenberg explains how the Food Safety and Inspection Service protects Americans from foodborne illness

The Food Safety and Inspection Service (FSIS) is the public health agency in the United States Department of Agriculture (USDA) responsible for protecting the public's health by ensuring the safety of the nation's commercial supply of meat, poultry and processed egg products. (Our partner agency, the U.S. Department of Health and Human Services' Food and Drug Administration, has jurisdiction over other foods, such as fruits, vegetables and dairy products.)

FSIS ensures food safety through the authorities of several federal laws. The Federal Meat Inspection Act (FMIA) was passed in 1906. The FMIA requires that slaughter and processing take place under sanitary conditions and bans the sale of adulterated or misbranded meat and meat products. The FMIA was followed by the Poultry Products Inspection Act (PPIA) in 1957.

Both laws require continuous federal inspection of slaughter operations and that state inspection programs be at least equal to federal standards. The Egg Products Inspection Act (EPIA) of 1970 and the Humane Methods of Slaughter Act (HMSA) of 1978 complete the set of major laws, providing FSIS with the authority and obligation to carry out its mission to protect public health and prevent foodborne illness.

Secretary of Agriculture, Sonny Perdue, has made agricultural trade a key priority of his tenure at USDA.

Carmen Rottenberg
Acting Deputy Under Secretary for Food Safety

As we look to imported product, FSIS has a robust equivalence system in place to ensure that countries seeking to export to the U.S. meet the same rigorous standards we expect of our domestic producers. For meat, poultry and processed eggs to be imported into the United States, a foreign country's inspection system must be found to be equivalent to the U.S. system. This equivalency status is not permanent but must be confirmed by periodic audits. 100% of meat, poultry and processed egg products imported into the U.S. is re-inspected at point-of-entry. This inspection may also include sampling to test for pathogens and banned chemical substances.

At FSIS, we never lose sight of our mission to protect public health by preventing foodborne illness. In his first speech as Secretary of Agriculture, Secretary Perdue named food safety as one of the top priorities. Our mission and goals line up perfectly with Secretary Perdue's vision and the new USDA Motto to "Do Right and Feed Everyone!" ■

As the U.S. continues to expand into markets overseas, at FSIS we are keenly aware of the role that food safety plays in an increasingly global agricultural marketplace. Food safety is the critical underpinning of this global economy.

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Climate change and its impact on beef cattle

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

Climate change and beef cattle

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

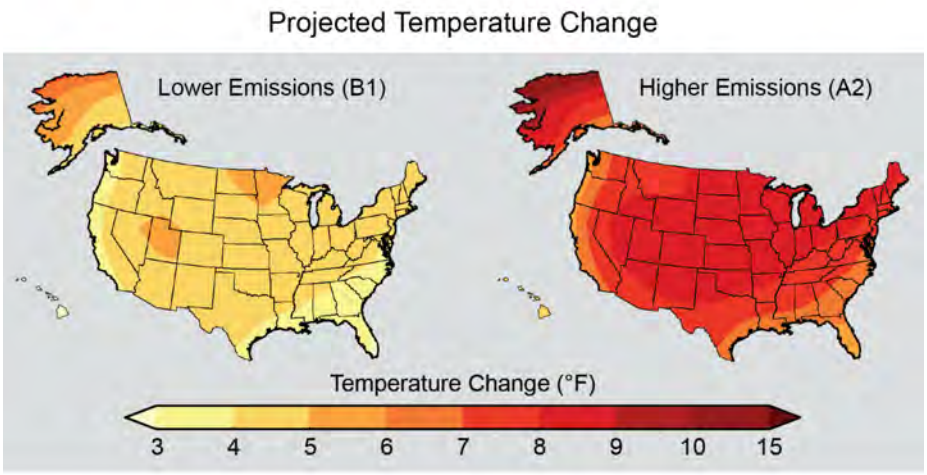

Figure 1: Projected Temperature Change. Warming is projected for all parts of the nation during this century. In the next few decades, this warming will be roughly 2°F to 4°F in most areas. By the end of the century, U.S. warming is projected to correspond closely to the level of global emissions: roughly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

Importance of genomics for improved thermotolerance

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

What is thermoregulation?

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

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

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

Genomics for climate smart beef

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

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

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

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Techniques for monitoring broiler embryo temperature

Dr E. David Peebles from the Poultry Science Department at Mississippi State University details the accurate determination of embryo temperature and its relationship to the functional characteristics of broiler hatching eggs

Eggshell temperature has been routinely used in commercial settings to pragmatically estimate internal egg temperature (Lourens et al. (2005) and to serve as a subsequent indicator of embryo body temperature (Janke et al., 2004). However, because eggshell temperature is influenced by the thermal conductivity of the eggshell and the pattern and velocity of air flow within the incubator (Lourens et al., 2011; Ozcan et al., 2010), it may not precisely reflect actual internal egg temperature.

"Further technological advancements and refinements of transponder implantation and temperature recording procedures may increase the practicality of temperature transponder use in commercial settings."

Direct measurement of the internal temperature of eggs has been used to more accurately assess the level of heat production and the body temperature of embryos during incubation (Janke et al. (2004). Various methods that have been employed to directly measure internal egg or embryo temperature have exhibited certain limitations, which include physiological invasiveness, egg contamination, the alteration of embryo metabolism and an increase in embryo mortality (Janke et al., 2004; Turner, 1990).

Nevertheless, Pulikanti et al. (2011a) have successfully inserted transponders into the air cells of broiler hatching eggs between 12 and 14 days of incubation without any associated adverse effects on eggshell porosity or embryogenesis or any noted physiological stress to the embryo. This relatively non-invasive procedure has allowed for the accurate determination of embryo temperature through the last week of the incubational period. This procedure also enables investigators to detect variations in embryo metabolism and subsequent heat production that other external methods, such as those used for measuring eggshell temperature, are unable to detect.

Relationship of embryo temperature to the functional characteristics of eggshells

Pulikanti et al. (2011b) used temperature transponders to record the temperature of the air in the incubator immediately surrounding the egg. At the same time, they implanted transponders in the air cells of those same eggs to record their internal temperature. These concurrent temperature readings were used to more accurately calculate the water vapour pressure gradient across the shell and for the subsequent precise calculation of absolute and relative (adjusted to egg weight) eggshell water vapour conductance.

Pulikanti et al. (2012b) later employed these same methods to further compute the conductance constants of eggs, in which the length of incubation was included as a variable in the calculation. Accurate determinations of the above variables are necessary in research studies where the specific functional properties of the eggshell are required.

"Further work conducted by Pulikanti et al. (2012a) showed that a higher relative eggshell conductance, calculated using internal egg temperature from transponder readings, results in an increase in embryonic metabolism which then leads to an increase in growth and yolk sac absorption."

Relationship of embryo temperature and the functional characteristics of eggshells to the physiological characteristics of embryos and posthatch broilers

Pulikanti et al. (2011b) reported that the internal temperature of live embryonated eggs exceeded those of non-embronated eggs between 10.5 and 18 days of incubation. The temperature difference increased from approximately 0.025°C on day 10.5 to 0.80°C on day 18, with the average difference over the entire period being 0.50°C. The semicircadian patterns in temperature observed were more accurately detected by transponders that were implanted in the air cells of the eggs.

Further work conducted by Pulikanti et al. (2012a) showed that a higher relative eggshell conductance, calculated using internal egg temperature from transponder readings, results in an increase in embryonic metabolism which then leads to an increase in growth and yolk sac absorption.

Pulikanti et al. (2013) also later confirmed that embryo temperature and subsequent relative eggshell conductance can influence physiological variables in birds during both the middle and late posthatch grow out periods. For example, it was shown that relative body and breast muscle weights on day 48 posthatch were positively correlated with relative eggshell conductance and eggshell conductance constant values and that relative breast muscle weight was negatively correlated with embryo temperature. These reports indicate that accurate determinations of embryo temperature and associated eggshell functional characteristics are necessary in determining the physiological status of the embryo and in predicting the posthatch performance of broilers.

Summary

Further technological advancements and refinements of transponder implantation and temperature recording procedures may increase the practicality of temperature transponder use in commercial settings. This methodology has the potential to provide commercial hatchery managers with a more accurate means by which to regulate incubation conditions to better suit the broiler embryo and to subsequently lead to increased production profits.

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Texas 2012: An entire field of corn is lost due to drought conditions

Global research on drought

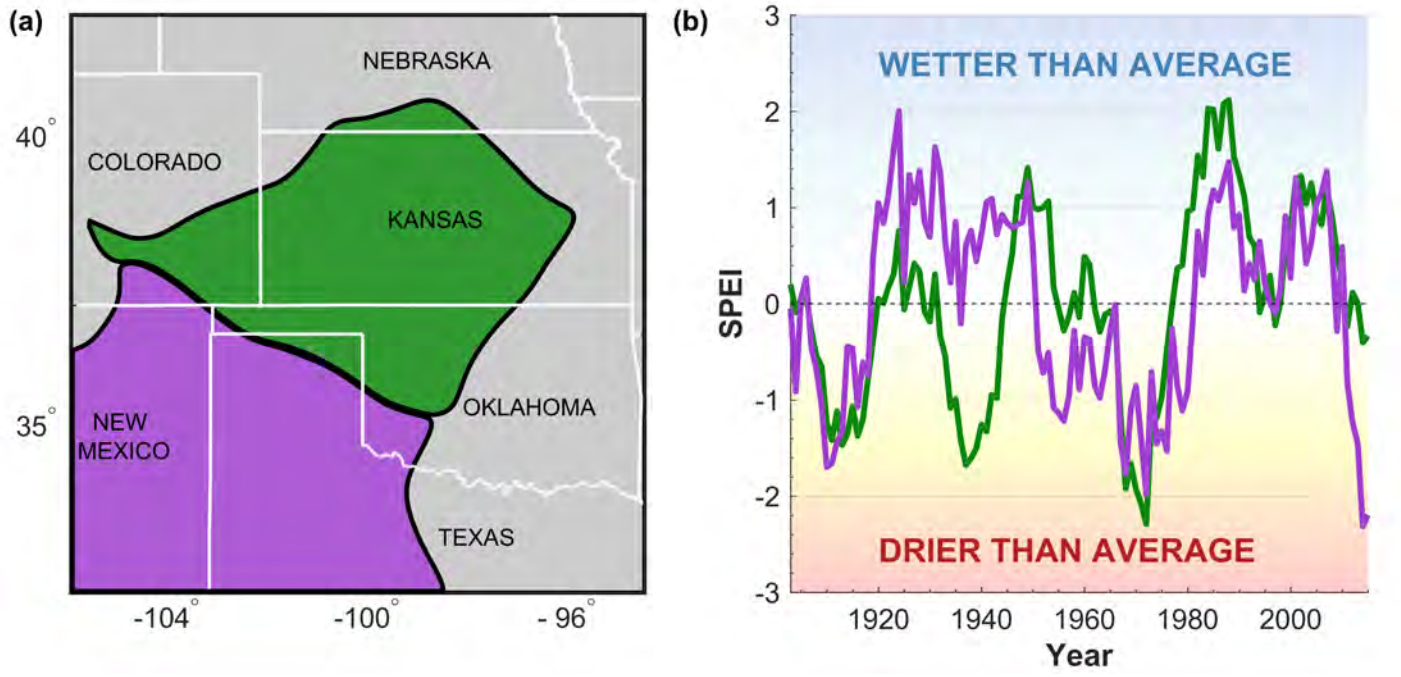
Professor Robert Aiken, Research Crop Scientist from Northwest Research–Extension Center provides his expert thoughts on the fascinating global research taking place on drought, including the vital role of satellite imagery

As a field agronomist from Northwest Kansas, I'm attending the 15th Ogallala Aquifer Program workshop in Lubbock, TX with irrigation engineers, hydrologists, economists and other water scientists, focused on extending the life of the aquifer to sustain rural economies (https://ogallala.tamu.edu/). The tension in the conference is palpable. "164 days since last measurable precipitation in the Texas High Plains." "This wheat crop is on the ropes." "If we don't get rain soon..."

We all recognise drought. The dull green vegetation; the pallor of dust-filled skies; the dry scratchy throat and persistent cough. Agriculture? Drought stops agriculture in its tracks. Here in the High Plains, agriculture affects a third of the regional economy. In Sub-Saharan Africa, drought affects the core food supply, leading to rural exodus and civil unrest. In Northwest India, drought amplifies the frequency of heat-related deaths. In Cape Town, South Africa, a two-year drought threatens the water supply for the four million residents. Drought touches our lives and communities in myriad ways.

Wayne Palmer published his drought index in 1965, considering drought cycles of the 1930s and 1950s. His metric uses monthly precipitation and atmospheric demand for water, contrived to report the deviation of soil water supply from 'normal' conditions. The concept of 'normal', or the long-term average weather is central to many drought indices used today. The United States Drought Monitor displays its index using fire colours – yellow, orange, red. Drought metrics provide early warning of impending disasters.

The American Meteorological Society hosted four sessions on drought and food security in its 2018 meetings. One of several global-scale drought monitoring programmes utilises satellite imagery to calculate and map the energy balance for land surfaces. This accounting scheme uses physics to sum inputs and outputs in terms of radiation, evaporation and warming/cooling of air and land. The thermal band from satellites, representing the surface temperature, conveys critical information of surface water availability. Warmer sectors indicate dry surfaces, while the wet regions display cooler temperatures.



(a) Two selected sub-regions in the Great Plains for spring drought variability and (b) their corresponding drought time series (filtered using a 10-year running average) for the period 1903-2015. Climate data used to calculate the drought index was retrieved from the Climatic Research Unit (CRU) TS v. 3.24.01 (Harris et al. 2014[1]). The drought index is the Standardized Precipitation Evapotranspiration Index (SPEI) on a three-month time scale (Vicente-Serrano et al. 2010[2]). Positive values of the SPEI represent wetter than average conditions and negative values represent drier than average conditions. There are notable differences in the drought conditions of these adjacent sub-regions during the 1930s (Dust Bowl era) and the period 2010-2015 (b). These temporal differences in drought variability across relatively short spatial distances provide evidence for the delineation of each sub-region and consideration in drought monitoring and climate change analyses.

Globally, agencies use these techniques to detect and report incipient and ongoing drought. These early warnings and updates inform emergency drought responses. Earth scientists recognise drought as an integral component of the hydrological cycle. The question remains: Has climate change affected the frequency, duration or extent of drought?

Zach Zambreski, a young, bright, dedicated meteorologist, tackled the problem of long-term drought dynamics in his graduate research (Kansas State University, Agronomy). He employed Empirical Orthogonal Functions (EOF, a type of principal component analysis) to characterise monthly drought metrics of the U.S. Great Plains over the 20th century (1903 to 2015). He then correlated the EOF with each of the localised time series of drought metrics to identify regions with similar historic patterns of wetting and drying cycles. Analyses such as this provide benchmarks against which climate change trends can be usefully compared.

This afternoon our groundwater conference closes. The overnight thunderstorm relieves the tension – for the moment. We muse about La Nina effects, the wet winter conditions in the Northern Great Plains and prospects for wheat harvest. Likely, there are similar conversations within the railroad companies, considering where to position their box cars to transport the wheat crop to export shipping terminals. As earth scientists, we recognise the tools at our disposal to identify and quantify drought. Collectively, as a global society, are we prepared to mitigate the effects of drought?

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National Institute of Food and Agriculture (NIFA)

The work of the National Institute of Food and Agriculture (NIFA) is examined here by Open Access Government

The National Institute of Food and Agriculture (NIFA) is a federal agency within the United States Department of Agriculture (USDA). The agency administers federal funding to address the agricultural issues impacting people's daily lives and the nation's future. To provide both leadership and funding for programmes that advance the progression of agriculture-related sciences, NIFA invest in and support initiatives that ensure the long-term viability of agriculture. They do this while applying an integrated approach to ensure that ground-breaking discoveries in agriculture-related sciences and technologies reach the people who can put them into practice.

NIFA collaborates with leading scientists, policymakers, experts and educators in organisations throughout the world to find innovative solutions to the most pressing local and global problems. These collaborations create spaces for constant scientific progress, made through discovery and application. Among the most important progressions in 2018 NIFA focuses on:

- The advances in the competitiveness of American agriculture;
- Bolstering the U.S. economy;
- Enhancing the safety of the nation's food supply;
- Improving the nutrition and well-being of American citizens;
- Sustaining natural resources and the environment and;
- Building energy independence.

It is clear to see that NIFA programmes aim to cover a wide spread of issues, while also serving as a vital contributor to science policy decision-making. NIFA has taken significant strides toward enhancing the impact of food agriculture, natural resources and human sciences in recent years and now more than ever it is vital to strike the balance between practising sustainable agriculture while also increasing productivity and production efficiency. The U.S. Department of Agriculture is propelling its scientists to develop research-based technologies that can make this possible.

February 2018 marked the announcement of The U.S. Department of Agriculture's (USDA) NIFA support for the Alfalfa Forage and Research Program (AFRP) with approximately $2.1 million in available funding to support AFRP. This programme funds research and extension programmes that improve alfalfa forage, seed yields and helps producers apply best practices.

"Alfalfa research helps ensure there are dependable and affordable supplies of forage available for dairy and other livestock producers around the country," states NIFA Director, Dr Sonny Ramaswamy. "This crop is also a part of conservation production systems that help protect fields from water erosion and provide a natural supply of nitrogen to the soil for use by other crops." Their principal goals are to increase alfalfa yields and quality; improve harvest and storage systems; develop methods to estimate forage yield and quality to support marketing while reducing producer risks and; explore new and novel uses for alfalfa.

Success in previous projects across America spurs on scientists to become innovators who explore new ways of tackling problems from all angles. For example, January 2017 saw several announcements regarding NIFA and the diverse allocation of funding and collaborative research:

- Four grants totalling more than $13.6 million allocated to combat a scourge on the nation's citrus industry, citrus greening disease, aka Huanglongbing.

- $18.9 million in funding for eligible 1890 land-grant colleges and universities to obtain or improve agricultural and food sciences facilities and equipment. The 1890 Facilities Grant Program helps the eligible institutions educate the future workforce in the food; agricultural and human sciences job sectors.

- The availability of $8.8 million in funding to support agricultural science education at Hispanic-serving institutions (HSIs). "Hispanic students earn only 8% of the degrees awarded in science, technology, engineering and math (STEM)", states Director Ramaswamy. "These investments help HSIs promote STEM education and agricultural industry careers to all their students, including Hispanic students."

In the same vein, NIFA tackles a few "challenge areas" using collaborative research and funding. The AFRI Resilient Agroecosystems in a Changing Climate Challenge Area is one of these and focuses on understanding the interaction between climate variability and agricultural production systems, so that we can develop the plants, animals and management systems that will be robust and productive under changing environmental conditions.

Research results from this challenge area will lead to improved management systems and crop varieties that consider the risks associated with a more variable environment. Another long-term outcome of this challenge area is reducing the environmental impact, while maintaining a productive food, feed, fibre and fuel system. This is a prime example of studies exploring maximised productivity alongside minimised environmental damage, it is becoming more and more obvious to the agricultural sector that environmental impacts need to be minimised, while also developing new ways to deal with the results.

Overall, it is evident that these above initiatives and programmes support their aims. In a press release, we find out that: "NIFA's mission is to invest in and advance agricultural research, education and extension that solve societal challenges." Their programmes propel cutting-edge discoveries from research laboratories to farms, classrooms, communities and back again. Through three main federal-funding mechanisms, NIFA supports programmes that address key national challenge areas. ■

https://nifa.usda.gov/announcement/usdas-national-institute-food-and-agriculture-announces-support-increasing-alfalfa

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

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

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

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

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

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

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

Production constraints

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

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

Cowpea as a trap crop for an emerging invasive pest

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

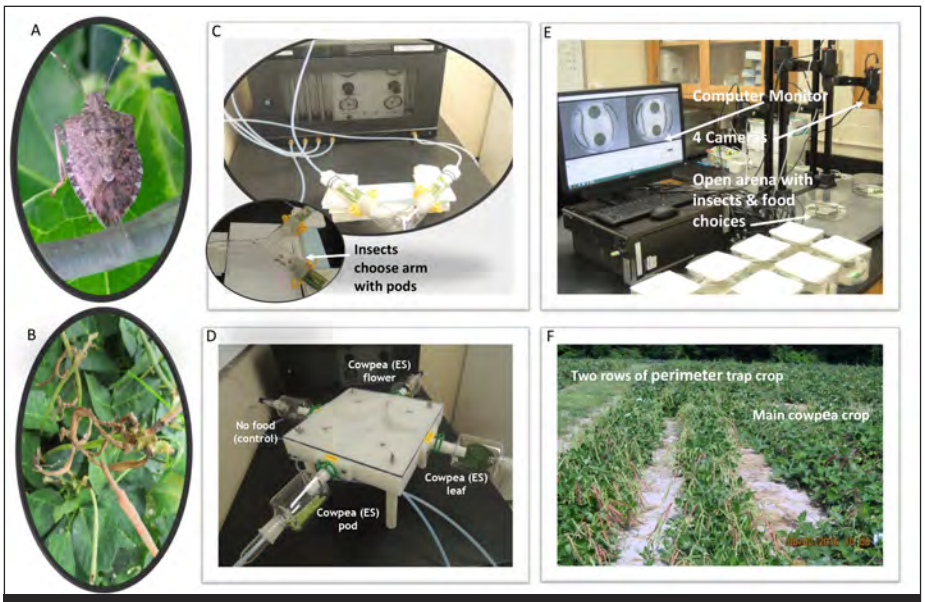

Figure 1: The brown marmorated stink bug (A) causes severe damage to cowpea (B). Several field and laboratory techniques are used in the discovery of a suitable trap crop for this insect including response to plant odors (Y-tube (C) and 4-arm (D) olfactometers and other behaviors related to attraction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

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

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

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

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

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

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

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

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Finding new solutions to agricultural problems in the U.S.

Open Access Government looks at the work of the Agricultural Research Service (ARS) in finding new solutions to agricultural problems in the United States

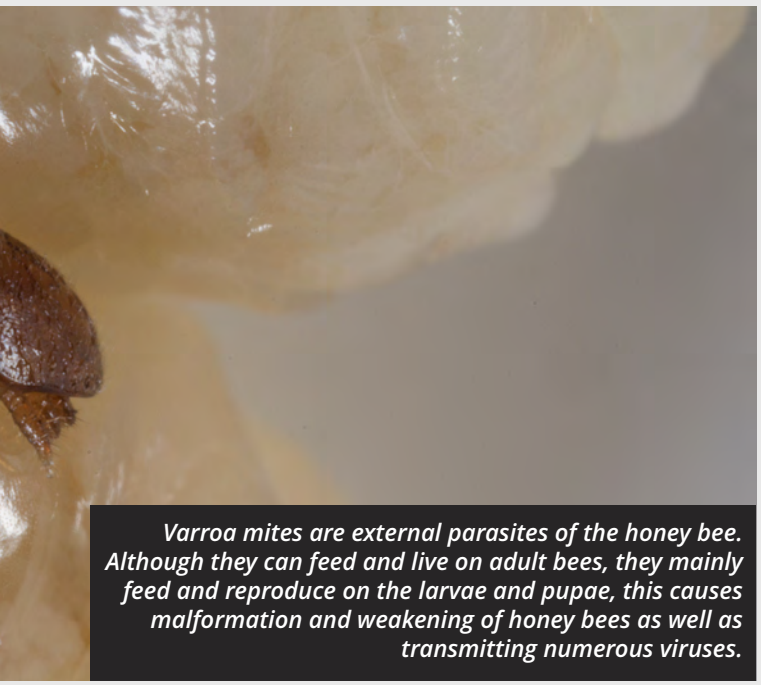
The Agricultural Research Service (ARS) is the U.S. Department of Agriculture's (USDA's) chief scientific in-house research agency. ARS is one of four agencies in USDA's Research, Education and Economics mission area. Their principal purpose is finding new solutions to agricultural problems that affect Americans every day from the field to the table, with the vision to "lead America towards a better future through agricultural research and information."

Their methods to solving agricultural problems are focalised through their four national programme areas: nutrition, food safety and quality; animal production and protection; natural resources and sustainable agricultural systems; and crop production and protection. Formed in 1953, the ARS has come a long way since then, rapidly growing in scope. Today, the organisation includes 690 research projects within 15 national programmes, 2,000 scientists and post docs, 90+ research locations, including overseas laboratories and a $1.1 billion fiscal year budget.

The ARS states that each dollar invested in agricultural research results in $20 of economic impact.

ARS scientists regularly collaborate with research partners from universities, companies, large organisations and numerous different countries. An example of this is the $1 million Funded International Consortium to Seek Honey Bee Disease Controls, which took place in March of this year. Agricultural Research Service (ARS) entomologist Steven Cook is leading this consortium of scientists, who together are attempting to seek new controls for Varroa mites, the honeybees' number one problem.

Along with the Bee Research Laboratory, (a part of ARS's Beltsville (Maryland) Agricultural Research Centre), Cook will be the principal investigator of a group that will include scientists from the United States, Canada and Spain. ARS is the in-house research agency of the U.S. Department of Agriculture (USDA). Laboratory and field studies will be conducted at



Varroa mites are external parasites of the honey bee. Although they can feed and live on adult bees, they mainly feed and reproduce on the larvae and pupae, this causes malformation and weakening of honey bees as well as transmitting numerous viruses.

facilities in Alabama, Georgia, Maryland and Ohio, as well as in Alberta, Canada.

In addition, laboratories in Nebraska and Spain will see scientists using advanced methods to work out an understanding of the molecular mechanisms by which Varroa mites develop resistance to various chemical controls. Honey bees specifically pollinate about 100 crops in the United States. Varroa mites have become resistant to many commercially available chemical control agents in recent years.

Recent additional research conducted by the ARS includes the work to counter the resistance of a common soil bacterial compound named Tunicamycin, which causes infection in both humans and animals. The ARS Website printed a press release on March 29th, 2018 regarding this research and stated that: "Researchers have known of tunicamycin for decades and were initially excited by its medical and veterinary prospects – especially to overcome the resistance of some germs to penicillin-based drugs like oxacillin and methicillin.

The problem was, tunicamycin also blocked a key protein in human and animal cells, undercutting its potential use in the ground war on germs." An ARS-led team of scientists and colleagues at the agencies National Centre for Agricultural Utilization Research (NCAUR) in Peoria, Illinois and the Chinese Academy of Sciences are working to devise a method to retool the compound so that it poses little to no danger to human or animal cells, but can still kill germs.

"Honey bees specifically pollinate about 100 crops in the United States. Varroa mites have become resistant to many commercially available chemical control agents in recent years."

The ARS pride themselves on their mission, that is constantly striving to ensure high-quality, safe food and other agricultural products; assessing the nutritional needs of Americans; sustaining a competitive agricultural economy; and enhancing the natural resource base and the environment. Furthermore, they hope to provide economic opportunities for rural citizens, communities and society as a whole; and supply the infrastructure necessary for creating and maintaining a diversified workplace.

With the recent death of the ARS Hall of Fame Scientist Ernest James Harris, we are called to remember some of the terrific work that has been done in the past, not just in the present day. Harris was internationally known for finding innovative ways to control fruit flies that threaten crops around the world and his technologies have been key to eradicating foreign fruit flies in California, Florida and other U.S. mainland states, as well as keeping areas free of these pests that would require costly quarantines and interfere with millions of dollars of agricultural exports.

The ARS website itself stated that: "he was a particularly strong role model for other African-American scientists and was known to his ARS colleagues in Hawaii for his positive attitude, kindness, gentle demeanour and humility". These kinds of scientists are exactly the kind of hard-working innovators that the ARS trust to carry out their research and make progress in the U.S. Department of Agriculture. ■

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Protecting human health and the environment

The work of the U.S. Environmental Protection Agency and the Office of Environmental Information, to protect human health and the environment, is unveiled by Open Access Government

The United States Environmental Protection Agency (EPA) was formed on December 2nd, 1970 as an agency of the federal government of the U.S. During these 47 years, their concrete mission has remained the same – to protect human health and the environment. Headed as 14th administrator of the EPA, Scott Pruitt believes that promoting and protecting a strong and healthy environment is among the lifeblood priorities of the government and that the EPA is vital to that mission.

The mission itself is supported by the Office of Environmental Information (OEI), which manages the life cycle of information surrounding the EPA's mission. Stated clearly on its website, the OEI is proud to support the EPA, by identifying and implementing innovative information technology and information management solutions that strengthen EPA's ability to achieve its goals. They ensure the quality of EPA's information and the efficiency and reliability of EPA's technology, data collection, exchange efforts and access services. The OEI also strives to provide technology services and manage EPA's IT investments.

Together, the EPA and the OEI act, by developing and enforcing regulations, giving grants, both teaching and studying environmental issues, sponsoring partnerships and publishing information to accomplish this important goal.

A recent illustration of some of these actions came about in January 2018, with the release of a report

outlining recommendations to promote agriculture, economic development, job growth, infrastructure improvements, technological innovation, energy security and the quality of life in rural America. As a member of the USDA Task Force on Agriculture and Rural Prosperity Release Recommendations to Revitalize Rural America, the Environmental Protection Agency (EPA) plays an important role in revitalising rural America. Pruitt confirmed his commitment to empowering rural America by stated that it will contribute to improving the "environmental outcomes across the country".

> "Together, the EPA and the OEI act, by developing and enforcing regulations, giving grants, both teaching and studying environmental issues, sponsoring partnerships and publishing information to accomplish this important goal."

In addition, EPA awards numerous grants to support state pesticide regulatory programmes ensuring these products are used properly, agricultural works are protected, and farmers can provide safe, healthy food for all Americans. More specifically, in May 2017 the EPA awarded $574k to the Washington State Department of Agriculture to support state-wide pesticide programmes. Administrator Pruitt states: "We are pleased to support the pesticide programs in ensuring that pesticides are used properly, agricultural workers are protected, and Washington's diverse agricultural landscape can thrive and remain a provider of safe, healthy food."

The U.S. agriculture sector itself is somewhat robust, producing nearly $330 billion per year in agricultural commodities. The U.S. is also unsurprisingly currently the world's leading exporter of agricultural products; the sector plays a critical role in the global economy. However, aspects of this are constantly under threat and with climate change becoming an ever-growing factor in the well-being of the agriculture sector, and as such, laws and regulations must be enforced to prevent lost capital.

On March 21, 2011, the EPA issued its final emission standards to reduce emissions of toxic air pollutants from industrial, commercial and institutional boilers located at area source facilities. An area source facility emits or has the potential to emit less than 10 tonnes per year of any single air toxic or less than 25 tonnes per year of any combination of air toxics. This final rule covers boilers located at area source facilities that burn coal, oil, or biomass, but not boilers that burn only gaseous fuels or any solid waste.

An area under threat in today's climate and toxic air pollution is forestry. While perhaps not the most obvious means of exportation, forests, in fact, provide several important goods and services, including timber, recreational opportunities, cultural resources and habitat for wildlife. They also create numerous opportunities to reduce future climate change by capturing and storing carbon by providing resources for bioenergy production.

Both agricultural and forestry production are sensitive to changes in climate, including changes in temperature and precipitation, more frequent and severe extreme weather events as well as increased stress from pests and diseases. However, certain adaptation measures, such as changes in crop selection, field and forest management operations and use of technological innovations, have the potential to delay and reduce some of the negative impacts of climate change and could create new opportunities that benefit the sector.

Clearly, both the EPA and the OEI take their roles very seriously as responsible for human health and the environment. A drastic change in the climate could not only be dangerous to both the environment and its inhabitants, but also drastically change the potential yields of agricultural and forestry products, shifting land allocation, crop mix and production practices throughout the U.S. It is, therefore, important to protect the environment through means such as grants and education to enable it to thrive, benefitting all. ■

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Greening the inner city: How do we choose the best trees?

Nina Bassuk from the Urban Horticulture Institute, School of Integrative Plant Science Cornell University shares her thoughts on the value of green spaces in inner cities and how we should choose the best trees for this purpose

The world's population is increasingly urban. In the United States alone, 85% of the population lives in urban areas and that trend is expected to continue. If we value the green spaces and trees in our cities and parks for all the benefits they give us, we need to choose the best trees that will thrive in challenging sites.

"By far, the most stressful urban condition for trees is the lack of accessible soil. This is caused by inadvertent and purposeful soil compaction. When any new road or building is built or demolished, the soil within the area inadvertently becomes compacted due to the use of heavy machinery and moving of earth."

There are four basic principles of urban tree selection:

- Trees should be pest resistant and adapted to urban environmental conditions.
- Trees should be highly diverse, including native and non-native species, but avoiding invasive species.
- Trees should meet functional and design objectives.
- Trees should match management limitations.

When we investigate these principles, it is worthwhile to delve into specifics.

Tree roots escape a confined space by growing under a sidewalk into a neighbouring lawn

Pest resistant – adapted to environmental stress

Due to the inherently heterogeneous nature of the urban environment, tree planting sites are subject to microclimates caused by buildings and paved surfaces and the aftereffects of urban development written in the soil. On a warm sunny day when the air temperature is 24°C, the surface temperatures of pavement or building walls can reflect 40-52°C temperatures. Taken altogether, this increased heat gives rise to the urban heat island where inner cities are considerably warmer than surrounding rural areas. With increased air temperatures, trees lose water from their leaves more rapidly than a rural tree. Coupled with often-restricted planting spaces or soil that is paved over, trees experience drought stress even during what would be considered normal summer temperatures and rainfall.

With the addition of climate change, cities experience longer periods without rain and then heavy downpours. The negative effects of too much water can also be stressful for trees when air-filled pores in the soil are filled with water depriving the tree roots of needed oxygen. Above ground, trees also have to compete with utility wires, streetlights, traffic and business signage. These cause conflicts if sight lines or electricity delivery is disrupted requiring drastic pruning to squeeze the tree's canopy into the allotted space.

Using air excavation tools we uncover roots

By far, the most stressful urban condition for trees is the lack of accessible soil. This is caused by inadvertent and purposeful soil compaction. When any new road or building is built or demolished, the soil within the area inadvertently becomes compacted due to the use of heavy machinery and moving of earth. Once compacted and crushed, it is difficult to bring back the soil so that it can support plant life. Moreover, when any pavement is laid, the soil beneath it must be purposefully compacted to bear the load of the new pavement to prevent subsiding or cracking.

Tree roots provide, water, nutrients and oxygen for healthy tree growth. When soil volume is restricted these basic building blocks for tree growth can be severely restricted. Combined with reflected heat from building and pavement, poor water infiltration due to impervious surfaces, waterlogged soils that don't drain and often poor nutrient availability, it is no wonder that urban trees live a shortened life.

However, most people who enjoy a tree covered street would say that things cannot be that bad. After all many trees get big and provide many of the benefits we enjoy.

Where are the roots?

Whenever there is a large tree, there is a corresponding large, wide-spreading root system that supports that tree to supply water and nutrients.

With the use of air excavating tools, we have peeled back the soil to find where roots are growing. In many narrow, green, planting areas adjacent to roads, tree roots break out of the limited soil by exploiting the area of weakness at the interface between the sidewalk and underlying soil. When they do this, roots find accessible soil in someone's front or backyard or nearby vacant lot. Inevitably the roots of a large tree may not be where you think they are. When roots grow under pavement and increase in girth by radial growth, sidewalks may be raised causing tripping hazards, which set up a conflict between trees and municipalities.

"The one factor that no tree is adapted to is compacted soil. Compaction physically restricts root growth and prevents the acquisition of water, nutrients and oxygen. When this occurs, soil remediation must occur to engineer a more sustainable soil condition."

We can select trees that are adapted or tolerant of to:

- Small planting envelopes (above and below ground) by choosing small trees;
- Heat and cold temperatures;
- Dry and wet soils;
- Poor nutrient availability and salts and;
- Insect and diseases.

Each one of these conditions is a filter reducing the potential trees that may be chosen. It is notable that the more we can reduce the stress on trees, the greater the choices we can make will be.

The one factor that no tree is adapted to is compacted soil. Compaction physically restricts root growth and prevents the acquisition of water, nutrients and oxygen. When this occurs, soil remediation must occur to engineer a more sustainable soil condition.

"It is clear that the urban environment has been fundamentally altered by development and human habitation. The choices of trees must consider these environmental conditions and choose plants that are adapted to them."

Highly diverse, non-invasive

I am often asked, "What is the best urban tree." There are many common street trees that are preferentially grown in cities worldwide. In the eastern United States, maples (Acer spp.) make up about 40% of the urban tree population. In Scandinavia and other parts of Europe, lindens (Tilia spp.) make up a very large percent of the urban tree population. The problem with growing just a few tried and true species is that if they become susceptible to an insect or disease (and inevitably there is always some new insect or disease!) the demise of these trees causes an enormous negative effect on the urban landscape. We have the example of Dutch Elm Disease decimating elms, Emerald Ash Borers killing all the ash trees, Asian Long Horned Beetles destroying maples and a host of other species, as well as other examples. The only true defence against pests is to plant a very diverse urban forest.

Native or non-native?

It is clear that the urban environment has been fundamentally altered by development and human habitation. The choices of trees must consider these environmental conditions and choose plants that are adapted to them.

The popular ideology promoting native species only disregards the fact that urban conditions are nothing like native conditions where many trees evolved.

The best choice is to use both native and non-native trees when they are adapted to urban site conditions. A few species have become invasive, causing economic and environmental harm, as well as harm to human health. Identifying these trees varies on a local level and should be avoided.

Trees provide ecosystem and aesthetic benefits

Increasingly we are recognising and quantifying the benefits that trees provide in the urban environment including reducing storm water runoff and pollution, providing habitat for pollinators, sequestering carbon, reducing air pollution and providing significant energy conservation in summer and winter. Tree choice affects the accrual of benefits. Trees with large canopies provide the greatest amount of energy conservation, storm water runoff reduction and carbon sequestration. A diversity of trees that flower from spring through fall will provide the greatest benefit to pollinators and other urban fauna.

What about the cost of tree management?

Many cities have quantified the benefits they receive from healthy trees. In all cases, the cost of management (preparing sites, choosing good trees and providing reasonable aftercare) is far outweighed by the ecosystem benefits that are gained.

We take trees for granted. Only when many trees are removed do people realise the difference trees make in their lives. Continued research focusing on better tree selection for challenging urban sites will provide long-term benefits that we can all enjoy.

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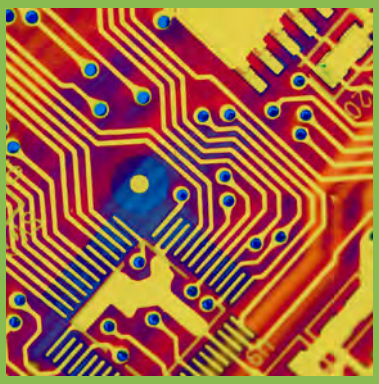





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The Antarctic notothenioid fishes: An especially interesting and unique marine species flock

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

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

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

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

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

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

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

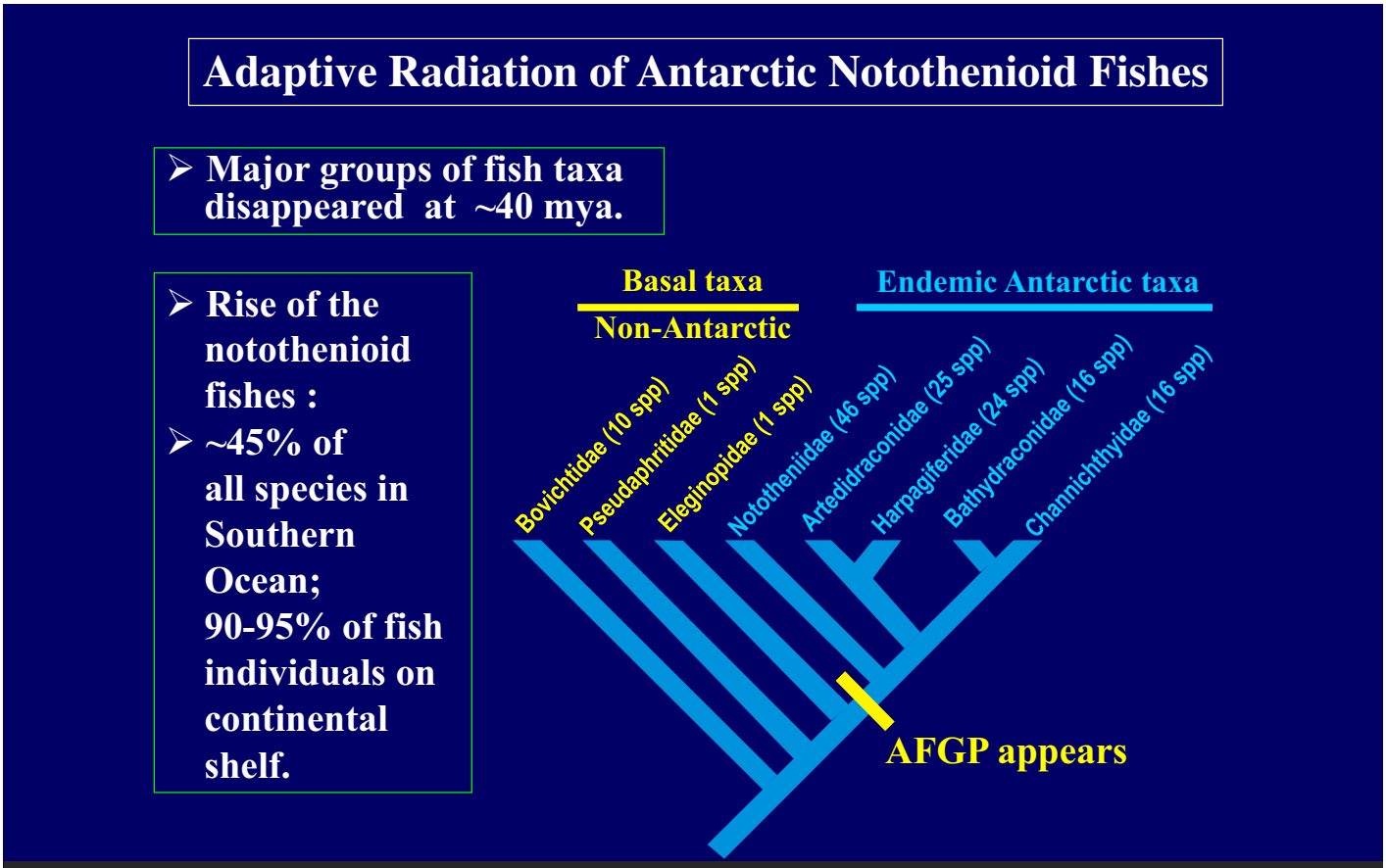

Figure 1. Cladogram of Antarctic fishes of the Suborder Notothenioidei and characteristics of the group

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

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

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

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

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Biodiversity: The extraordinary variety of life on Earth

Pamela S. Soltis, Director of the University of Florida Biodiversity Institute provides a fascinating analysis of her department's research on biodiversity – that is, the extraordinary variety of life on Earth

Biodiversity – the extraordinary variety of life on Earth – is fundamental to a healthy, sustainable planet, yet the connections between biodiversity, ecosystem function and services that contribute to human well-being are less well understood. These 'ecosystem services' derive from healthy ecosystems and include clean air, clean water, flood resistance, protection from weather extremes, pollinators of crops, sources of foods, fibres and medicines, recreational opportunities and spiritual and cultural experiences, to name a few (Fig. 1).

The current concept of ecosystem services traces to the 2005 United Nations Millennium Ecosystem Assessment. Classification of ecosystem services – by function or other properties – provides a basis for quantifying and valuing these contributions. For example, the U.S. Environmental Protection Agency (EPA) defines 'final ecosystem goods and services' as components of nature, directly enjoyed, consumed, or used to yield human well-being, in contrast to 'intermediate ecosystem services', which are benefits that lead to the final service. The recognition of ecosystem services as final versus the intermediate is important for assigning economic value to these benefits.

Ecological economists note the effect of invasive species (>$120 billion annually in the U.S. alone) and have begun to quantify the economic benefit of ecosystem services, but the valuation of ecosystem services is complex and includes both market and non-market values. For example, both a market (or dollar) value assigned to a specific ecosystem or component thereof and non-market values, such as societal preferences, intrinsic value and improved public health, may contribute to the value of an ecosystem service.

Increasingly, representatives of local to national governments, as well as non-government organisations and the private sector, are incorporating the economic impact of ecosystem services into policy. Thus, sound research that integrates biodiversity and environmental science, social science and economics is required for appropriate valuation of ecosystem services. To this end, the U.S. President's Council of Advisors on Science and Technology (PCAST) in 2011 called for the improved accounting of ecosystem services and greater protection of environmental capital, citing the need for further biodiversity science and application of informatics to enhance our understanding of ecosystem services and develop appropriate policy to protect them.

More recently, the International Platform on Biodiversity and Ecosystem Services (IPBES), with 118 member nations and modelled after the Intergovernmental Panel on Climate Change (IPCC), has begun assessing the scientific and social knowledge of Earth's biological diversity and how environmental change will impact ecosystems and human societies. Integrated, accessible science and technology platforms are needed to leverage novel planetary data, models and tools to create and link knowledge to policy.

To meet the scientific and societal challenges of a changing planet,

Figure 1. Diagrammatic representation of ecosystem services, showing the benefits themselves, the natural resources that provide the benefits and the drivers of change. (From the United States Environmental Protection Agency. EnviroAtlas. Ecosystem Services in EnviroAtlas. Retrieved: April 5th, 2018 from www.epa.gov/enviroatlas/ecosystem-services-enviroatlas)

including the identification and valuation of ecosystem services, the University of Florida (UF) Biodiversity Institute promotes interdisciplinary, integrative biodiversity science. The mission of the UF Biodiversity Institute is to conduct high-quality research and develop programs to advance three primary goals:

1. Initiate and lead large-scale, collaborative biological surveys to document and monitor biodiversity on a global scale;

2. Conduct collaborative and interdisciplinary research on biodiversity, with an emphasis on the use of Big Data;

3. Translate biodiversity science to solve major societal problems.

Research on ecosystem services of Florida's forests, grasslands and springs is quantifying the economic value of these important resources and developing methods for valuation of ecosystem services that can be exported to other regions and resources worldwide.

By working with scientists, economists and social scientists at UF, elsewhere in the U.S. and abroad, we hope to bring greater appreciation for the many benefits that we derive from healthy ecosystems and demonstrate the significant cost – financial and otherwise – of lost biodiversity and deteriorating ecosystems.

The UF Biodiversity Institute was introduced in the August 2017, issue of Adjacent Government. Launched in 2016 to bring together scientists, social scientists and policy experts to address critical societal issues of the 21st century related to biodiversity, the interdisciplinary UF Biodiversity Institute is accelerating synthetic research on biological diversity to serve stakeholders in Florida (a biodiversity hotspot) and globally through efforts to understand and manage biodiversity, develop relevant conservation, educational and outreach programs and shape policy to protect and enhance environmental capital. Newly synthesised knowledge from the UF Biodiversity Institute is available to individuals and organisations seeking validated biodiversity information.

Previous articles in this series have (1) introduced the UF Biodiversity Institute, (2) described how iDigBio, the U.S. national centre for digitisation of natural history collections, promotes digitisation of collections, serves digitised data (including images and other media) for biodiversity research and education, enables the use of digitised data in biodiversity science and engages with biodiversity resources worldwide and (3) outlined a strategy for integrated training in biodiversity and data sciences to meet the needs of a global 21st-century workforce.

Note: Supported by the UF Biodiversity Institute.

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Supporting the earth sciences in the United States

The Earth Sciences (EAR) Division of the National Science Foundation (NSF) is placed under the spotlight by Open Access Government

The National Science Foundation (NSF) is an independent federal agency in the United States that supports fundamental research and education across all disciplines of science and engineering. In fiscal year (FY) 2018, its budget is $7.8 billion. NSF funds research throughout all 50 states to almost 2,000 colleges, universities and other institutions. Each year, NSF receives no less than 50,000 competitive proposals for funding and funds around 12,000 projects to keep the United States at the leading edge of discovery in areas from astronomy to geology to zoology.

The Division of Earth Sciences (EAR)

The Division of Earth Sciences (EAR), part of the NSF, gives unwavering support to proposals for research that intends to improve our understanding of the structure, composition and evolution of the earth itself, the life it supports and the processes that govern the formation and behaviour of the earth's materials.

The results of such research will clearly create a better understanding of the earth's changing environments, as well as the natural distribution of its mineral, biota, water and energy resources, not to mention providing methods for predicting and mitigating the effects of geologic hazards, such as volcanic eruptions, earthquakes, floods and landslides.

In a nutshell, we know that earth science is the study of the earth's structure, properties, processes and in the view of the NSF, it is also the study of four and a half billion years of biotic evolution. Certainly, understanding such phenomena is essential to the maintenance of life itself on the planet. The increasing world population demands more resources; heightens losses from natural hazards and creates more pollution.

The NSF website also points us to the way earth science benefits society. We learn that the knowledge gained, as well as the work of earth scientists, help society cope with its environment in many ways. The knowledge of earth scientists concerns the structure, stratigraphy and chemical composition of the earth's crust and helps us locate resources that sustain and advance our quality of life. The NSF's website explains this point in more detail to us: "Understanding the forces in the crust and the natural processes on the surface allows us to anticipate natural disasters such as volcanoes and earthquakes and geologic environments, such as damaging mining practices or improper waste disposal, gives us information to correct such practices and design more benign procedures for the future." (1)

"In a nutshell, we know that earth science is the study of the earth's structure, properties, processes and in the view of the NSF, it is also the study of four and a half billion years of biotic evolution. Certainly, understanding such phenomena is essential to the maintenance of life itself on the planet. The increasing world population demands more resources; heightens losses from natural hazards and creates more pollution."

Petrology and Geochemistry (CH) Division

Within the Division of Earth Sciences at the NSF, lies the Petrology and Geochemistry (CH) Division. Their work specifically involves the support of basic research concerning the formation of planet earth, including its early differentiation and subsequent petrologic and geochemical modification via igneous and metamorphic processes.

Proposals in this programme generally address the petrology and high-temperature geochemistry of igneous and metamorphic rocks (including mantle samples), volcanology, mineral physics and economic

geology. The Division's website explains that they focus on the development of analytical tools, theoretical and computational models and experimental techniques for applications by the igneous and metamorphic petrology, as well as geochronology communities and high- temperature geochemistry. (2)

Examples of NSF-supported research on volcanology

An interesting example of how NSF supports and funds research into the earth sciences, for example, is around volcanology. In news from the field, the NSF website draws our attention to Frank Spear of Rensselaer Polytechnic Institute who thinks he's found the source of water that fuels earthquakes in volcanoes in subduction zones. This can be done by applying a new spectroscopy technique to garnet containing fragments of quartz, metamorphic petrologist, we are told. Spear's research is supported by a three-year $419,247 grant from the NSF.

"The real culprit in powerful volcanoes and earthquakes is water, but scientists have been unable to determine where that water comes from," said Spear, a professor and head of the Rensselaer Department of Earth and Environmental Sciences. "Conventional thermodynamic equations predict that water is released at too shallow a depth to occur at the known locations of volcanoes and earthquakes. But when you factor in the overstepping we've discovered, the locations coincide. The idea of overstepping is an enormous paradigm shift" he explains. (3)

In closing, it's worth noting another fascinating area of volcanology research supported by NSF, which can be found in detail about a study from New Zealand volcano by Brown University, which suggests that a volcanic system's response to tidal forces could provide a tool for predicting a certain type of eruption.

Prior to a surprise eruption of New Zealand's Ruapehu volcano in 2007, a seismic tremor near its crater became tightly correlated with twice-monthly changes in the strength of tidal forces, the new study reveals. The research suggests that signals associated with tidal cycles could provide advanced warning of kinds of volcanic eruptions. This interesting point is explained further by Társilo Girona, the study's lead author.

"Looking at data for this volcano spanning about 12 years, we found that this correlation between the amplitude of seismic tremor and tidal cycles developed only in the three months before this eruption. What that suggests is that the tides could provide a probe for telling us whether or not a volcano has entered a critical state."

The research was funded by the National Science Foundation (1454821). Professor Christian Huber, also involved in this project said that they'd like to collect more data from other eruptions and other volcanos to see if this tidal signal shows up elsewhere "Then we can start to think about using it as a potential means of predicting future eruptions of this kind", he says. (4)

Closing remarks

Such research is an excellent example of why NSF was created by Congress in 1950, one of the reasons of which was: "to promote the progress of science" and to fulfil the vital task of keeping the United States at the leading edge of discovery in numerous areas of exciting scientific discovery. ■

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The priorities of the U.S. Energy Department

Open Access Government charts the history of the U.S. Energy Department and some of its present-day priorities, including clean energy and solar manufacturing

The mission of the U.S. Energy Department, according to their website, is: "To ensure America's security and prosperity by addressing its energy, environmental and nuclear challenges through transformative science and technology solutions." [1] This article will look at the background to the Department's work, including some of its present-day work, including driving energy-efficient technologies and promoting clean energy, as well as solar manufacturing.

By way of background, the U.S. Energy Department is said to have one of the most diverse histories in the U.S. Federal Government. While it began its life in 1977, the U.S. Energy Department's lineage can be traced back to the Manhattan Project effort to develop the atomic bomb during World War II and to other energy-related programmes that were covered by several federal agencies.

During its long history, the U.S. Energy Department has shifted its emphasis and focus in accordance with the changing needs of the nation. In the late 1970s, the emphasis was very much on energy development and regulation. During the 1980s, the priorities changed towards nuclear weapons research, development and production. Following the end of The Cold War, the focus turned to the environmental clean-up of the nuclear weapons complex and the non-proliferation and stewardship of the nuclear stockpile.

After the millennium, the U.S. Energy Department's objective has been to ensure the nation's prosperity and security. This is achieved by addressing its energy, environmental and nuclear challenges by means of innovative science and technology solutions. The U.S. Energy Department seeks to transform the U.S.'s energy system and secure leadership in clean energy technologies, pursue world-class science and engineering and enhance nuclear security through defence, non-proliferation and environmental efforts.

Driving energy productivity improvements and efficient technologies

A more recent example of the U.S. Energy Department's work is evidenced in an announcement on 10th April 2018 about their partnership with the National Association of Manufacturers (NAM). This intends to help U.S. manufacturers drive energy productivity improvements and accelerate the adoption of energy-efficient technologies.

"Working alongside our private sector partners, we are driving cost savings and a stronger, more secure U.S. industrial base," says Secretary of Energy in the U.S., Rick Perry. "The Department's partnership with the National Association of Manufacturers will further spotlight industrial leadership and boost awareness of the resources across the DOE enterprise to boost manufacturing competitiveness through energy savings."

NAM President and CEO Jay Timmons adds: "Manufacturers accept the responsibility to better the future of our communities, our environment and our children, which is why over the past decade, we have reduced emissions by 10% even as our value to the economy has increased 19%. This initiative is another example of the Trump Administration's true partnership with manufacturers in America and it will take our sustainability efforts to a new level of progress." [2]

Clean energy policy and solar manufacturing

Today, a clean energy revolution is said to be taking place across America, underlined by a steady expansion of the U.S. renewable energy sector. The clean energy industry is predicted to continue the trend of rapid growth in the future. There is a marvellous economic opportunity ahead for the countries that invent, manufacture and export clean energy technologies, we are told.

The responsible development of all of America's rich energy resources – including geothermal, bioenergy, solar, wind, water, & nuclear – will help ensure America's continued leadership in the field of clean energy. Moving forward, the U.S. Energy Department aims to drive strategic investments in the transition to a cleaner, domestic and more secure energy future.

In January 2018, the U.S. Energy Department announced a $3 million prize competition to revitalise innovation in U.S. solar manufacturing. The aim of this is to incentivise the nation's entrepreneurs to develop new products and processes that will reassert American leadership in the solar marketplace. U.S. Secretary of Energy Rick Perry explains more about this, in his own words.

"The United States possesses the talent, expertise and vision to surpass the rest of the world in solar technologies and forge a new solar energy landscape around the globe. The American Made Solar Prize will galvanise our country's entrepreneurs, allow them to utilise technologies and innovations developed through DOE's early-stage research and development and, ultimately, bring new American-made products to market."

In addition, this solar prize brings together the country's research base with its entrepreneurial support system which is made up of energy incubators, universities and the U.S. Energy Department's 17 national laboratories, who together can create a sweeping portfolio of innovations primed for private investment and commercial scale up. [3]

Reducing the costs of solar energy

The U.S. Department of Energy has a Solar Energy Technologies Office, who support early-stage research and development to improve the affordability, performance and reliability of solar energy technologies on the grid. This includes investment in innovative research aimed at securely integrating more solar energy into the grid, enhancing the use and storage of solar energy and to lower the costs of solar electricity.

To end this article on a positive note, we know that with the dramatic reduction in the cost of solar, installations in the U.S. have risen dramatically. This encouraging development, of course, creates fresh challenges for the country's ageing electricity grid. To cater for these changing needs, the office announced in September 2017 a continued focus on solar energy research and development efforts that aid the country's critical energy challenges, which are: grid reliability, resilience and affordability. ■

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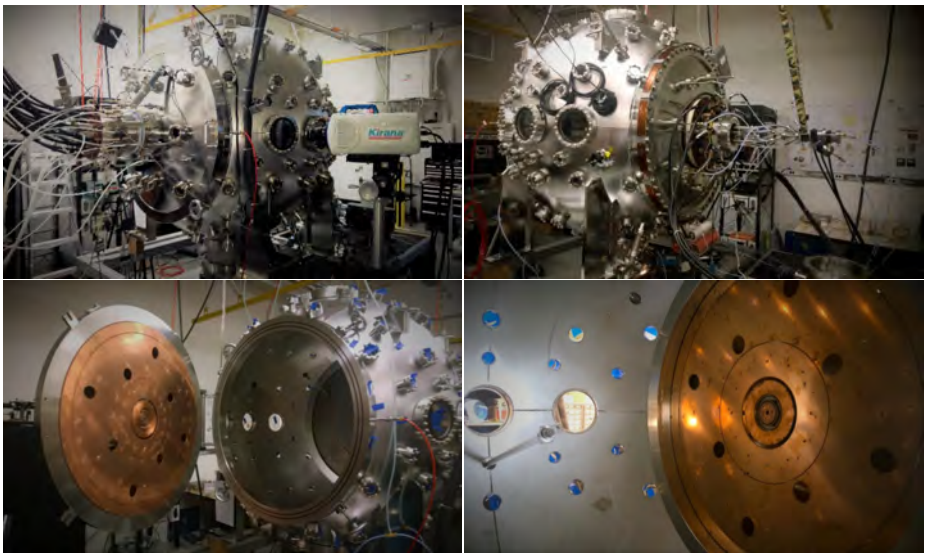
Research on self-organisation in plasmas

Setthivoine You from the Department of Aeronautics & Astronautics at the University of Washington shares his insights into the intriguing world of self-organisation in plasmas



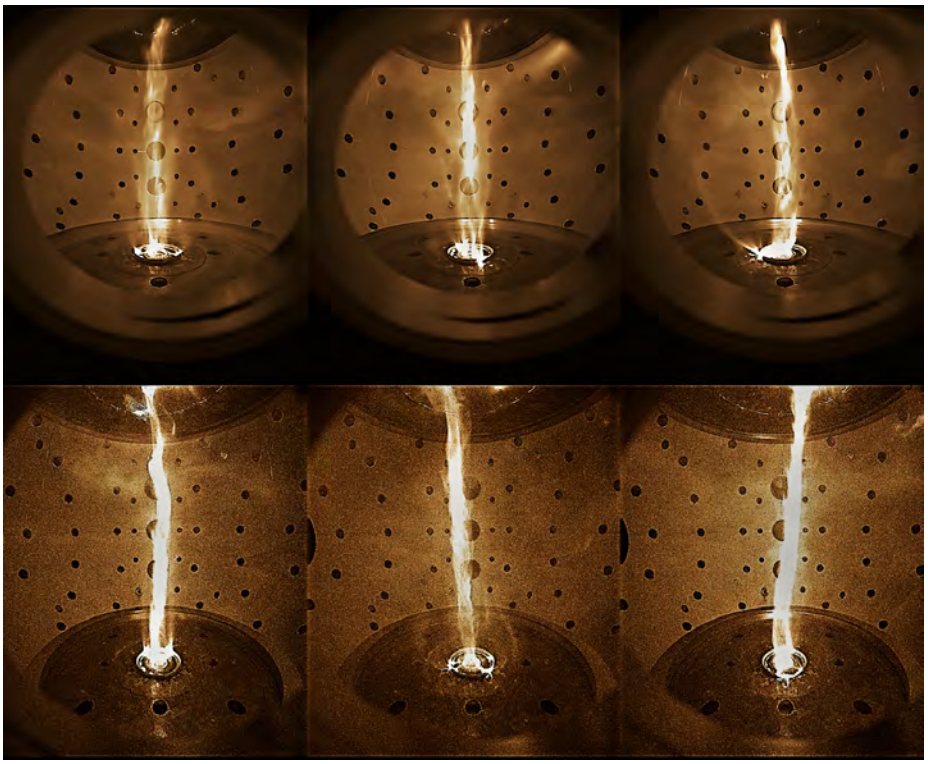
Research into plasma self-organisation lies at the intersection of fusion energy, astrophysics and space propulsion. The aim is to understand the ability of plasmas to spontaneously re-arrange themselves into different shapes. Harnessing this remarkable property can make fusion power plants more compact, therefore more economical and lead to fusion rocket engines. Fusion energy is a breakthrough technology for producing limitless clean energy on Earth and for colonising the Solar System.

Plasmas are ionized gases, heated to temperatures beyond 11,000ºC. Above these temperatures, the gas particles are broken into ions and electrons that interact with electric and magnetic fields. We can, therefore, keep the plasma away from cold walls or accelerate it to provide thrust with suitable arrangements of electric and magnetic fields.

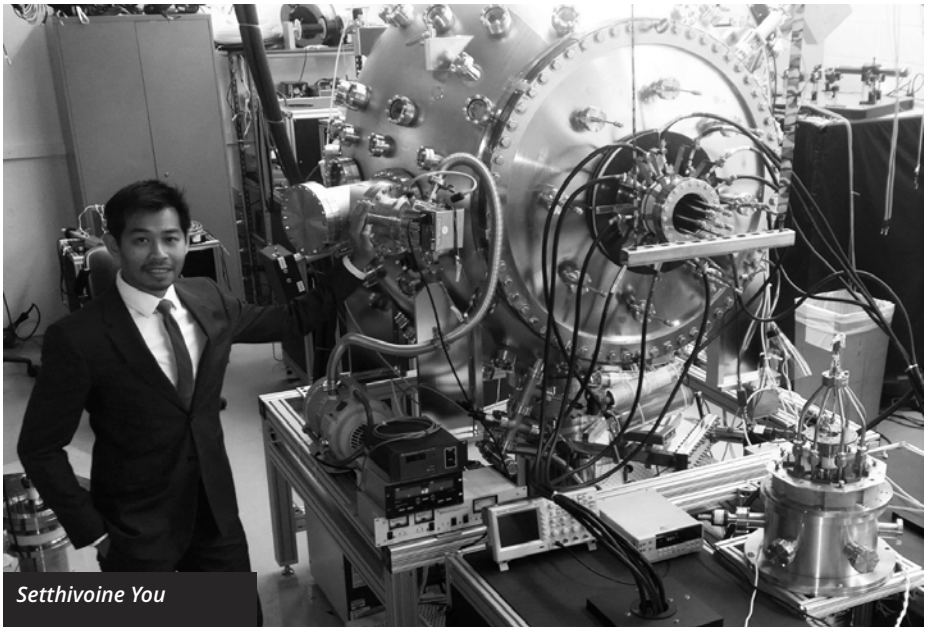
This is how conventional concepts for fusion energy or plasma rocket engines operate. For example, the world's largest fusion energy experiment, ITER in the south of France, uses doughnut-shape magnetic fields arranged in a special configuration called a tokamak to confine the plasma. Then, just like a microwave oven, radio-frequency electromagnetic waves then heat the plasma to more than 150 million degrees, whereupon deuterium and tritium particles fuse to create helium and release neutrons. The neutrons are captured to heat steam, turn turbines and generate electricity. The experiment, currently under construction, aims to demonstrate 500 MW of fusion power from 50 MW of heating with a gigantic 16,000 m^3 apparatus that weighs 23,000 tonnes and holds an 840 m^3 burning plasma.

Plasma rocket engines use electricity to accelerate the plasma and generate thrust for spacecraft propulsion. Examples include ion thrusters used on the soon-to-launched Bepi-Colombo mission to Mercury or Hall thrusters used in the Deep Space 1 spacecraft. The primary benefit of using plasmas for in-space rocket engines is that the propellant can be ejected at velocities much greater than is possible with chemicals, so less propellant is needed to fly faster. These engines are limited by the available electricity, so solar electric propulsion is limited by the size and mass of solar panels compounded by the decreasing amount of sunlight available farther out of the Solar System.

How do we make power plants smaller and how do we break the solar power limit? One possibility is to exploit the spontaneous interaction between plasmas and magnetic fields to generate large flows or magnetic structures. With the right conditions, plasmas suddenly form flows in the magnetic doughnut that doubled the plasma confinement time. This fortuitous discovery in the 1980s made fusion reactors smaller than would otherwise have been the case and forms the basis of operation of the ITER tokamak.



Another discovery shows that with the right conditions, the plasma can form a different kind of magnetic doughnut that can also confine the plasma. These other doughnuts are variously called spheromaks, or field-reversed configurations and are smaller than the equivalent tokamak. Merging two of these configurations generates strong flows and converts magnetic field energy into heat. This could be exploited to heat plasma to fusion temperatures without using microwaves nor compression. The spontaneous conversion of magnetic fields to flows or vice-versa while generating heat or new magnetic configurations is a signature of plasma self-organisation.



Setthivoine You

In nature, this property is observed over a wide range of scales. Reconnection of magnetic fields and re-arrangement of magnetic tubes are at the heart of solar prominences, the mystery of solar coronal heating and the origin of magnetic fields around planets and stars throughout the Universe. Astrophysical jets are manifestations of matter rotating around stars linked by magnetic fields.

The Mochi.LabJet experiment is thus designed to observe the self-organisation of plasmas in a simple experiment designed to mimic an astrophysical jet. Using technology derived from fusion and plasma space propulsion experiments, nested electrodes with magnetic fields produce long stable jets of plasma that travel at 80 km/s. The experiment demonstrates how astrophysical jets can be remarkably stable, collimated and straight.

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Sustainable aviation fuels, the next frontier for air transport

Michael Gill, IATA Director Aviation Environment imparts his expertise on sustainable aviation fuels and why he believes these are the next frontier for today's air transport

Air transport is going through an astonishing period of growth. Ten years ago, there were 2.5 billion passengers' journeys a year. In 2017, there were more than 4 billion. In 20 years' time, we anticipate the number will have almost doubled, to 7.8 billion. Each new journey offers opportunities to open up new business markets, generate social and educational possibilities, bring far-flung families and friends together and provide a chance for people to explore and understand our wonderful, diverse world.

But such growth in air transport brings a huge environmental challenge – one that the industry is aware of and planning for. A decade ago, the aviation industry set out clear goals for carbon emissions, including carbon-neutral growth from 2020 and to cut CO_2 emissions in half by 2050, compared to 2005 levels. Behind these goals lies a comprehensive four-pillar strategy, encompassing new technology and operations, better infrastructure and a global carbon offset and reduction scheme (called CORSIA), which is scheduled to come into effect in 2021.

One of the key components of the technology pillar is sustainable aviation fuels (SAF). These offer an exciting path to carbon reduction, potentially cutting emissions by 80% over the carbon lifecycle compared to conventional jet fuel. Progress on using SAF has already moved faster than many predicted. In the 2000s, when the aviation and carbon debate began in earnest, many experts felt that SAF flights wouldn't happen before the mid-2010s. In fact, the first SAF flight occurred in February 2008, when a Virgin Atlantic 747 flew a test flight from London to Amsterdam.

In the decade since, a number of airlines have conducted test flights that have ensured several different types of SAF – everything from algae to jatropha plants, to municipal waste – can now be turned into certified aviation fuel. In recent years, sufficient amounts of SAF have become available that some airports, notably in Norway and Australia and several airlines, such as Cathay Pacific, United and KLM, have been able to secure a continuous supply, albeit for the time being in limited quantities.

The result of all this work has been that the number of flights using a SAF-JetA1 blend has moved from 1 in 2008, to 100,000 in 2017 and we hope to reach 1 million flights in 2020. But this is just the start. The next step is to move into large-scale production in order to create a lasting and increasing reduction in aviation's carbon emissions.

This is where public policy becomes crucial. Biofuels for the automotive sector have long received encouragement or even outright subsidy from the public sector to incentivise production. It is now high time that SAF is put on the same pedestal. This is all the more crucial as aviation, unlike automotive, has no alternative to liquid-energy fuels in the short-medium term. Hitherto, fuel refiners have not had sufficient incentive to generate aviation fuels at price levels the industry could afford.

Why should they, when the policies encouraged them to go for automotive biofuels? Slowly, this is changing. In the United States, policies exist to ensure that a proportion of alternative fuels refined must be for aviation use. And in Europe, the Renewable Energy Directive is being revised. Already the European Parliament has indicated that aviation biofuels should be encouraged. Now we're urging the European Commission and the European Council to agree to this enhancement.

In addition, globally we are calling for measures including:

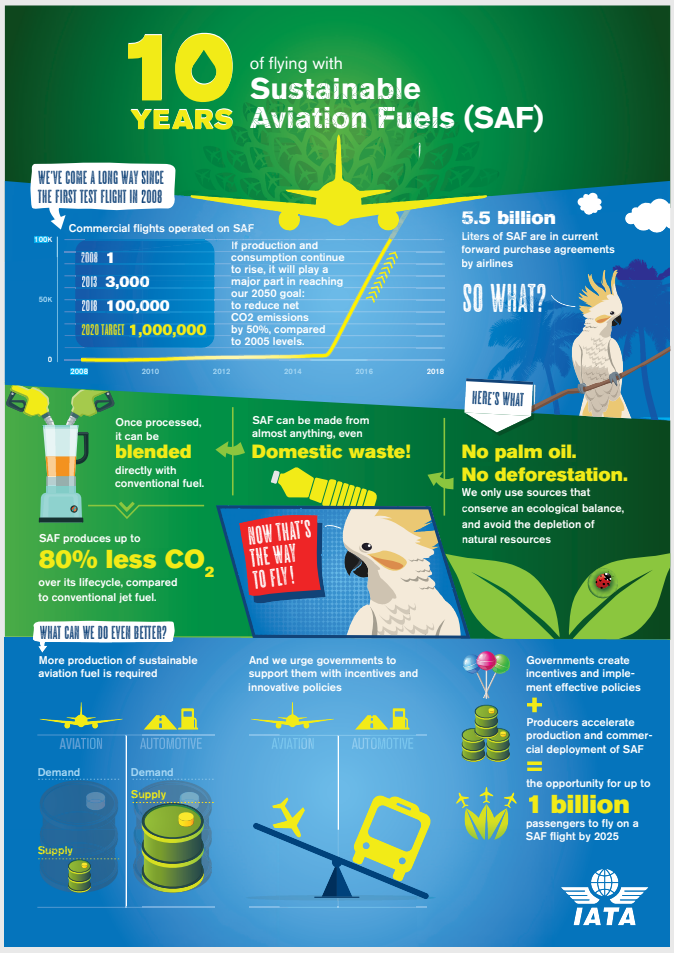
- Implementing the policy to de-risk investments into SAF production plants, including loan guarantees and capital grants for production facilities;
- Support for brokering aviation off-take agreements;
- Support for SAF demonstration plants and supply chain research and development;
- Tax incentives for public-private partnerships for early-stage plant development and;
- Developing a harmonised transport and energy policy including inter-department coordination, such as agriculture, transport, energy and military.

We recognise that in the past, the biofuel sector has not been without controversy. First generation automotive and biomass fuels were criticised for encouraging deforestation or promoting agri-monoculture. Fortunately, lessons have been learned. Most aviation biofuels are certified by the Roundtable on Sustainable Biomaterials.

> "In the United States, policies exist to ensure that a proportion of alternative fuels refined must be for aviation use. And in Europe, the Renewable Energy Directive is being revised. Already the European Parliament has indicated that aviation biofuels should be encouraged. Now we're urging the European Commission and the European Council to agree to this enhancement."

Even more importantly, following unanimous adoption of a resolution at the 2017 IATA AGM, the aviation industry is, in the words of our Director General and CEO Alexandre de Juniac: "Clear, united and adamant that we will never use a sustainable fuel that upsets the ecological balance of the planet or depletes its natural resources." We are in a process of defining new sustainability criteria for SAF to understand how it might play a role in the CORSIA scheme, which would be a big fillip for SAF take-up if it were approved.

If policies can be aligned to ensure aviation biofuels get a fair chance, then we believe it is possible that 1 billion



people would have the opportunity to fly on a plane powered by a mix of traditional jet fuel and SAF by 2025. That is a fabulous prize to aim for.

Sustainability is the next great frontier for the industry. But aviation has a history of taming frontiers – and for providing opportunities for people to explore their own personal frontier, whether for work or pleasure. We are confident that with the correct policy support, we can continue that great tradition. We all owe it to future generations, who expect to fly and expect to do so with minimal impact on the planet. ■

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Canada's plan to reduce carbon emissions and strengthen their clean growth economy

Minister of Environment and Climate Change in Canada, Catherine McKenna details the country's plan to reduce carbon emissions and strengthen their clean growth economy

In mid-February, thousands of Canadians gathered in Ottawa for the 40th edition of Winterlude, one of the country's most famous winter festivals.

They skated along the Rideau Canal, the UNESCO World Heritage Site that runs through the heart of the national capital. They fuelled their excursions with cinnamon-flavoured deep-fried dough called Beaver Tails and tire d'érable, a dessert of frozen maple syrup.

And at Ottawa City Hall, they attended an exhibit of photos of Sirmilik National Park, a 22,000-square-kilometre protected area on Baffin Island in Canada's extreme north. The photos were taken by students who travelled through that magnificent region last summer. They captured Sirmilik's unquestionable beauty. But they also served as a sobering reminder.

It is in this region where the unprecedented challenge of climate change is most readily visible. While Canada's temperature increases are outpacing the global average, temperatures are rising even faster in the country's northern areas.

While Winterlude celebrates Canada's unique, winter culture – Canada's High Arctic is warming at three times the rate of the rest of the country. So, the Sirmilik exhibit was a perfect complement to Winterlude because Canadians see climate change with increasing awareness and concern.

The Government of Canada is committed to doing its part to achieve the global goals set out in the 2015 Paris Agreement. Canada was one of the first countries to sign and ratify the historic pact.

Our country's goal? To reduce greenhouse gas emissions by 30% below 2005 levels by 2030.

As a first step, Canada undertook a broad process that involved all provincial and territorial governments, as well as Indigenous leaders. We wanted to develop a comprehensive national plan to address climate change.

People across the country helped inform this groundbreaking strategy through town hall meetings from coast to coast and an interactive website.

The result was the Pan-Canadian Framework on Clean Growth and Climate Change, which was adopted on December 9, 2016. The Pan-Canadian Framework outlines over fifty concrete measures to reduce carbon pollution and help us adapt and become more resilient to the impacts of a changing climate.

The Framework will foster clean technology solutions and create good jobs that contribute to a stronger economy. A plan to price carbon pollution is at its centre. Our national carbon-pricing approach, announced two years ago, will require all Canadian jurisdictions to have prices on carbon pollution in place by the end of 2018.

Of course, the Framework includes other components. For example, last December, we outlined a design for Canada's Clean Fuel Standard. It will lead to new regulations requiring the use of cleaner fuels in vehicles, industries and buildings.

The Clean Fuel Standard is the single largest emission-reduction policy in Canada's climate and clean-growth plan. It could reduce Canada's greenhouse gas emissions by 30 million tonnes a year, by 2030.

In 2017, we also announced plans to accelerate the phase-out of traditional coal-fired electricity by 2030.

And to encourage countries around the world to take similar action, we launched the international Powering Past Coal Alliance with the United Kingdom.

Today, pollution from coal power contributes close to 10% of Canada's total greenhouse gas emissions. We also published draft regulations to cut methane emissions from the oil and gas sector by 40-45% by 2025. Reducing methane emissions will achieve the same reductions as taking about 5 million passenger vehicles off the road each year.

This is the lowest cost GHG reduction opportunity in the energy sector. Through the new methane regulations, Canada's oil and gas sector will become a global leader in responsible energy production.

Then there are our investments in infrastructure to support electric vehicles. Canada is investing $182.5 million in green infrastructure and clean technologies and partnering with the private sector to support demonstration and deployment of new charging stations for electric vehicles, as well as refuelling stations for alternative fuels such as hydrogen and natural gas.

These measures take advantage of the fact that over 80% of Canada's grid is powered by non-emitting electricity. The Pan-Canadian Framework also commits provincial and territorial governments to work to improve efficiency in Canadian buildings and develop new building codes. The goal is to develop the net-zero buildings of the 21st century.

And in the area of clean technologies, our government will make smart and strategic investments in research and development and in supporting commercialisation.

The global market for clean technology is projected to increase significantly. Canadian companies are poised to provide solutions to global challenges.

Canada is home to 13 of the 2018 Global Cleantech Top 100 list that was recently revealed at the annual Cleantech Forum San Francisco. The government is working to help our private sector seize new opportunities with large investments in clean energy, green infrastructure and clean technology.

Meeting our climate commitments and investing in clean growth are central to our plan to grow our economy as we achieve our environmental goals.

Canada will continue to advance global momentum on climate action through its international efforts. The Powering Past Coal Alliance, which we helped kick-start is only the most recent such example.

Last year, we published final regulations of the Kigali Agreement – an amendment to one of the most successful environmental treaties ever, the Montreal Protocol, which Canada helped organise 30 years ago.

Kigali will reduce hydrofluorocarbons used in refrigerators and air conditioners that can be thousands of times more powerful than carbon dioxide in inducing climate change.

Canada is also helping developing countries access clean energy and climate solutions. In 2016, we committed to contributing $2.65 billion over the next five years to this goal.

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.

Climate change is as much an economic issue and a social one as it is environmental. It is as much about transitioning to ways of living and working that do no environmental harm as it is about protecting our natural world from further damage. ■

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Canadian education and Indigenous peoples

Vice President of the Canadian Society for the Study of Education, Dwayne Donald shares his expert perspective on Canadian education and research on Indigenous peoples

Over the past decade in Canada, Canadians and Indigenous peoples have together been critically scrutinising the character of the historic and current relationships linking them. This broad social, cultural, educational and political movement was instigated by the Truth and Reconciliation Commission on Indian Residential Schools that began in 2010. The Commission brought focus on the painful history of Indian Residential Schools in Canada and the multiple intergenerational traumas suffered by the peoples and communities subjected to them.

Indian residential schools were founded in the 1880s in Canada based on the belief that Indigenous children needed to be removed from their families and communities and forced to assimilate to more modern ways of living if they were to become useful citizens. In this way, their usefulness as citizens was understood as dependent on how well they could learn to imitate Canadians.

This institutional and societal practice of pathologising Indigenous peoples and their children is deeply rooted in Canadian culture and tremendously influential in the formation of policies and initiatives intended to address the educational needs of Indigenous peoples and communities. Up until very recently, most educational initiatives focused on Indigenous themes and issues were couched in logic that denies the oppressive history and instead characterise the educational struggles of Indigenous peoples as resulting from their own separate cultural preoccupations. Such work is founded on the assumption that Indigenous students will be more motivated to stay in school if they are provided opportunities to connect in some way with their own cultures and languages.

Ironically, however, failure in school is also considered a consequence of Indigenous children clinging to ancestral cultures that render school meaningless to them. By persistently framing the educational struggles of Indigenous children as their own strange cultural problem, Canadian educational policymakers and leaders have effectively hidden their own complicity in the perpetuation of colonial violence against Indigenous peoples. By fixating on the problematics of Indigenous cultures, they have failed to consider Canadian culture as also part of the problem.

> "...there is an urgent need to expand the realm of teaching and learning in Canadian educational institutions so that people can be provided with meaningful opportunities to come to terms with the difficult implications of the Calls."

Canadian educational policymakers and institutions have recently been challenged to shift this unethical relationship and initiate a different kind of relationship with Indigenous peoples when the Truth and Reconciliation Commissioners issued 94 Calls to Action to redress the damaging legacies of the residential schools and advance processes of reconciliation in Canada.

The Calls to Action (2015) seek to facilitate depth engagement with Indigenous themes, experiences and worldviews as a societal commitment while simultaneously fostering ethical exploration of the possibilities such engagement provides in imagining new ways of living together that are not fully circumscribed by colonial logics. Educational institutions across the country and at all levels are expected to implement measures in response to the Calls on an ongoing basis.

Thus, there is an urgent need to expand the realm of teaching and learning in Canadian educational institutions so that people can be provided with meaningful opportunities to come to terms with the difficult impli-

cations of the Calls. There are three general ways to understand this need. First, Canadians have not been taught oppressive colonial histories involving their own country and naturally resist seeing themselves and their nation implicated in them. This resistance, its various manifestations and the pedagogies associated with helping people unlearn colonialism in the Canadian context need to be better understood.

> "Indian residential schools were founded in the 1880s in Canada based on the belief that Indigenous children needed to be removed from their families and communities and forced to assimilate to more modern ways of living if they were to become useful citizens. In this way, their usefulness as citizens was understood as dependent on how well they could learn to imitate Canadians."

Second, thoughtful attentiveness needs to be given to the experiences of Indigenous students participating in these reconciliation processes and how it feels for them to be the subjective data of their own studies.

Third, careful consideration needs to be given to the possibility that foundational Indigenous wisdom traditions can provide insightful reconciliatory guidance on how to reimagine education and reconceptualise the human being at the heart of the educative processes in Canada. The hope is that responses to the Calls to Action from educational institutions and policymakers in Canada can be inspired by the very knowledge systems that the Indian Residential Schools were designed to eradicate. ■

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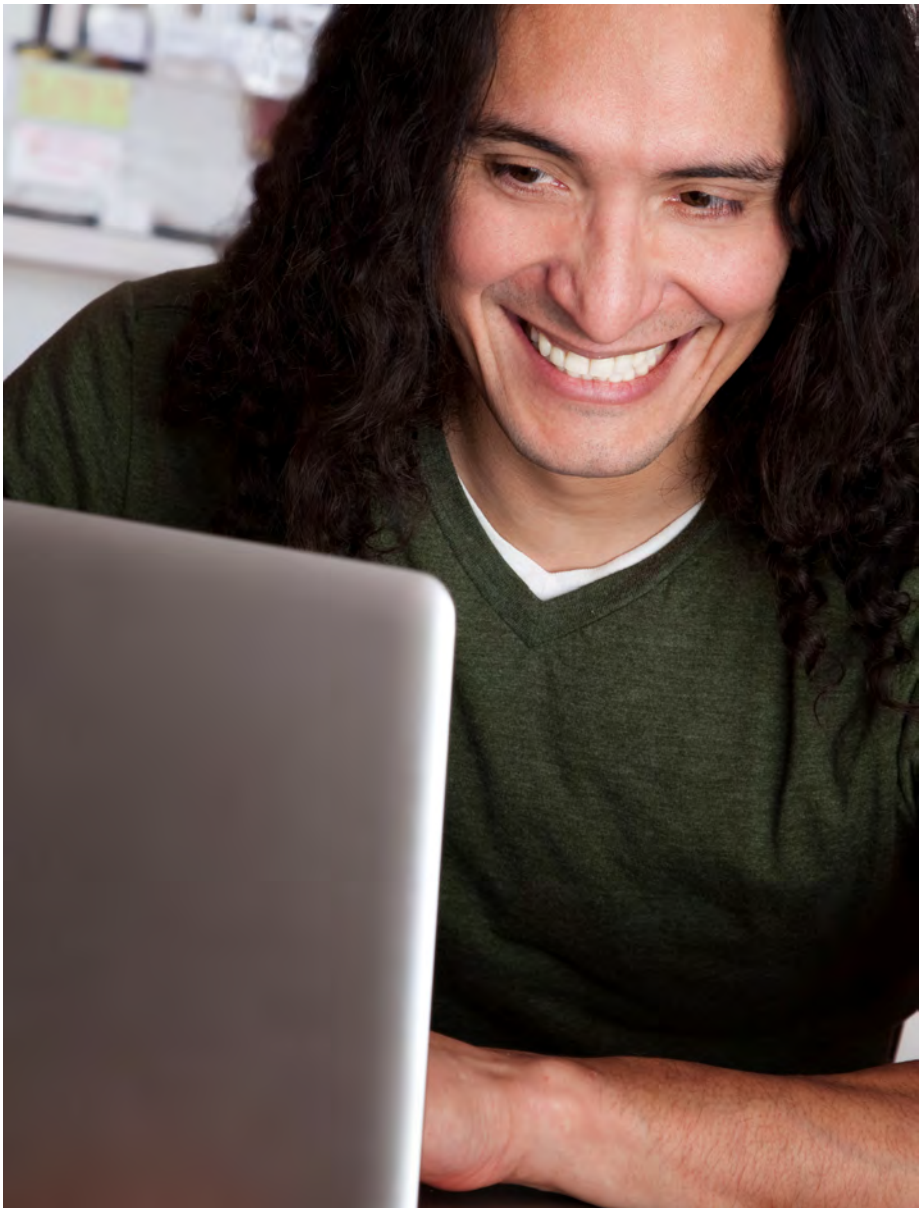
Non-Indigenous individuals' responsibilities within higher education contexts

Dawn Zinga, from the Department of Child and Youth Studies at Brock University explore the responsibilities of non-Indigenous individuals within higher education settings and the inequalities that exist

As a non-Indigenous scholar working in the area of Indigenous education, I spend a lot of my time thinking about my own role in perpetuating inequality within higher education and answering questions posed by non-Indigenous faculty, staff, and students. These questions usually fall into two broad categories. The first category consists of questions about why I am raising an issue or why something is important, while the second category tends to focus on questions about what individuals can do now, so that they know about the inequities that exist. These two categories of questions point to some interesting aspects about the responsibilities of non-Indigenous individuals' within higher education settings. One of the first responsibilities is to become educated about the realities of Indigenous peoples and related the systems of inequality. The second responsibility that I will focus on is what to do with the knowledge that you gain when you become educated.

Starting with myself, I am a several-generations-removed immigrant to the ancestral lands on which I reside and I have experienced a position of some privilege in the mainstream structures of society, such as education, health services, and other governmental systems. While I grew up in a blue-collar home and experienced the discrimination that can be associated with class and being a girl, I was afforded many privileges and rarely had cause to question that I belonged in the classrooms that I occupied. I frequently saw myself and my life experiences reflected in the classroom and my experiences within society. From a young age, I had a questioning mind and often challenged teachers about why some voices and some life experiences were not represented in the curriculum or were represented in very narrow and proscribed ways. Through my own search for knowledge and the generous teachings of my Indigenous colleagues, I became aware of the systems of racism and inequity experienced by individuals who are minoritised by the mainstream systems of privilege and discrimination that continue to be reinforced throughout society and particularly within systems of education. In my role as a university professor, I am also responsible for exposing undergraduate and graduate students to these systems of inequity and to challenge their taken-for-granted assumptions.

Some of my students resist any challenges to their understanding of society and the status quo and remain facing the first responsibility of education. Other students engage in the teaching but sink into guilt and seem paralysed by the immensity and



complexity of the issues thy have just learned exist. The second responsibility of what to do with the knowledge once you have learned it is easier to address than the resistance to learning that the world does not necessarily operate in a way that you thought that it did, and that with or without your knowledge, you have occupied a position of power and privilege. The first thing for non-Indigenous individuals to realise is that guilt is an emotion that will not be helpful. It must be experienced but in the end we are not responsible for the actions of those who preceded us, but we are responsible for how we address the legacy that was left behind. Essentially, non-Indigenous individuals must focus on how to act on the knowledge that has been gained.

Non-Indigenous individuals have a choice. They can choose to close their eyes to uncomfortable realities and continue on perpetuating them or they can chose to use their individual voices to make a difference. Using one's voice can be as simple as speaking up when an inequality is being perpetuated, or challenging a policy that negates other people's experiences or lived realities. It can be exposing others to knowledge they may not be aware of or supporting someone when that person's viewpoint is being shut down as invalid or irrelevant. Sometimes it can be listening to another perspective and being open to being challenged and educated about how your own actions or lack of action may have reinforced inequalities or alienated Indigenous individuals.

Addressing these two responsibilities within educational contexts can lead to educational settings in which Indigenous students and other Indigenous individuals feel welcome and accepted. It can open up important spaces to talk about ways of moving forward together towards positive change that does not reproduce or perpetuate systems of inequality. While I have focused on higher education contexts, this can also be extended to other educational contexts. Making a choice to address these responsibilities daily is a choice to move beyond resistance and guilt to positive action and strong relationships that can help us all negotiate a new future of education for all students.

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From wheelchair to high heels: Realising the potential of stem cells

Dr Michael A Rudnicki, CEO & Scientific Director at the Stem Cell Network gives an expert view on a new era in health care, powered by stem cells

In 1996, a 21-year-old aspiring police officer, Jennifer Molson, was diagnosed with aggressive multiple sclerosis (MS). Within five years, Jennifer was unable to manage everyday tasks, including cutting her food and taking a shower. The prognosis was that she would live her life in a wheelchair and require constant care. Dr Mark Freedman from The Ottawa Hospital was Jennifer's neurologist. He and his research partner Dr Harry Atkins, a clinician/researcher, enrolled Jennifer in a clinical trial that took her stem cells, purified and fortified them and after extreme chemotherapy to knock out her immune system, returned the stem cells to rebuild a new, disease-free immune system. Today, with all traces of the disease eradicated, Jennifer has been cured. She has her life back – she works, enjoys family, skis and wears her high heels proudly. Jennifer's story is extraordinary and is a demonstration of what can be achieved through the application of stem cells.

Stem cells are powering a new and exciting scientific field – regenerative medicine – and this field is expected to have a global market value of $53.7 billion by 2021. Stem cells are special, as they can make many copies of themselves and give rise to more specialised, or "adult" cells. We now know that most tissues contain their own rare populations of adult stem cells that help with maintenance and repair. One particular type of stem cell is especially powerful: known as the pluripotent stem cell, it is akin to a blank slate, capable of making any cell type in the body. Stem cells are invaluable to researchers for their ability to model development and diseases that may otherwise be difficult to study and have vastly expanded our understanding of how the body heals or succumbs to disease. This knowledge is fuelling the delivery of new ways to regenerate or repair cells, tissues and organs. The potential is extraordinary for fighting chronic diseases and illnesses that cost the Canadian healthcare system upwards of $190 billion annually.

In Canada, stem cell-based treatments are being utilised to fight severe blood disorders such as leukaemia, as well as aggressive multiple sclerosis and some rare diseases. And this is just the beginning. With support from the Stem Cell Network, clinical trials are underway in British Columbia and Alberta that are testing a novel stem cell therapy for type 1 diabetes. The research from these trials may change the way those who have type 1 manage the disease by eliminating constant measuring of blood sugar levels and eliminating insulin dependence.

> "Regenerative medicine is at a tipping point in Canada. It's time to build on our foundation of scientific excellence and harness the benefits of regenerative medicine for the health of Canadians and the economic prosperity of our nation."

In Montreal, researchers and clinicians are working with a specialised molecule and state-of-the-art technology that allows stem cells found in cord blood to be expanded or grow. This is critically important work for developing a stem cell product that is not only affordable but safe and effective for the treatment of blood diseases, particularly for patients who are currently ineligible or do not respond well to current therapies.

Jurisdictions around the world recognise the benefits of investing in stem cells – economic, population health and individual patient outcomes. California, Japan and the United Kingdom are all fighting to lead the field that matters the most for health. Canada is well positioned to compete; in fact, it was two Canadians who proved the existence of stem cells in the early 1960s. And it was two more Canadian scientists who were behind the 2016 launch of BlueRock Therapeutics – a multi-national biotech supported with a USD$225 million Series A investment. BlueRock is focused on bringing forward

Image: © Dwayne Brown Studio / The Ottawa Hospital

stem cell-based therapies for the treatment of cardiovascular and neurological conditions. Powered with Canadian ingenuity, we know this company will succeed.

> "Stem cells are special, as they can make many copies of themselves and give rise to more specialised, or "adult" cells. We now know that most tissues contain their own rare populations of adult stem cells that help with maintenance and repair."

It is just the beginning for stem cells and regenerative medicine. The challenge is to ensure the regulatory environment will allow for stem cell therapies to move through the clinical trials process effectively. We also require stable and predictable funding for research so that next generation therapies can be realised. Canada's small but growing regenerative medicine sector requires support to scale-up and commercialise its products. It also requires access to a skilled and talented labour pool. And of course, the healthcare system must evolve and be able to integrate innovative therapies as the new standard of care.

Regenerative medicine is at a tipping point in Canada. It's time to build on our foundation of scientific excellence and harness the benefits of regenerative medicine for the health of Canadians and the economic prosperity of our nation. ■

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Cannabis developments in North America

Writer, medical cannabis patient, a grower and budtender for GrassRoots Medicinal in Squamish, Caleb McMillan, provides his thoughts on cannabis developments in North America today

American states nullifying federal laws on cannabis prohibition. Canada poising to legalise the herb sometime this year. There is a sense of moving forward. But a scratch below the surface reveals another story.

Alcohol companies, police unions and private prisons have all lobbied against legalisation in California. A pharmaceutical company gave $500,000 to a group opposing legalisation in Arizona, only to later get DEA approval for a synthetic form of cannabis. Coupled with an unfriendly administration in Washington DC, complete with an Attorney General who has vowed to axe the policy of leaving legalised states be, the outlook in America is grim and uncertain.

In Canada, former police chiefs and politicians are licensed commercial sellers of medical cannabis. While an already existing market, colloquially known as "BC Bud," are so-far locked out and referred to as organised crime, indistinguishable from biker gangs.

Yet, despite this, cannabis continues to provide relief to patients and recreational consumers alike. Whether one uses for therapeutic or medicinal purposes, everyone has cannabinoid receptors in their body. The scientific literature is quite clear we're dealing with a substance far removed from tobacco or alcohol.

For these reasons and others, cannabis should be fully embraced by the global medical profession. Cannabidiol (CBD) oil is already halting seizures within minutes of ingestion. From my experience working at a dispensary, countless patients have weaned off medication that treats inflammation but with damaging side effects. I, myself, reversed anxiety and depression with the non-psychoactive CBD oil. But a holistic approach to the plant includes Tetrahydrocannabinol (THC), the component that gets users "high" or "stoned." It is THC that shows promise in treating cancer tumours.

If the medical community requires clinical studies and drug identification numbers before cannabis can go

"Cannabidiol (CBD) oil is already halting seizures within minutes of ingestion. From my experience working at a dispensary, countless patients have weaned off medication that treats inflammation but with damaging side effects."

mainstream, then so be it. Clinical trials and cannabis testing are already underway by companies like CannaTech Global, CI Therapeutics, EndoCRO and Steep Hill.

The idea is simple: put government money towards research and ram through legalisation in a highly controlled and regulated manner. One that considers liability issues since the medical profession needs to be able to study and test cannabis without health risks to their patients or broader public health and safety.

But the issue is complex. The standard steps drug companies take from research to market don't apply here. Aside from its centuries-old history as a medicine, prohibition has stunned our knowledge of cannabis and (in consequence) has made the plant a special "bottom-up" grassroots medicine rather than a traditional "top-down" pharmaceutical.

Meaning, it requires looking at government policy differently rather than trying to shoehorn cannabis into traditional regulatory models.

Cannabis is simple and effective. Whether vaped, consumed as an oil, or in a tincture — anecdotal evidence is abundant. It is now time for the medical profession to catch up. But having governments throw money at the issue is like trying to hammer in a screw.

Public policy would be better served to cultivate the underground cannabis industry that exists in North America. These are your cannabis experts, after all. Additionally, gutting some regulations governing the actions of medical professionals and patients will promote risk-taking and thus innovation and opportunity. But a culture overly concerned with legal liability makes this suggestion a hard sell. ■

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How trusted data is helping to liberate the power of medical cannabis

Bradley Moore, CEO of GCAC discusses how artificial intelligence and blockchain (trusted data) solve the paradox of limited medical cannabis data and anecdotal user information

Jane Carter is an active young woman in her 30s who works as a software engineer, likes the outdoors and is planning to raise a family. Jane also has epilepsy.

As someone who has dealt with the condition her whole life, Jane is accustomed to maintaining control over her seizures. However, when her usual medication started to feel less effective, Jane confessed her concerns to a friend, who suggested medical cannabis as a potential treatment. Jane had never considered this possibility, but when she tried to learn more about it, she struggled to find trustworthy sources. Therefore, she turned to her physician, Dr Lisa.

Dr Lisa told Jane that although the benefits of cannabis have been discussed among doctors for a few years, she herself hadn't yet seen any evidence from reputable studies showing clinical benefits of cannabis. The doctor explained that as a practitioner and a scientist, she liked to have solid evidence and clinical experience before she prescribed medication to her patients; therefore, she would not prescribe cannabis to treat Jane's epilepsy.

Jane's story is not unique and illustrates the medical cannabis paradox.

The medical cannabis paradox

The medical benefits of cannabis – including pain management, seizure remediation, muscle spasms management and others – have been well known for centuries. However, over the past century, cannabis has become a proscribed substance and treated as a law-enforcement challenge. As a result, it has become difficult for researchers to get approval and funding for properly controlled cannabis studies and users are unable, or unwilling, to share their experiences. Consequently, doctors and other practitioners lack trusted information on which to base clinical decisions.

Altogether, these factors have led to significant under-prescription of medical cannabis, there has been a large, unfilled demand for quality research, new product delivery methods and consumer information on the uses and effects of this substance.

The Citizen Green community

In an effort to bring together the global medical cannabis community and motivate its members – including patients, practitioners, scientists, cultivators and manufacturers – to share their knowledge of and experiences with medical cannabis, Global Cannabis Applications Corporation (GCAC) has developed the Citizen Green platform. This cutting-edge platform will facilitate the sharing of information between consumers, caregivers and researchers, as well as regulators and members of other industries, such as healthcare and cosmetics.

The Citizen Green platform is powered by the following technologies: CannaCube database, artificial intelligence (AI), mobile apps and blockchain.

AI, Chatbot and CannaCube

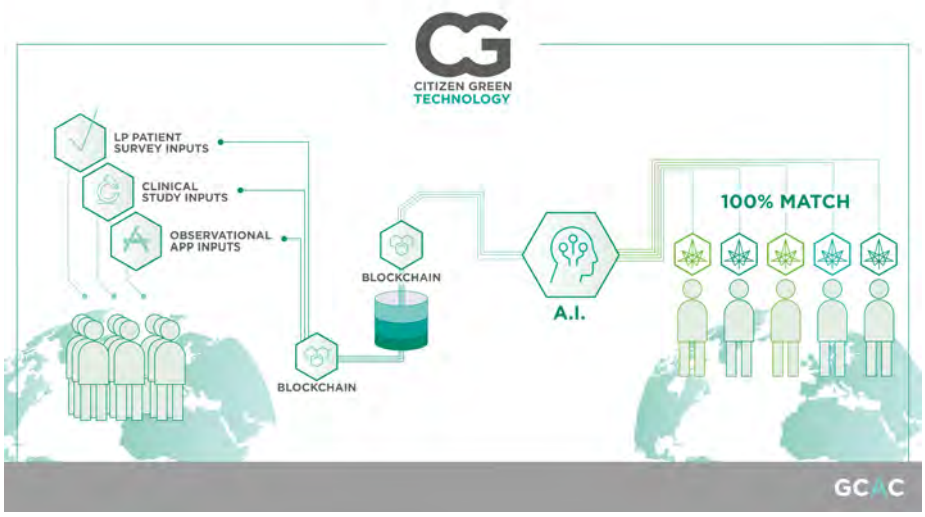
Artificial intelligence provides GCAC with the ability to bring to life all of the data collected and managed.

AI is used for multiple applications in our platform: chatbot, advanced analytics, predictive analysis and machine learning tools. And its capability to integrate observational and clinical research findings allows us to offer deeper insights and better outcomes for patients and the entire community.

The AI models the relationship between patients' demographics and medical conditions, medical cannabis features and treatments effectiveness, thereby closing the loop between "pain and strain". (TM pending)

Sanna, GCAC's proprietary chatbot, facilitates stronger engagement with its adaptive user experience and personalised recommendations via our apps, CannaLife and Prescriptii. The chatbot will grow smarter over time as it will bridge missing information in users' profiles.

CannaCube is GCAC's medical cannabis database. Equipped with



world-class data encryption and storage, this database curates 'noisy' data aggregated from CG apps, doctor references, social listening and various industry inputs against thousands of clinical study reports for validation and expansion of the data sets.

Mobile Apps

The client-facing components of Citizen Green are two easy-to-use mobile apps: CannaLife and Perscriptii. Connected by the CannaCube database, these apps collect and share 360-degree data relating to medical cannabis production, research, prescription and usage.

CannaLife is an app for networking, sharing peer-to peer-feedback and searching experiential user data related to cannabis consumption and consumer behaviour. Using screen capture technology, users can find information on medical cannabis, create a post and share it with other like-minded users. Then, when seeking information, users can call upon Citizen Green's chatbot, Sanna, who, coupled with the world's first cannabis-specific Google search engine, helps them find answers to specific health and cannabis queries.

Prescriptii is the first consumer-facing app for medical cannabis license holders. It takes users through an ailment-related questionnaire and based on CannaCube analysis, recommends the appropriate products to the condition described. An interactive map helps users to find nearby retailers that offer the recommended products.

Sanna, the chatbot, encourages users to evaluate their experience with the cannabis prescription. Fed back to CannaCube this information optimises further recommendations and can help patients and their practitioners to assess.

Blockchain

The GCAC blockchain gives medical cannabis users ownership over their data in a secure and encrypted environment. Unlike centralised applications, blockchain uses a distributed, decentralised digital ledger to record all transactions. GCAC recently released a White Paper discussing the digital token it is introducing on the blockchain to incentivise users.

How CannaLife Changed Jane's Life

When Jane saw a news report about the CannaLife app, she was intrigued enough to install it and as she familiarised herself with the Citizen Green community, she found many stories from other epilepsy sufferers. This made her reconsider how cannabis might help her own condition.

Jane presented Dr Lisa with CannaLife, showing her the large database of anecdotal patient information, as well as research studies and manufacturers' results. After reading a large number of consumer testimonials and some of the research, Dr Lisa felt confident enough to prescribe Jane a medical cannabis license, using the Prescriptii app as a guide. Three months later, Jane's epilepsy symptoms had decreased considerably, and she very rarely had seizures.

As she works with Jane on her progress in Prescriptii, Dr Lisa is getting a feel for what other treatments work best with medical cannabis. She will definitely be using the app as part of her diagnostic toolkit going forward.

Jane, meanwhile, has returned to a much-improved quality of life. She is back to coding, rock-climbing and considering with her husband whether it is time to try for a baby.

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Medical cannabis advocacy and education

Board Member for Canadians for Fair Access to Medical Marijuana (CFAMM), Peter Thurley, shares his views on medical cannabis advocacy and education issues

Canadians for Fair Access to Medical Marijuana (CFAMM) is a patient-run medical cannabis advocacy and education organisation that began when founder and outgoing Executive Director Jonathan Zaid ran into access barriers in obtaining his legal medicine. Suffering with a condition known as new daily persistent headache (NDPH), Zaid found that of the myriad of options offered by various doctors, only cannabis provided him with the relief he needed. Instead of taking away his ability to function (a recurring criticism of cannabis-use), it provided him with new ways to thrive.

While attending the University of Waterloo in 2014, he successfully petitioned his student union to include his medical cannabis in their health care coverage plan, becoming the first person to obtain insurance coverage for cannabis in Canada. Since then, he has grown CFAMM into the leading patient advocacy group in Canada. With a large advisory team of patients and working with leaders from across both activist circles and industry boardrooms, CFAMM has highlighted affordability and access issues within the current medical cannabis regime, as well as worked with government, official cannabis growers known as licensed producers and the insurance industry to set up insurance best practices.

While CFAMM has been successful in many measures, there is still a lot of work to do, particularly around affordability issues. Recently, the most pressing issue has been the Liberal government's stated intention to apply either a $1/gramme or 10% excise tax to both the existing medical market and the recreational market, set to come online in early fall 2018.

Medical cannabis has been legal in Canada for more than 15 years, won largely through hard fought court battles, several of which were heard in the Supreme Court of Canada. Because of longstanding prohibitionist policies dating back to the 1930s, cannabis has not undergone the usual series of clinical trials that are usually required to prescribe a product as a medicine.

Unlike other legal medications, there is no Health Canada approved Drug Identification Number (DIN) for the product, meaning that it is not eligible for any provincial or federal drug coverage. As a result, cannabis is the only medicine in Canada to which sales taxes apply. With scarce insurance coverage and average costs between $7 - $11/g, costs for patients add up fast, especially for persons with chronic illness(es) who live on a fixed government income.

> "If there are any lessons the global community should take from the Canadian cannabis experiment, it should be that placing stigma at the feet of medical patients in a half-witted attempt to make an example out of them is a poor way to earn the trust of existing patients. At the end of the day, it will always be medical cannabis patients who will form the backbone of any future open global cannabis markets. Governments risk crossing them at their peril."

Claiming a desire to maintain a fully functional medical market, Finance Minister Bill Morneau introduced the excise tax by explicitly saying that the Government of Canada does: "not want the taxation levels to be an incentive for people to utilise [the medical] system inappropriately."

There is limited evidence to suggest that recreational consumers rely on the existing legal medical system to provide the product they want, choosing instead a broken illicit market. Indeed, this new tax accomplishes

little else than to further increase costs for patients who rely on cannabis as a medication and risks subjecting them to further stigma.

In response to this, CFAMM launched a National #Dont-TaxMedicine campaign to soften the Finance Minister's position before the 2018 budget. Joining together with the Arthritis Society of Canada, Jonathan Zaid and team amassed more than 16,000 signatures in two months, sending a letter and petition to each signatories' local Member of Parliament, as well as the Minister of Finance. By using a collaborative approach with industry partners and health care patient agencies, CFAMM effectively harnessed the online support of hundreds for visits with local elected officials, where each person delivered the consistent message that cannabis is an important part of their medical treatment.

Despite this work, which also included a protest in front of the Minister's constituency office, the 2018 budget contained little relief for patients across Canada. While token overtures, such as the exemption of low-THC and CBD only cannabis products, were made, Prime Minister Justin Trudeau and his Minister of Finance stuck to the party line.

In a recent column in the Ottawa Citizen, Dr Jenna Valleraini, a post-doctoral researcher whose work focuses on cannabis markets in Canada, notes that the Liberal government's approach is ultimately "wrapped up in ideas of stigma and distrust of cannabis' potential as a medicine, likely tied to its "recreational" use. ... cannabis comes with a relatively low risk profile and it reportedly helps many patients achieve a better quality of life. We should support responsible access to medical cannabis, rather than exacerbate issues around access, affordability and coverage."

If there are any lessons the global community should take from the Canadian cannabis experiment, it should be that placing stigma at the feet of medical patients in a half-witted attempt to make an example out of them is a poor way to earn the trust of existing patients. At the end of the day, it will always be medical cannabis patients who will form the backbone of any future open global cannabis markets. Governments risk crossing them at their peril.

As Jonathan Zaid prepares to pass the reins over to newly appointed President and CEO James O'Hara, CFAMM remains committed to keeping the rights of medical cannabis patients front and centre.

If you are Canadian and haven't already, please register your support for the #DontTaxMedicine campaign by signing the petition over at http://donttaxmedicine.ca. If you need support visiting your elected officials, send CFAMM a note at info@cfamm.ca and we would be happy to provide you with some resources for a productive meeting.

"Medical cannabis has been legal in Canada for more than 15 years, won largely through hard fought court battles, several of which were heard in the Supreme Court of Canada. Because of longstanding prohibitionist policies dating back to the 1930s, cannabis has not undergone the usual series of clinical trials that are usually required to prescribe a product as a medicine."

Peter Thurley became a cannabis patient in 2015 after the removal of a 25lb desmoid tumour that burst his bowels and left him with significant neuropathic chronic pain, a panic disorder and PTSD. After seeing a reduction in opioid use and an increase in quality of life, Peter became an accidental medical cannabis advocate. He lives in Kitchener, ON and has recently been appointed to CFAMM's Board of Directors. ■

CANADIANS FOR FAIR ACCESS TO MEDICAL MARIJUANA

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Brock University

Department of Child & Youth Studies

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

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

Watch the CHYS website for more details:

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

www.brocku.ca