ISSN 2055-7612 • February 2018

# OPEN ACCESS GOVERNMENT

## NORTH AMERICA ANALYSIS

10

## ADVANCING THE FRONTIERS OF COMPUTING

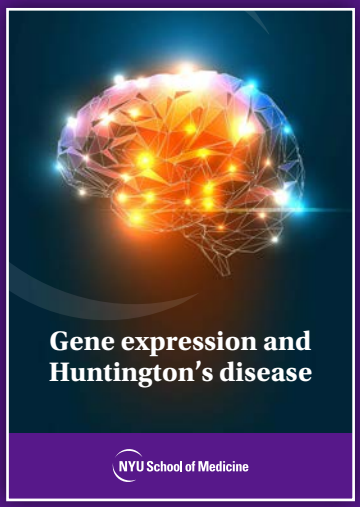
ERWIN GIANCHANDANI AND MICHAL ZIV-EL FROM THE NATIONAL SCIENCE FOUNDATION (NSF) PROVIDE A FASCINATING INSIGHT INTO HOW FUNDAMENTAL COMPUTING RESEARCH IS PROFOUNDLY TRANSFORMING OUR LIVES

## 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




**Click here to view our ebook**

NYU School of Medicine

**Jonathan Miles**
Editor

**Production Coordinator**
Nick Wilde

**Designers**
Andrew Bosworth
Ben Green



ADJACENT
DIGITAL POLITICS LIMITED

**Adjacent Digital Politics Ltd**
Datum House
Electra Way
Crewe Business Park
Crewe
Cheshire CW1 6ZF

Registered in England & Wales.
Company Reg No. 8667479.
VAT Registration No. 169 9152 64.

OPEN ACCESS

# INTRODUCTION

Welcome to the February 2018 edition of North America Analysis. One of the highlights of this packed edition is a fascinating guest article from Richard F. Green, Director, Division of Astronomical Sciences at the U.S. National Science Foundation (NSF) who explores the wonders of astronomy and the amazing universe of discovery.

Following on, Erwin Gianchandani and Michal Ziv-El from the National Science Foundation (NSF) provide a fascinating observation into how fundamental computing research is profoundly transforming our lives today.

This insightful edition is full of many more profound perceptions, but one that really struck me came from the U.S. Department of Agriculture. Jaime Adams, senior advisor for international affairs argues that we need open data policies, especially in government so that we can feed the world. She expands on this point further, by saying: "This global perspective will help identify existing data and data gaps and sharpen the focus on how open data can foster innovation and collaborative research, enabling comprehensive solution sets."

In further inspiring US content, Senior Research Advisor from the American Association of Geographers, Yonette Thomas, Ph.D. discusses the important role that geography can play in addressing global health needs, in terms of both research and practice.

Then, heading up the Canada section, The Honourable Marc Garneau, Canada's Minister of Transport explores the Oceans Protection Plan and how this is transforming marine safety in Canada today. Also, Dr. Fang Liu, Secretary-General of the International Civil Aviation Organization, explores how international aviation contributes to Agenda 2030 by empowering local sustainable development through global connections.

I hope that you find this wide-ranging edition both thought-provoking and useful. I would certainly welcome any comments you have on this February 2018 edition. Please also feel free to drop me a line about any suggestions for content you might like to supply in the future.

**Jonathan Miles**
**Editor**

@Jonathan_AdjDig

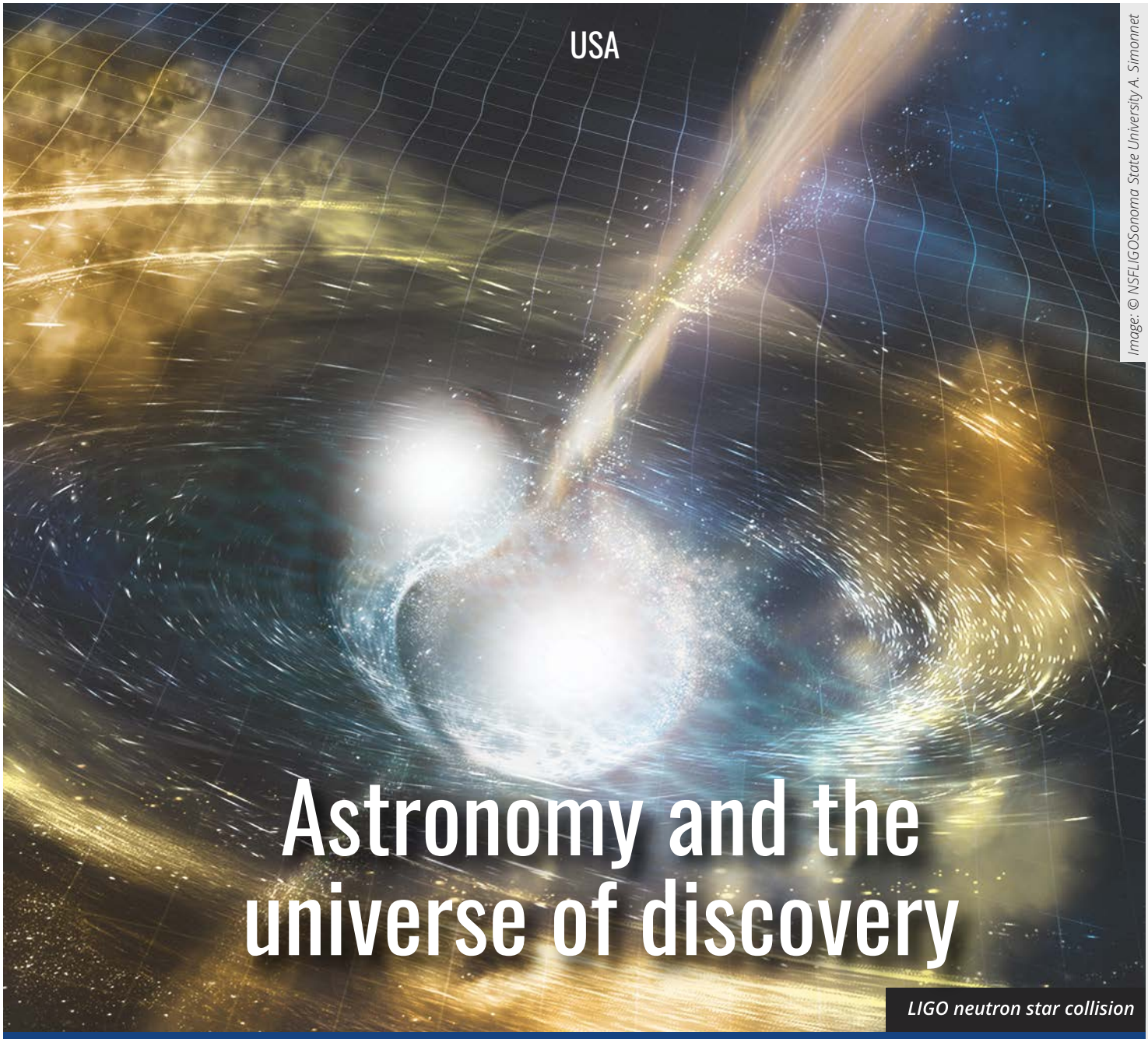
# CONTENTS



## USA



## CANADA





# Astronomy and the universe of discovery

*LIGO neutron star collision*

**Richard F. Green, Director, Division of Astronomical Sciences, U.S. National Science Foundation (NSF) explores the wonders of astronomy and the universe of discovery**

In October 2017, telescopes across the globe observed a kilonova radiating from a galaxy 130-million-light-years from Earth. Thousands of scientists saw the event unfold, the explosive aftermath of paired neutron stars colliding. Selected by Science Magazine as its Breakthrough of the Year, it was the first time in history that the world's telescopes were guided to a new discovery by gravitational wave detectors and it ushered in a new era for astronomy.

The merger's initial detection by NSF's Laser Interferometer Gravitational Wave Observatory (LIGO) and Europe's Virgo facility was exciting, but the historic breakthrough was the rapid deployment of other observatories to identify and then image, the radiating emissions. Six research teams independently made the initial optical identification; four were based in the United States and NSF Astronomy supported all four. NSF continues to highlight this multi-messenger revolution as one of its major cross-cutting themes: Windows on the Universe.

The NSF Division of Astronomical Sciences has a mission to promote such excellence in U.S. ground-based astronomy. Toward that goal, the Division invests in three approaches: support the programmes of individual investigators, provide access to world-class research facilities and datasets; and enable the development of new instrumentation and next-generation facilities – all through competitive merit review.

*Aerial of CTIO in Chile*

**The result? Breakthrough science**

For example, on December 6th, 2017, Nature published online the discovery of the most distant quasar yet detected, a massive radiator of energy powered by an 800-million-solar-mass black hole. The research team, supported by our division, selected quasar candidates with distinct colour patterns using data from the NSF-supported Dark Energy Camera Legacy Survey on the NSF Blanco 4-metre telescope. The discovery was important not only for what it revealed, but also for the questions it raises. The black hole is from a time when the universe was only 5% of its current age – much less time than current models predict for a small black hole to grow to that size by accreting that much mass.

Also last year, the Atacama Large Millimeter Array (ALMA) captured the telltale signature of the cold gas and dust energised by newly formed stars. While such a signature is not uncommon, this discovery also raised interesting questions: the newly formed stars are in the immediate vicinity of the four-million-solar-mass black hole in the centre of our Milky Way Galaxy. Conventional wisdom suggests the powerful radiation and particle jets from that black hole disrupt the cold condensation of gas that leads to new stars, so the discovery is a surprise and a puzzle.

> "The NSF Division of Astronomical Sciences has a mission to promote such excellence in U.S. ground-based astronomy. Toward that goal, the Division invests in three approaches: support the programmes of individual investigators, provide access to world-class research facilities and datasets; and enable the development of new instrumentation and next-generation facilities – all through competitive merit review."

And perhaps most widely reported and tied to the nation's most popular astronomical event in some time, NSF's National Solar Observatory (NSO) recruited citizen scientists to track the U.S. solar eclipse in August 2017 for the entire duration of its transit. The resulting video captured the public's imagination and raised NSO's profile and provides the longest data set of its kind.

This year, NSO also drew attention for its recent development of state-of-the-art techniques for sharpening real-time images of the sun to correct for the blur of the Earth's turbulent atmosphere. The resulting images reach a resolution of 40 km over an extent of 25,000 km on the sun's surface. This same technology applied at the nearly completed Daniel K. Inouye Solar Telescope (DKIST) will achieve 2.5 times sharper imaging, enabling scientists to understand in detail the bubbling of gas that transports heat to the sun's surface along with the magnetic fields that create space weather.

The current flagship facilities in ground-based astronomy are truly multi-national in nature. For example, the three executives of ALMA are NSF, the European Southern Observatory and the National Astronomical Observatory of Japan, with Chile, Canada and Taiwan as collaborators. ALMA consists of 66 radio dishes located at an elevation of 5 km above sea level in the Atacama Desert of northern Chile.

The Gemini twin, 8-metre, optical-infrared telescopes are a fusion of national and international efforts. One of the telescopes is located on Cerro Pachón in northern Chile, while its twin is located on Mauna Kea in Hawai'i. The Gemini Observatory is operated as a partnership among the U.S. (represented by NSF), Canada, Chile, Brazil and Argentina, with South Korea as a limited-term collaborator.

Hawai'i is also the site of NSF's DKIST on the island of Maui, which is generating considerable excitement as it will be the world's largest solar telescope when completed in 2020. It will revolutionise our understanding of the sun's magnetic energy and its impact on space

Image: © NOAO/AURA/NSF

weather and the Earth. The UK and Germany are contributing to the first-light instrument complement.

Similar excitement is building for the Large Synoptic Survey Telescope (LSST), which will be a neighbour of Gemini South on Cerro Pachón in Chile. Its 8-metre primary mirror will focus on a 3-billion-pixel CCD camera, taking exposures every 20 seconds to produce a movie of the sky in multiple colours. It will ultimately measure the detailed properties of dark matter and dark energy, while opening up the uncharted discovery space of the faint transient universe – the explosions and pulsations of distant stars and black holes and the motions of the myriad bodies in the inner and outer solar system.

LSST is supported by NSF, the Department of Energy and an international partnership including 23 countries through the LSST Corporation. Dealing with the flood of data from DKIST and LSST will require a new generation of techniques and data-handling interfaces, another major NSF initiative we call Harnessing the Data Revolution.

Recent advances in astronomy have been heavily driven by discovery from new data, new facilities and state-of-the-art instrumentation. The NSF Division of Astronomical Sciences supports the discoverers and their tools to drive those advances. ■

"The views expressed in this article do not necessarily represent the views of the National Science Foundation or the United States."

**Richard F. Green**
**Director**
Division of Astronomical Sciences, U.S. National Science Foundation (NSF)
Tel: +1 (703) 292 8820
info@nsf.gov
www.nsf.gov/div/index.jsp?div=AST

# Training a global biodiversity workforce for the 21st century

Director of University of Florida Biodiversity Institute, Pamela S. Soltis gives a compelling insight into the world of biodiversity and the importance of training the workforce behind it

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, such as the flow of fresh water and pollination of crops, are less well understood.

Global responses to societal problems arising from the biodiversity crisis (that is, the loss and alteration of biodiversity) suffer from a myriad of problems, ranging from limited access to requisite data to inadequate policies for sustainable use of natural resources. The ongoing assembly of global biodiversity data into computer-accessible formats in publically available repositories (such as GenBank, GBIF (the Global Biodiversity Information Facility), iDigBio (Integrated Digitized Biodiversity Collections), the Atlas of Living Australia, the U.S. National Ecological Observatory Network (NEON) and many others) provides burgeoning resources to address significant biodiversity-related issues in novel ways.

Moreover, sophisticated software and cyberinfrastructure – such as computational and storage clouds, machine learning techniques, workflow platforms for data analysis – are expanding the storage and analytical requirements of a new biodiversity science that is inextricably linked to informatics and data science.

However, the global workforce is generally unprepared to take advantage of these recent developments in data assembly, software design and cyberinfrastructure implementation. Innovative training that combines biological knowledge with data science and informatics is needed to produce a workforce capable of shaping the biodiversity science of the future, as well as meeting the societal needs of a changing planet.

The promise of integrative, data-rich, computational approaches for understanding and conserving biodiversity has never been greater or more attainable. However, most professionals and students alike lack the expertise needed to access and synthesise the wide gamut of resources needed for integrative analyses.

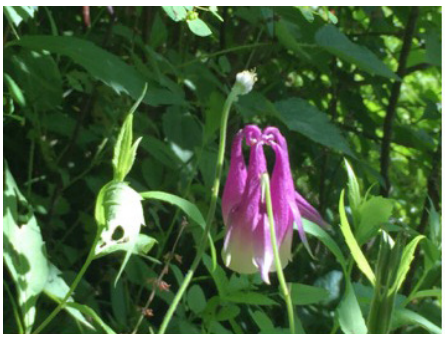
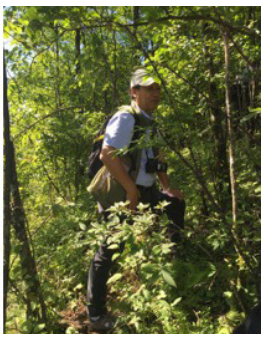
The need for graduate training geared toward rapid changes in biodiversity science and aligned with new developments and changing workforce needs were identified by the American Institute of Biological Sciences in 2015, in a report entitled, “Addressing Biological Informatics Workforce Needs”.

That report noted that students are often interested in training at the nexus of biology and data infrastructure, but few programmes are available, and this training gap is a key factor limiting the integration of relevant data and the development of sustainable knowledge. Programmes to fill this gap and provide synthetic training while stimulating innovative, cutting-edge research is needed.

Addressing the societal problems posed by the biodiversity crisis requires an integrated research and training agenda. Central to this agenda is the development of synthetic conceptual and technical frameworks for understanding the factors that dictate the distributions of species and allow for predictive modelling in the face of climate change. Coupled with this enhanced approach to understanding biological diversity is the design and deployment of robust data science and informatics toolkits for management, analysis, integration and storage of biodiversity data and knowledge.

This marriage of biodiversity and data science will provide critical skill sets for an empowered, 21st-century science and engineering workforce to tackle our hardest challenges for global use of natural resources, with applications to human health and agriculture. Leveraging resources and connecting biodiversity scientists and engineers via an integrated training programme can hasten the development of a workforce to enable the next generation of integrative biodiversity science.

Finally, a successful training programme requires that the products of innovative science should be made available and actionable by the broad-

est community of users, thus emphasising the significant role of communication to scientists, managers, policy makers and the public. In contrast to the classic view of a biodiversity scientist in muddy boots in a jungle, the next generation of biodiversity data scientists will be equally comfortable exploring the jungle, discussing biodiversity theory, developing statistical and machine learning techniques and optimising code for high-performance computing platforms.

The University of Florida (UF) Biodiversity Institute, in partnership with the UF Informatics Institute, has initiated an integrative graduate training programme in biodiversity and data sciences to meet the needs described above. Coursework and research, coupled with real-world experiences such as collaborative practicums and internships, form the core of this programme, which also provides training in communicating with multiple stakeholders.

Partnerships with other institutions and with undergraduate programmes engage diverse participants and extend this new vision of biodiversity science to other disciplines. Fellowships funded by the UF Biodiversity Institute enable students to focus on synthetic research at the intersection of biodiversity and data sciences. Although rare, other programmes uniting biodiversity and data sciences are also springing up elsewhere.

Moreover, many of the skills needed for integrative research can be obtained via short courses, 'boot camps', workshops and webinars, such as those offered by Data Carpentry (www.datacarpentry.org), Software Carpentry (www.software-carpentry.org) and iDigBio (www.idigbio.org). Global collaboration to develop and implement next-generation training in biodiversity science is both encouraged and necessary if we are to meet the societal challenges ranging from food security to invasive species to response of species to climate change.

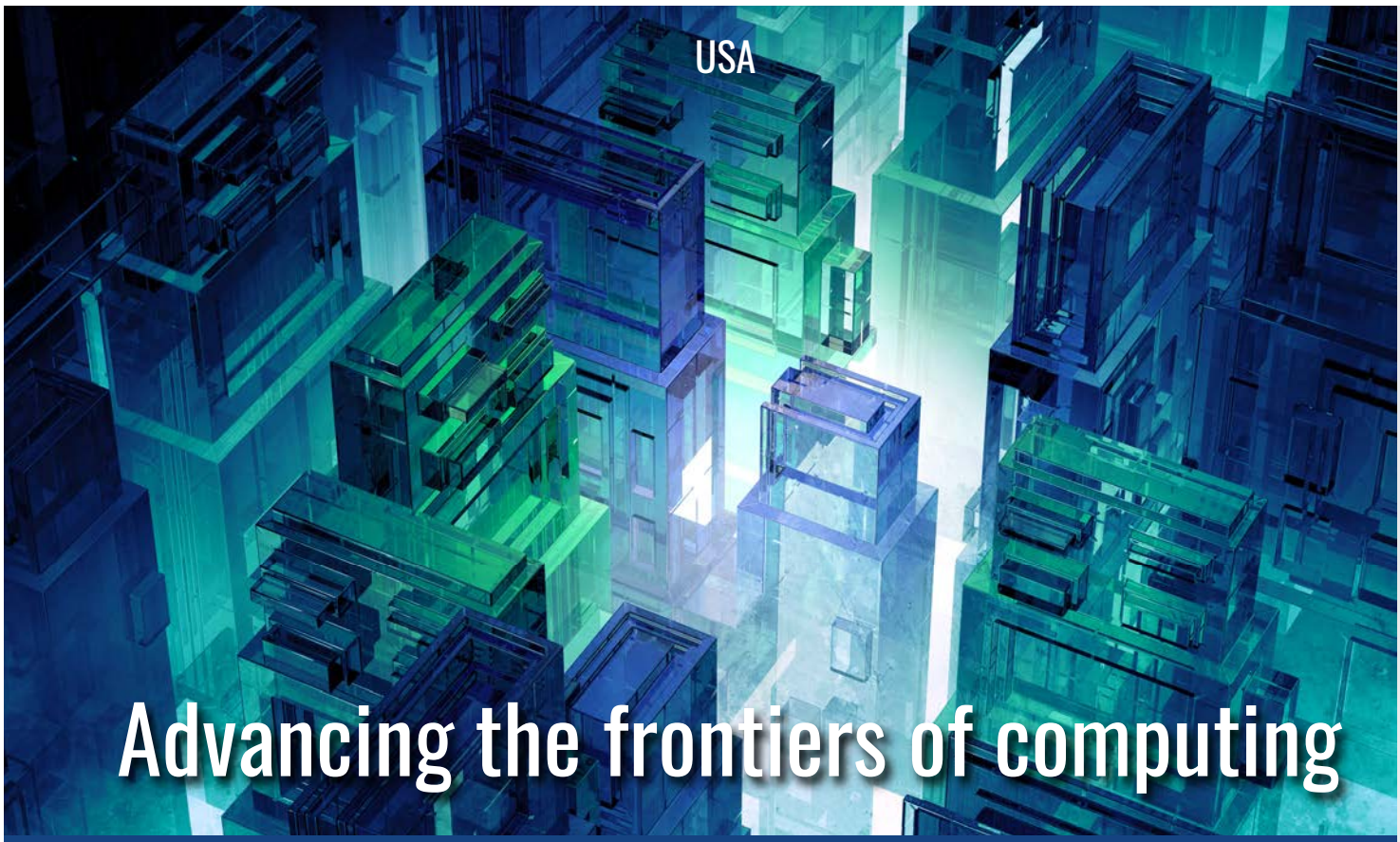
The UF Biodiversity Institute was introduced in the August 2017, issue of Adjacent Government. Launched in 2016 to bring together scientists, social scientists and policy experts to address critical societal issues of the 21st century related to biodiversity, the interdisciplinary UF Biodiversity Institute 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 programmes and shape policy to protect and enhance environmental capital. Newly synthesised knowledge from the Institute is available to individuals and organisations seeking validated biodiversity information.

Previous articles in this series have (1) introduced the UF Biodiversity Institute and (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. Upcoming articles will focus on the role of the UF Biodiversity Institute in applying data science and informatics to biodiversity-centred problems and case studies of how biodiversity scientists are addressing societal problems.

Supported by the UF Biodiversity Institute.

UF UNIVERSITY of FLORIDA | Biodiversity Institute

**Pamela S. Soltis**
**Director**
University of Florida Biodiversity Institute
University of Florida
Gainesville, Florida 32611, USA
Tel: +1 352 273 1964
psoltis@flmnh.ufl.edu
https://biodiversity.institute.ufl.edu/



# Advancing the frontiers of computing

**Erwin Gianchandani and Michal Ziv-El from the National Science Foundation (NSF) provide a fascinating insight into how fundamental computing research is profoundly transforming our lives**

From cybersecurity to autonomous vehicles and assistive robotics, investments by the National Science Foundation's (NSF) CISE directorate have resulted in myriad breakthrough technologies over the last several decades that in turn have profoundly transformed our lives, addressed national priorities and driven economic competitiveness.

For example, in the mid-1990s, Google co-founders Sergey Brin, a former NSF Graduate Research Fellow and Larry Page, whose work was supported through an NSF Digital Library Initiative grant, created the "page-rank" algorithm that would become the basis for their groundbreaking search engine.

Around the same time, NSF-funded researchers at the Massachusetts Institute of Technology (MIT) developed algorithms to quickly deliver content via a geographically-distributed network of servers, reducing Internet congestion. This work launched a multi-billion-dollar industry and two members of the research team founded Akamai Technologies. Akamai is now valued at $10 billion and routes between 15 and 30% of the world's Internet traffic.

Today, NSF's CISE directorate aims to continue to advance the frontiers of computing, thereby enabling America to uphold a position of world leadership in computer, communication and information science and engineering; promoting understanding of the principles and uses of advanced computing, communications and information systems in service to society; supporting and providing advanced cyberinfrastructure to enable and accelerate discovery and innovation across all science and engineering disciplines; and contributing to universal, transparent and affordable participation in an information-based society.

To achieve these goals, CISE supports investigator-initiated research in all areas of computer and information science and engineering; helps develop and maintain cutting-edge cyberinfrastructure to enable research and education across all fields of science and engineering; and contributes to the development of a computer and information technology workforce with skills essential for success in an increasingly competitive global market.

In the recently-completed fiscal year 2017, CISE awarded more than 1,800 grants with a budget of $936 million, supporting nearly 18,000 people including faculty, postdoctoral researchers and graduate and undergraduate students. Furthermore, about 83% of all federally-funded fundamental, academic computer

science research was supported by NSF in the fiscal year 2017 and most of that through CISE.

The CISE directorate is organised into four primary units. The Division of Computing and Communication Foundations (CCF) advances computing and communication theory, algorithms for computer, computational and information sciences and architecture and design of software and hardware systems. The Division of Computer and Network Systems (CNS) invents new computing and networking technologies, while ensuring their security and privacy and finds new ways to make use of existing technologies.

The Division of Information & Intelligent Systems (IIS) studies the interrelated roles of people, computers and information to increase the ability to understand and harness data, as well as mimic the hallmarks of intelligence in computational systems through advances in artificial intelligence, computer vision, robotics, machine learning, natural language processing, computational neuroscience, cognitive science and related areas.

And the Office of Advanced Cyberinfrastructure (OAC) supports and coordinates the development, acquisition and provision of state-of-the-art cyberinfrastructure resources, tools and services essential to the advancement and transformation of all fields of science and engineering. Each CISE division/office comprises a number of programmes that collectively fund a portfolio of grants spanning a broad range of research, research infrastructure and education activities.

CISE-supported activities are aligned with emerging national challenges – and also with a set of 10 bold, long-term research and process "Big Ideas" that identify areas for future investment at the frontiers of science and engineering. For example, recent grants through the Transdisciplinary Research in Principles of Data Science (TRIPODS) program, co-led by CISE and NSF's Directorate for Mathematical and Physical Sciences, aim to bring together computer scientists, mathematicians and statisticians to develop better data mining and machine learning approaches and enhanced visualisation techniques.

The TRIPODS awards are aligned with NSF's Harnessing the Data Revolution for 21st-Century Science and Engineering Big Idea, which aims to advance fundamental research in data science and engineering; the development of a cohesive, federated, national-scale approach to research data infrastructure; and the nurturing of a 21st-century data-capable workforce.

Similarly, the almost decade-long Cyber-Physical Systems (CPS) program, led by CISE in partnership with NSF's Directorate for Engineering and six other federal agencies, funds research that is integrating physical infrastructure, such as transportation networks and the energy grid, with "cyber" capabilities to yield new jobs and contribute to economic growth in cities and communities all across America.

CISE is also building the knowledge base for rigorous, engaging computer science education that can be accessed by all Americans: CISE co-funded with NSF's Directorate for Education and Human Resources the development of a new Advanced Placement® (AP®) Computer Science Principles (CSP) framework and exam; more than 50,000 students took the first offering of the AP CSP exam in spring 2017, making it the largest single exam launch in the AP program's 60-year history and the exam also saw enhanced diversity among the test takers.

It's an exciting time to be in computer science! Computing is everywhere, touching all fields of science and engineering and impacting all facets of society – and it's continuing to rapidly expand and evolve. As with Google and Akamai decades ago, sustained investments in fundamental research, research infrastructure and education by NSF's CISE directorate today are powering the technological breakthroughs that will transform society for tomorrow. ■

**Erwin Gianchandani, PhD**
**Deputy Assistant Director**
Directorate for Computer and Information Science and Engineering
National Science Foundation (NSF)

**Michal Ziv-El, PhD**
**American Association for the Advancement of Science (AAAS) Science & Technology Policy Fellow**
Directorate for Computer and Information Science and Engineering
National Science Foundation (NSF)
Tel: +1 703 292 5111
info@nsf.gov
https://www.nsf.gov/dir/index.jsp?org=CISE
www.twitter.com/NSF

# Can Open Data Feed the World?

## Jaime Adams at U.S. Department of Agriculture explores the role of open data technology and if this can help feed the whole world

Over 7.4 billion[1] people currently inhabit the Earth and an estimated 800 million[2] go to bed hungry every night – predominantly women and children. Experts tell us we currently produce enough food to adequately feed the global population[3], so why do so many go to bed hungry? What steps must we take to reduce this number as the global population is projected to grow to over 9.7 billion people by 2050?[4]

If we are going to feed the world, we need open data policies, especially in government, to enable comprehensive decisions based on facts and evidence. This global perspective will help identify existing data and data gaps and sharpen the focus on how open data can foster innovation and collaborative research, enabling comprehensive solution sets.

What is open data and what does it mean to have an open data policy in government? Generally speaking, open data is data that can be freely used, reused and redistributed by anyone. The adoption of government policies to open government data promotes value creation, accountability and transparency. The Global Open Data for Agriculture and Nutrition (GODAN) initiative – comprising more than 600 international organisations representing governments, donors, businesses and not-for-profits – continues to be a leader in advocating for the adoption of open data policies. GODAN focuses on opening agriculture and nutrition data as a mechanism to support sustainable development and solve long-standing global food security challenges.

People around the world use data to make decisions every day. Although we may not see or understand all of the intricate details, we utilise vast amounts of data every day. For example, when heading out of town, most of us check the forecast wherever in the world we are travelling to before packing our bags. If the forecast calls for rain, we pack an umbrella and a raincoat. If it is going to be cold, perhaps we pack gloves and a hat. How much data does a service like weather forecasting require? The National Centers for Environmental Information (NCEI) is a critical open government data source that has enabled global weather forecasting. The NCEI "hosts and provides public access to one of the most significant archives for environmental data on Earth.[5]" The NCEI provides over 25 petabytes of comprehensive global atmospheric, coastal, oceanic and geophysical data.

We haven't always had the luxury of detailed weather forecasting at the tip of our fingers. Only in the last 10-15 years has technology enabled us to consume the information produced from this vast data source, through smart phone weather applications. And yet today, when we travel we may find ourselves packing food in our suitcase because we don't know what may be available when we arrive. A farmer may not know the best market to sell their products at the best prices. A mother may not have access to nutritious food for her child or have the tools/knowledge to make better choices in selecting nutritious food within what is available. We have a global, comprehensive, open data set that enables weather forecasting, but nothing comparable to food security? Open agriculture and nutrition data is a powerful tool, critical for solving global food insecurity, yet currently, we do not have a global, comprehensive data ecosystem that spans the global farm to fork spectrum.

We can do better. The decisions made to address food security are valiant attempts to do the best with the information currently available, but we can and should do better. Ensuring that decision makers are fully informed enables good decisions. A first step would be for governments around the world to adopt and imple-

"If we are going to feed the world, we need open data policies, especially in government, to enable comprehensive decisions based on facts and evidence. This global perspective will help identify existing data and data gaps and sharpen the focus on how open data can foster innovation and collaborative research, enabling comprehensive solution sets."

ment open data policies. Second, when implementing open data policies, FAIR (Findable, Accessible, Interoperable, Reusable)[6] principles should be applied. FAIR is a useful framework for thinking about sharing data in a way that will enable maximum use and reuse. A testament to the U.S. commitment to make agriculture and nutrition data available, accessible and usable for unrestricted use worldwide is the publication of U.S. government data that is continuously uploaded within the consolidated Federal catalogue at www.data.gov. The U.S. Department of Agriculture (USDA) has made over 800 datasets publicly available through Data.gov. USDA welcomes suggestions from the public for additional datasets to make open, this enables USDA to prioritise resources with a focus toward improved customer service.

Eight hundred million people go to bed hungry every night. If the situation does not improve and population grows as predicted, the number of people that go hungry every night may dramatically increase by 2050. By making data open and building capacity for open data use by all stakeholders, we stimulate economic growth and support farmers, scientists, consumers and entrepreneurs who are working to solve the world's long-term food security needs. If we can forecast the weather around the world utilising today's available data and technologies, we have the capacity to solve global food insecurity. We need a global comprehensive data ecosystem to enable and empower us to find the right balance of solutions. ■

1 https://www.census.gov/popclock/
2 http://www.fao.org/3/a-i4646e.pdf
3 http://www.fao.org/state-of-food-security-nutrition/en/
4 https://esa.un.org/unpd/wpp/Publications/Files/WPP2017_KeyFindings.pdf
5 https://www.ncei.noaa.gov/
6 https://www.nature.com/articles/sdata201618
https://www.dtls.nl/fair-data/

**Jaime Adams**
**Senior Advisor for International Affairs**
Office of the Chief Scientist, Office of the Secretary
U.S. Department of Agriculture
Tel: +1 202 617 4747
Jaime.Adams@osec.usda.gov
www.usda.gov
www.twitter.com/usda/

# A call for international research and funding on locusts

Dr. Hojun Song from the Department of Entomology, Texas A&M University explores the future for international research and funding on locusts swarms in the U.S. and Europe

Locust swarms darkening the sky may be mere stories in the Bible for most people living in the U.S. and Europe, but to the people in many developing countries in Central and South America, Africa, the Middle East and Central Asia, as well as China and Australia, locusts are one of the most feared ancient agricultural enemies that have continuously threatened the livelihoods and food security for millennia. Locust upsurges and plagues still affect one in ten people on Earth, resulting in massive crop losses and costing hundreds of millions of dollars in control efforts.

Nevertheless, today there is relatively little emphasis on research and funding to study locusts. The main purpose of this article is to diagnose why locust research has slowed down in recent years and to advocate for more international collaborative efforts and funding to advance our knowledge on locusts for effective and preventative management.

Locusts are grasshoppers that can express an extreme form of density-dependent phenotypic plasticity, known as locust phase polyphenism, in which cryptically coloured, shy individuals (solitarious phase) can transform into conspicuously coloured, gregarious individuals (gregarious phase) in response to increases in population density, forming cohesive nymphal bands and adult swarms, capable of concerted, long-distance marching and flying. There are less than 20 known species of locusts (out of nearly 6,800 species of grasshoppers), but this small number of species wreaks havoc globally.

Since Sir Boris P. Uvarov, the father of modern acridology (grasshopper research), discovered locust phase polyphenism in the 1920's, a tremendous amount of fundamental and applied research has been conducted to understand the biology of locusts. Because locusts affected many regions that were former colonies of the British Empire and the French Colonial Empire, most of what we know about locusts have come from the research centres in the United Kingdom and France. The world's first dedicated research centre on locusts, the Anti-Locust Research Centre (ALRC), was established in 1945 in London under the Colonial Office, which was headed by Sir Uvarov.

For the next four decades, the ALRC, which later became the Centre for Overseas Pest Research (COPR) in the 1970's, was the premier centre for locust research, but the shifts in government-sponsored research priorities and politics eventually led to the termination of this program in the 1990's.

In France, CIRAD (French Agricultural Research Centre for International Development) was established in 1984 to focus on agricultural research on tropical regions around the world. In addition, its locust research unit in Montpellier was the next centre for locust research in the post-ALRC era. This unit is still active, but it too has been affected by the recent shifts in research priorities and the deteriorating funding situation in France today.

While most of the research conducted at ALRC and CIRAD had a distinctly applied angle, locusts have also been a subject of basic science research because locust phase polyphenism is such a fascinating biological phenomenon.

For the past three decades, individual university laboratories in the U.K, Belgium, Germany, Japan, Israel, Australia, China and the U.S have used locusts as a model system to study physiology, neurobiology, chemical ecology, behavioural ecology and genetics. Especially, two of the most important locust species in the world, the Desert Locust (*Schistocerca gregaria*) and the Migratory Locust (*Locusta migratoria*), have been studied in-depth in a laboratory setting and now we have a very good understanding of their proximate mechanisms of phase polyphenism.

Unfortunately, however, the number of active locust researchers has gradually become less over time as they retire or switch their fields of research. Added to this, the funding for basic science has become increas-

*A Plague of Locusts in the Judea Desert, Israel*

ingly difficult and competitive to obtain. As a result, only a handful of laboratories around the world currently focus on locust research.

Although the gradual decline in locust research is a serious issue, a more urgent issue has to do with the practical and geopolitical aspects of locust control. Many locust species inhabit remote and scarcely populated areas, which creates tremendous obstacles for their population monitoring and control. Ground locust surveys are too time- and labour-intensive and often inadequate to address the enormous spatial scale of the locust problem.

Furthermore, locusts produce outbreaks at irregular intervals and as a result, these outbreaks are often "unexpected." Typical locust control strategies are essentially curative, consisting of large-scale applications of broad-spectrum insecticides to infestations, which is not sustainable and certainly harmful to the environment.

In addition, management of these pests is largely dependent on donor's geopolitical interests, availability of funds, stakeholder inputs and numerous other socioeconomic aspects. Although some locust-affected countries, such as Mexico, Australia and China, have governmental organisations for locust monitoring and control, many developing countries lack such infrastructure.

The Food and Agriculture Organization of the United Nations (FAO) has established the "Locusts and Transboundary Plant Pests and Diseases" unit that monitors and provides early warning for locust outbreaks and works with regional commissions and national authorities for locust control campaigns, particularly in Africa and Central Asia. However, recent changes in the global political dynamics could affect the future capacity to raise necessary funds to deal with locust-driven humanitarian crises.

Despite a century of research into the field, there is still a lot we do not know about locusts, while they are still menacing as ever, affecting many parts of the world. What we need to fight these ancient pests is a renewed global effort to deepen our understanding of locust biology and phase polyphenism to develop an innovative and transformative solution for an environmentally sustainable, preventative management system.

Simply speaking, we need to be able to predict in real-time when and where locusts begin to develop into the gregarious phase and specifically target and control these pests before they swarm. To realise this goal, we need improvements and innovations in remote sensing and drone technology, as well as in control methods utilising effective biological control agents and novel molecular pesticides such as RNA interference and CRISPR-based gene drives.

We also need to understand similarities and differences in the mechanisms of phase polyphenism in different locust species. These research outputs then need to be translated into a practical management scheme that can be effectively implemented by local governments and international organisations. This endeavour is understandably a hefty undertaking, as it will require a large amount of continuous funding and a complex international coordination among academia, governments and local stakeholders. However, if it becomes a reality, we will be able to claim that we have conquered the oldest and the most devastating agricultural pests of the entire human history.

**Dr. Hojun Song**
Department of Entomology,
Texas A&M University
Tel: +1 979 845 2481
hsong@tamu.edu
http://schistocerca.org/SongLab/

# Agriculture, Climate, Change

Research crop scientist from the K-State Northwest Research-Extension Center, Professor Robert Aiken explores agriculture and crop research issues in the United States today

As an agricultural scientist, I consider it my duty to anticipate questions and problems which may confront farmers in the future. When I'm successful, designing and conducting effective field studies, we have the information needed to formulate feasible solutions, before problems get out of hand.

In my semi-arid region of the U.S. Central High Plains, our crop systems contend with heat stress, desiccating winds, lack of rainfall, flood-generating rains and unexpected arctic air masses, inducing winter-kill or bringing the season to a chilling conclusion. Adapting to climate change? In a sense, we prepare for climate change by helping farmers adjust to the challenges of the current growing season.

*Rural Nebraska landscape*

Our growers recognise long-term warming trends and shifts in weather patterns. A recent report[1], prepared by the State Climatologists of Texas, Oklahoma and Kansas, indicates climate change has been written into the historical weather record. Below are three quotes from the report:

"Both temperature and precipitation have increased across the Southern Plains since the beginning of the 20th century. Temperature increases so far have averaged about 1.5ºF (0.8ºC) over the 20th century and precipitation has increased by as much as 5%, albeit with large variations from year-to-year and decade-to-decade. Heavy rainfall events have increased in frequency and magnitude. Historical data for tornadoes and hail are not reliable enough to be used to determine whether a trend is present in these types of severe weather."[1]

"Variations in drought conditions from year-to-year and decade-to-decade are triggered by changes in sea surface temperature patterns in the Pacific and Atlantic oceans. The Dust Bowl drought is thought to have been exacerbated by poor land use practices, while precipitation may have been enhanced in recent decades by growth in irrigated agriculture and surface water."[1]

"Temperatures will continue rising over the long-term, as carbon dioxide and other greenhouse gases continue to become more plentiful in the atmosphere. By the middle of the 21st century, typical temperatures in the Southern Plains are likely to be 4ºF to 6ºF (2.2ºC to 3.3ºC) warmer than the 20th century average, making for milder winters (with less snow and freezing rain), longer growing seasons and hotter summers. Rainfall trends are much less certain. Most climate models favour a long-term decrease, but most projected changes are small compared to natural variability. Extreme rainfall is expected to continue to become more intense and frequent."[1]

I have specific concerns deriving from these warming trends: declining yield potential because of increased night temperatures, diminished photo-protection systems under persistent heat

stress, increased risk of reproductive failure with heat stress at critical development stages, increased crop water requirements, degradation of soil with intensive rainfall events and increased potential for large-scale methane emissions unleashed by thawing permafrost[2]. These concerns rise to the top of my "watch list" for climate change impacts.

Crop productivity is expected to benefit from historic and on-going annual increases in global $CO_2$ concentrations. Assimilation rates can be maintained with modestly reduced crop water requirements. Cool-season grass crops and broadleaf crops will likely gain photosynthetic efficiencies. However, warming trends can detract from the beneficial effects of elevated $CO_2$ levels.

"When elevated temperatures exceed optimal conditions for assimilation, stress responses can include damage to the light-harvesting complex of leaves, impaired carbon-fixing enzymes, thereby reducing components of yield including seed potential, seed set, grain fill rate and grain fill duration. Field studies conducted under conditions of elevated $CO_2$ indicate that benefits of elevated $CO_2$ are reduced by heat-induced stress responses."[3]

Warmer temperatures, the most reliable feature of climate change, can extend the growing season, but also impair plant productivity. Persistent heat stress pushes plant metabolism to the edge of toleration. The complexity of plant metabolic processes can be astounding. Many of these processes are temperature-sensitive, with optimum temperatures for photosynthesis ranging from 25 to 30°C (77 to 86°F) for winter wheat[4], up to 32°C (90°F) for soybean[5] and up to 38°C (100°F) for maize[6]. Chronic heat stress, with daily temperatures exceeding this range, can accelerate the breakdown of thermo-protective mechanisms and can result in permanent damage to crop canopies.

Hot conditions prior to and during flowering can result in crop failure. Grain production requires effective pollination of ovules for 'seed set', followed by development and growth of the kernels, harvested as grain. Excessive temperatures (i.e., daily mean temperatures > 25°C for grain sorghum[7], wheat[8]) for a few days in the ~15-day period around flowering can decrease yield potential due to impaired pollination and seed-set; complete failure can occur with daily mean temperatures of 35°C (wheat) or 37°C (sorghum).

Night temperatures drive the metabolic rates of a plant, with the associated respiratory release of $CO_2$[9] as well as cell degradation[10]. In a sense, plant respiration depletes the supply of carbohydrates available for plant growth and development. As a long-term trend, warmer night temperatures can sap crop productivity.

Chronic high temperatures add to the evaporative demand on crop systems. This increases the water requirement for crop growth. Warmer temperatures can sap yield potential by impairing heat-tolerance protective mechanisms; by reducing the duration of grain-filling; and by increasing the respiratory cost, the water requirement for growth and the risk of reproductive failure of cereal crops. Warmer temperatures carry a complex drumbeat of warnings for crop productivity. Needed research is underway to adapt crop cultural practices to avoid heat stress; and to seek genetic advances for crop cultivars that are capable of tolerating or resisting effects of warming temperatures.

1 "Climate Considerations." John Nielsen-Gammon, Gary McManus, Xiaomao Lin and David Brown. White paper developed for "Resilient Southern Plains Agriculture and Forestry in a Varying and Changing Climate: Conference Report" July 18-19, 2017; El Reno, OK. http://twri.tamu.edu/el-reno

2 https://nsidc.org/cryosphere/frozenground/methane.html

3 Aiken, R. "Climate change impacts on crop growth in the Central High Plains." Proceedings of the 21st Annual Central Plains Irrigation Conference. Colby, Kansas, February 24-25, 2009.

4 Yamasaki, T., T. Yamakawa, Y. Yamane, H. Koike, K. Satoh and S. Katoh. 2002. Temperature acclimation of photosynthesis and related changes in photosystem II electron transport in winter wheat. Plant Physiol. 128:1087-1097.

5 Vu, J.C.V., L.H. Allen, Jr., K.J. Boote and G. Bowes. 1997. Effects of elevated $CO_2$ and temperature on photosynthesis and Rubisco in rice and soybean. Plant, Cell and Environment 20:68-76.

6 Crafts-Brandner, S.J. and M.E. Salvucci. 2002. Sensitivity of photosynthesis in a C4 plant, maize, to heat stress. Plant Physiol. 129:1773-1780.

7 Prasad, P.V.V., M. Djanaguiraman, R. Perumal and I.A. Ciampitti. 2014. Impact of high temperature stress on floret fertility and individual grain weight of grain sorghum: sensitive stages and thresholds for temperature and duration. Front Plant Sci. 6:820.

8 Prasad, P.V.V. and M. Djanaguiraman. 2014. Response of floret fertility and individual grain weight of wheat to high temperature stress: sensitive stages and thresholds for temperature and duration. Functional Plant Biology 41:1261-1269.

9 Tan, K.Y., G.S. Zhou and S.X. Ren. 2013. Response of leaf dark respiration of winter wheat to changes in $CO_2$ concentration and temperature. Chines Science Bulletin 58(15):1795-1800.

10 Narayanan, S., P.V.V. Prasad, A.K. Fritz, D.L. Boyle, B.S. Gill. 2014. Impact of high night-time and high daytime temperature stress in winter wheat. J. Agronomy and Crop Science 201(3):206-218.

K-STATE Research and Extension

**Robert Aiken, Associate Professor**
**Research Crop Scientist**
Northwest Research-Extension Center
Tel: +1 785 462 6281
raiken@ksu.edu
www.northwest.k-state.edu/

# The global challenge of antibiotic resistance

**Roxane Feller, AnimalhealthEurope Secretary-General provides a fascinating insight into the global challenge of antibiotic resistance**

Antibiotics have had very positive effects on animal health over the years. Our pets are living much longer than they were decades ago and livestock are raised much more efficiently through our ability to control bacterial disease. As with people, antibiotics play an important role in alleviating pain, treating disease and ensuring the health of our animals.

They also serve a One Health purpose, ensuring good animal health and welfare for over 600 million cows, sheep, pigs, goats and chickens in Europe, contributing to the sustainable production of safe food and helping to prevent food-borne illnesses in people. They also help to ensure that our pets remain healthy members of more 70 million pet-owning homes in Europe, contributing to the general well-being of dogs, cats, rabbits and people!

There are currently no alternatives to antibiotics for treating bacterial infections in animals. But these miracle solutions do have a 'kryptonite factor'. As warned by the pioneer of penicillin, Alexander Fleming during his Nobel Prize acceptance speech in 1945, "...the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." Antibiotic resistance is recognised as a global challenge impacting people and animals alike and affecting the environment in which we live.

For the past 2 decades, the animal medicines industry in Europe has been proactively leading the charge against the challenge of resistance development on a number of different levels to try to preserve the efficacy of these precious tools. Actions are wide-ranging such as awareness-raising and promoting responsible use of antibiotics in compliance with the correct dosage and treatment length; promoting disease prevention practices; encouraging the use of diagnostics; contributing to data collection regarding use and resistance development; providing input into policy tools; and more.

Equally important, in terms of action, is a renewed impetus for investment in antibiotic innovation – provided that new EU rules offer adequate data protection - and new solutions for managing infectious diseases, such as prevention through vaccines, immunostimulants, or novel anti-infectives for suitable veterinary use, etc. The range of different antibiotic classes approved for veterinary use is limited compared to those for human use and the last new antibiotic class approved for veterinary use was over 25 years ago. Nothing new has been developed since.

To maintain a balance in treatment options for both people and animals it is, therefore, essential to look at this from a One Health perspective. From the animal health industry's perspective, the WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals published towards the end of 2017, were disappointingly lacking in this regard.

The guideline largely ignores the needs of animals in terms of health and welfare and the wider impact of healthy animals in terms of food safety, disease transmission and sustainable farming. Previous communications from the WHO state that their list of medically important antimicrobials should be revised on a regular basis in a collaborative and coordinated approach by FAO, OIE and WHO, but these new guidelines appear to largely ignore the OIE list of Antimicrobial Agents of Veterinary Importance and do not adequately look at the fundamental need for antibiotic treatment in animals.

Some recommendations appear to contradict the OIE list and such a single-focused approach is out of touch with the progress made through the EU One Health

*Roxane Feller, AnimalhealthEurope Secretary-General*

action plan against AMR and the EMA's One Health approach to the categorisation of critically important antibiotics which carefully considers the needs of animal health and welfare whilst safeguarding public health.

In the ongoing EU revision of the legal framework for veterinary medicinal products, the industry supports proposals for EU decision-making on the categorisation of critically important antibiotics to be entirely science-based, following the recommendations of EU scientific experts within the EMA. Legislative proposals that would curb the unnecessary prophylactic use of antibiotics in livestock can also be supported, provided there is no negative impact on animal health.

It is vital not to ignore the needs of animals in terms of health and welfare. And the wider impacts of healthy animals in terms of food safety, disease transmission and sustainable farming cannot be ignored either. Keeping farm animals healthy is becoming ever more important as the world population continues to grow, requiring a safe and sustainable food supply. All international and regional bodies agree – from the United Nations 'Sustainable Development Goals[1]' to the European Commission's Communication on the 'Future of Food[2]' – that more sustainable agricultural practices are central to ensuring a better future.

Even with excellent bio-security and animal husbandry on farms, or the best health management including vaccination and nutrition, some animals still become ill with infectious bacterial diseases causing disruption for the farmer, lower quality products or potentially total loss of produce, more need for inputs like feed and water and greater potential for food-borne illnesses.

> "For the past 2 decades, the animal medicines industry in Europe has been proactively leading the charge against the challenge of resistance development on a number of different levels to try to preserve the efficacy of these precious tools."

Going beyond the economic and sustainable development arguments for ensuring access to and preserving the efficacy of our antibiotics, there is a strong ethical dimension to the issue. Inflammatory conditions like mastitis, for example, are extremely painful for the animal concerned and we have both a moral and legal duty to avoid and alleviate suffering.

Keeping livestock healthy by ensuring access to use all the necessary tools, including antibiotics, means that not only are animal welfare levels higher, responding to consumer demands, but the animals produce more efficiently and provide safer meat and dairy products, the essentials of a nutritious diet. ■

1 http://www.un.org/sustainabledevelopment/

2 https://ec.europa.eu/agriculture/sites/agriculture/files/future-of-cap/future_of_food_and_farming_communication_en.pdf

More information on www.animalhealtheurope.eu, on Twitter as @animalhealthEU and on Facebook: www.facebook.com/WeCare.petsEurope

**Roxane Feller**
**Secretary-General**
AnimalhealthEurope
Tel: +32 2 543 7560
info@animalhealtheurope.eu
www.animalhealtheurope.eu
www.twitter.com/animalhealthEU

# The conundrum of human health versus beef fat consumption

Raluca Mateescu from Mateescu's Animal Genetics and Genomics Lab explores the conundrum of human health versus beef fat consumption and opportunities for improving the health properties of beef

Animal fat has been stigmatised due to a perceived association with several diseases, from cardiovascular diseases to cancer. Because beef is perceived to have a high fat content, consumption of beef has suffered the most from this negative image.

Although the association between animal fat and disease is being challenged by new research, the idea that 'fat is bad for you' is well entrenched in consumers' mind and very few people question the definition of 'fat' used by proponents of this argument or are aware of differences in 'fat' composition. As a result, the 'fat-free' label is still a powerful marketing tool.

There are three types of naturally occurring fatty acids, each with a different chemistry: saturated, monounsaturated and polyunsaturated. There is also trans-fat that is bad for your health (just think how often you saw the label "NO TRANS-FAT" to indicate a healthy food choice?) and is the result of the process of hydrogenation of liquid oils done by food processors to firm them up.

The other class of fat that has been linked to negative effects on health is the saturated fat. Epidemiologists identified statistical associations between a diet high in saturated fat and the incidence of coronary heart disease and colon, prostate and breast cancer. This led to the recommendation: "eat a low-fat, low-cholesterol diet." Most of us have heard this simple recommendation so often, over the past two decades, that we can recite it in our sleep. Touted as a way to lose weight and prevent cancer and heart disease, it is no wonder much of the entire nation hopped on board. With beef labelled as a food high in saturated fat, per capita consumption of beef declined.

> "I would say that the beef industry today is in a good position to respond to the demands of health-conscious consumers. To capitalise on this trend, the industry needs to focus its research and promotion efforts towards the nutritional and health benefits of meat consumption."

It turned out that this simple message is actually wrong. Detailed research carried out in the last decade shows that the total amount of fat in the diet, whether high or low, is not really linked with diseases. What really matters is the type of fat in the diet. Results from the large and long "Women's Health Initiative Dietary Modification Trial" showed that eating a low-fat diet for eight years did not prevent heart disease, breast cancer, or colon cancer and did not do much for weight loss, either. What is becoming clearer is that bad fats, meaning trans-fat and some short-length saturated fats, increase the risk for coronary heart disease as well as other diseases, while good fats, meaning mono- and polyunsaturated and longer-length saturated fat, lower this risk. The key to a healthy diet is not to reduce total fat intake but to substitute bad fats for good fats.

**Beef fat composition**

How is beef fitting into this scenario? Marbling fat is an important meat quality trait in relation to juiciness, aroma and tenderness and is the fat depot of most interest in relation to fatty acid composition and human health. It refers to the white flecks or streaks of adipose tissue between the bundles of muscle fibres and is closely linked to intramuscular fat content.

Beef intramuscular fat (figure 1) consists on average of:

- 50% saturated fatty acids. However, about 32% is stearic acid or C18:0 – a longer chain saturated fatty acid which does not increase plasma low-density lipoprotein (or bad cholesterol) level;
- 45% monounsaturated fatty acids and;
- 5% polyunsaturated fatty acids (including omega 3, omega 6 and CLA or conjugated linoleic acid).

Beef is also a major dietary sources of conjugated linoleic acid (CLA), which possesses a range of health promoting

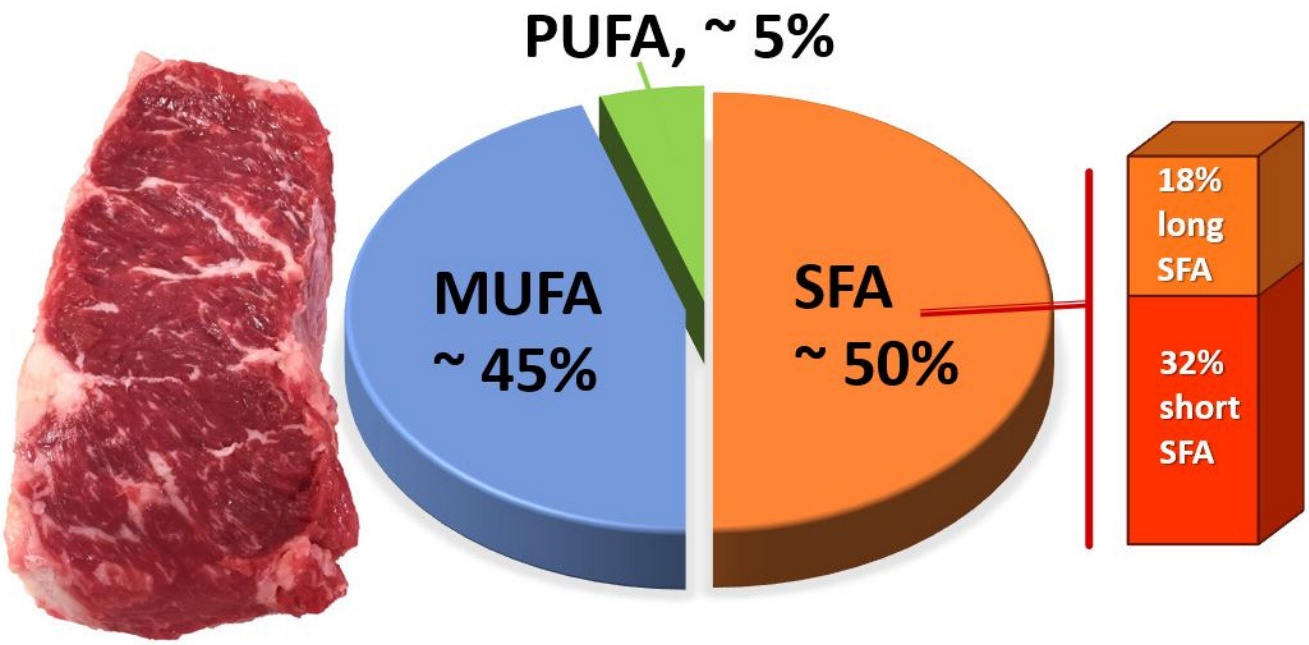



*Figure 1. Fatty acid composition of beef marbling. Intramuscular fat in beef consists of, on average, 50% of saturated fatty acids (SFA), 45% monounsaturated fatty acids (MUFA) and 5% polyunsaturated fatty acids (PUFA). About 18% of the SFA are short-chain fatty acids which have been shown to be neutral with respect to human health.*

biological properties (antioxidant, reduces circulating cholesterol, reduces cardiovascular risk, protects against atherosclerosis, anti-carcinogenic, reduces body content of adipose tissue and lipid, enhances the immune system). Beef contributes significantly to man's intake of the important fatty acids EPA and DHA (omega 3 fatty acids), of which there are few rich sources apart from oily fish.

**Genomics research on healthfulness of beef**

Ongoing research in the Department of Animal Sciences at University of Florida is focusing on characterising the nutritional and health value of beef from *Bos Indicus* influenced cattle. The goals are to determine the extent to which phenotypic variation is controlled by genetics and to develop genomic tools that will allow identification of genetically superior animals, with respect to these traits and so they can use this information for selection, management and marketing.

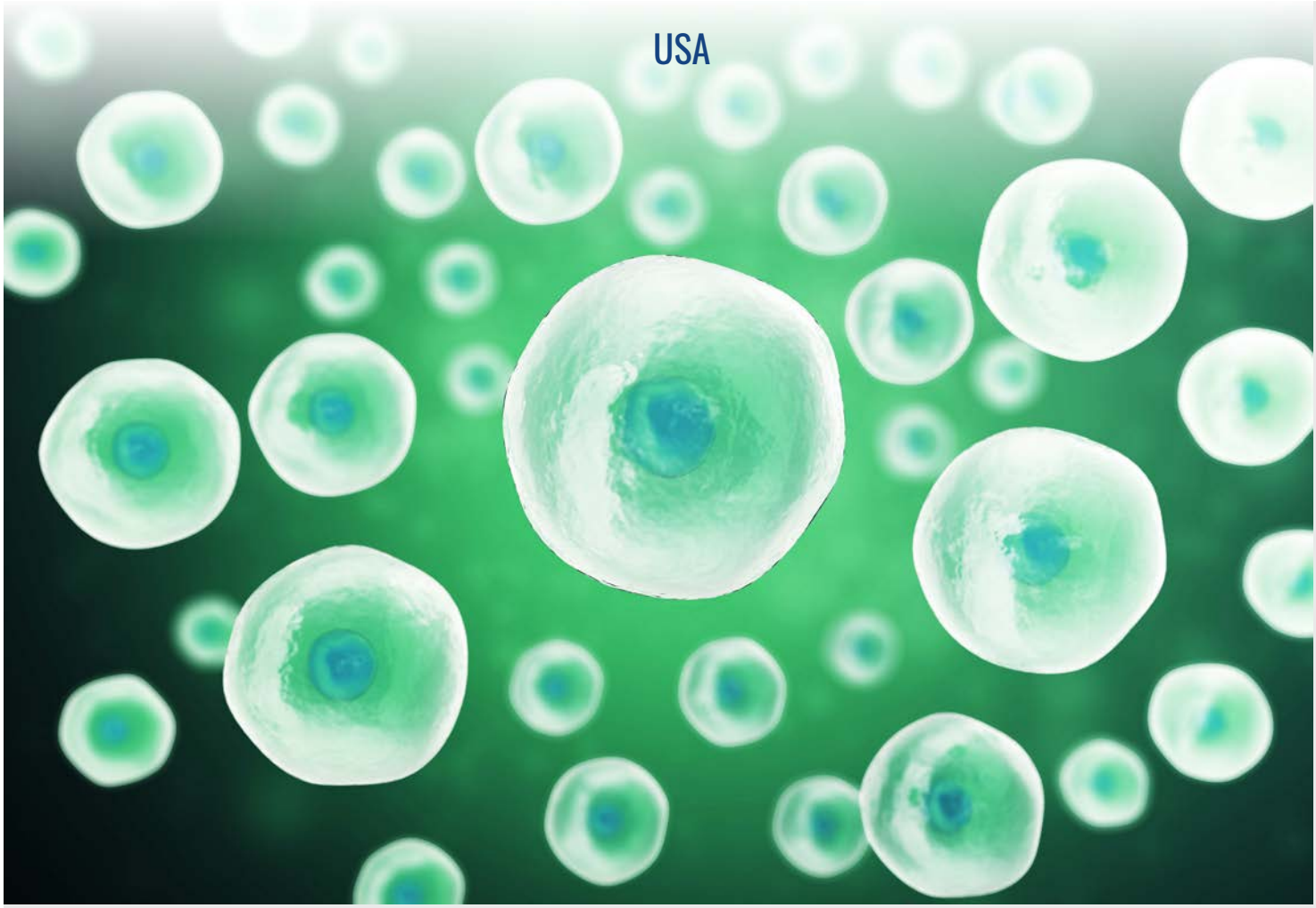
If beef producers could select cattle that have more beneficial fatty acid profiles, they could enhance the nutritional and health value of such beef. Such beef could increase profit to producers because consumers likely would be willing to pay a premium for beef that consistently has both high nutritional and health value. In addition, this nutritionally enhanced beef is likely to increase the overall demand for beef and to ensure the continued growth of the industry.

Our findings could be great news for producers raising *Bos Indicus* influenced cattle, as our preliminary data shows they may have a healthier fatty acid composition. This may open the door for producers to appeal to health-conscious consumers, through marketing beef that has a more desirable fatty acid composition. Additionally, research continues towards finding genetic markers that will allow producers to identify and select animals that will produce beef with higher percentages of polyunsaturated fatty acids, as well as lower percentages of saturated fatty acids.

In conclusion, I would say that the beef industry today is in a good position to respond to the demands of health-conscious consumers. To capitalise on this trend, the industry needs to focus its research and promotion efforts towards the nutritional and health benefits of meat consumption.

UF IFAS Research
UNIVERSITY of FLORIDA
Department of Animal Sciences
*The Foundation for The Gator Nation*

**Raluca Mateescu**
**Associate Professor of Quantitative Genetics & Genomics**
**Graduate Program Director**
Mateescu's Animal Genetics and Genomics Lab
Tel: +1 352 392 2367
raluca@ufl.edu
www.ralucamateescu.com



# What is developmental biology and why is it important?

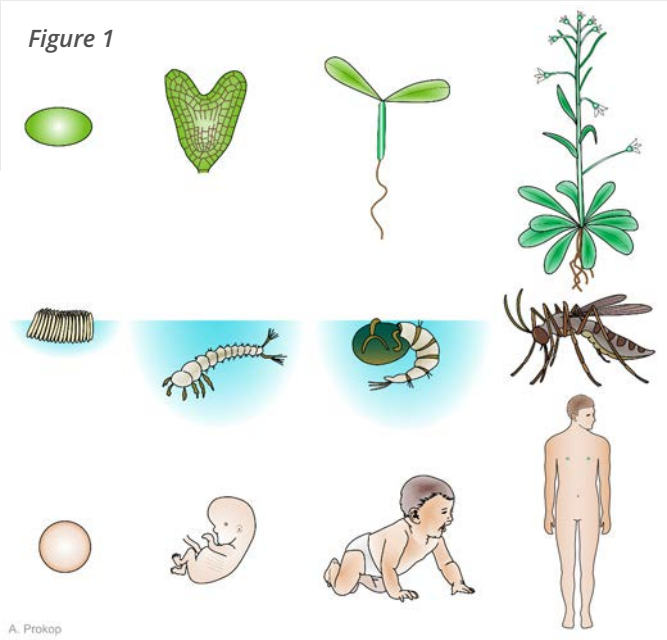
## Andreas Prokop from the British Society for Developmental Biology explores how developmental biology (DB) addresses questions of societal importance

The life science discipline Developmental Biology (DB) aims to understand the processes that lead from the fertilisation of an egg cell (or equivalent) to the formation of a well-structured and functional multicellular organism (Fig.1). At first sight, this may appear a mere curiosity-driven academic goal, not necessarily worth taxpayers' money. Here I argue that the opposite is true: DB is a key discipline in the life sciences, a motor for research into human disease and fertility, food sustainability and biological responses to environmental pollution and global warming.

According to the US' National Research Council, over half of initial pregnancies are affected by developmental defects, ~3% of live births suffer from major developmental aberrations, ~70% of neonatal deaths and 22% of infant deaths have developmental causes and ~30% of admissions to paediatric hospitals are due to developmental defects. The causes can be random errors, inherited or acquired gene mutations or toxins – as illustrated by severe limb malformations of thousands of new-borns during the thalidomide/Contergan drug scandal in the 1950s, or the stark increase in birth defects after the Bhopal gas catastrophe in 1984.

These numbers and examples clearly cry out for scientific investigations into the developmental processes affected – not only to understand or even treat human disorders but also to deliver profound arguments that convince policy makers, for example, to reduce toxic

Image: © A. Prokop




wastes, fumes and plastics which pose threats to our healthy genes and development. DB is a scientific discipline at the centre of such investigations and it has two important strategic strengths, as will be explained in the following article.

## DB asks profound questions at the level of whole organisms or organs

DB investigates questions such as "how does the kidney or brain develop?", or "how do limbs or leaves achieve their characteristic shapes and positions?" To address such questions, a typical DB research strategy may start by identifying the genes or gene networks regulating the respective developmental processes in a chosen animal or plant. These genes can then be functionally manipulated or eliminated to study the resulting developmental aberrations. The findings often allow deductions about how the involved genes and processes function in health; they may also reveal parallels to clinical cases of human developmental disorders, thus directing further biomedical research into such conditions.

To investigate processes from the genetic level all the way up to the organism/organ level, DB must be highly inclusive and interdisciplinary, making active use not only of genetics but also biophysics, biochemistry, cell biology, physiology and anatomy. In this way, it drives discoveries at the various levels of complexity, acts as an umbrella discipline that can provide a common focus towards essential biological questions and builds bridges to clinicians or plant/animal breeders who tend to think at the organism/organ level.

## DB makes strategic uses of model organisms

Most DB research does not use human embryos but covers the breadth of the animal and plant kingdoms. This ambition might seem to bear the risk of overstretching our research capacities, but it is, in fact, a great strength of DB and gold mine for discovery. It turned out that many genes and functional gene networks that steer fundamental biological processes have ancient evolutionary origins and are still being used by very different species for similar purposes (Fig. 2); ~75% of human disease genes have a counterpart in fruit flies and ~50% of yeast genes can be functionally replaced with human genes.

Capitalising on this principle of 'deep homology', highly efficient and cost-effective, hence economically responsible research can be done in smaller organisms, such as worms, flies or even yeast. The genes and concepts learned can then be tested in mammals (most frequently mice) and eventually used for clinical trials. This discovery pipeline has led to significant understanding of human biology and disease, as evidenced by an impressive number of Nobel Prizes in Physiology and Medicine awarded to scientists working with these "model systems".

## What DB has done for us (so far)

DB research starts with the fertilisation of egg cells; studying the underlying processes has provided the foundations for much of what fertility clinics can do these days. DB investigates how fertilised egg cells divide in regulated manners to grow into full-size bodies, how the cells formed in this process communicate in meaningful ways to become different from each other, migrate, change shape and attach to each other, thus assembling into tissues and complex organs. Many of these processes are needed again during wound repair and DB research helps to speed up wound healing, prevent scars and overcome chronic wounds.

Also 'tissue engineering', which aims to grow replacement tissues in a plastic dish, is essentially guided by DB research. In cancer, cells lose their identity, divide excessively, detach from their local environments and migrate to form metastases. Much of this understand-

*Continued on page 25* ➔

# YOUR OPINION MATTERS

Whether you agree, disagree, or have another viewpoint with any news and features on our website, we want to hear from you.

Leaving a comment on any item on our website is easy, so please engage and join the debate today.

www.openaccessgovernment.org

OPEN ACCESS GOVERNMENT

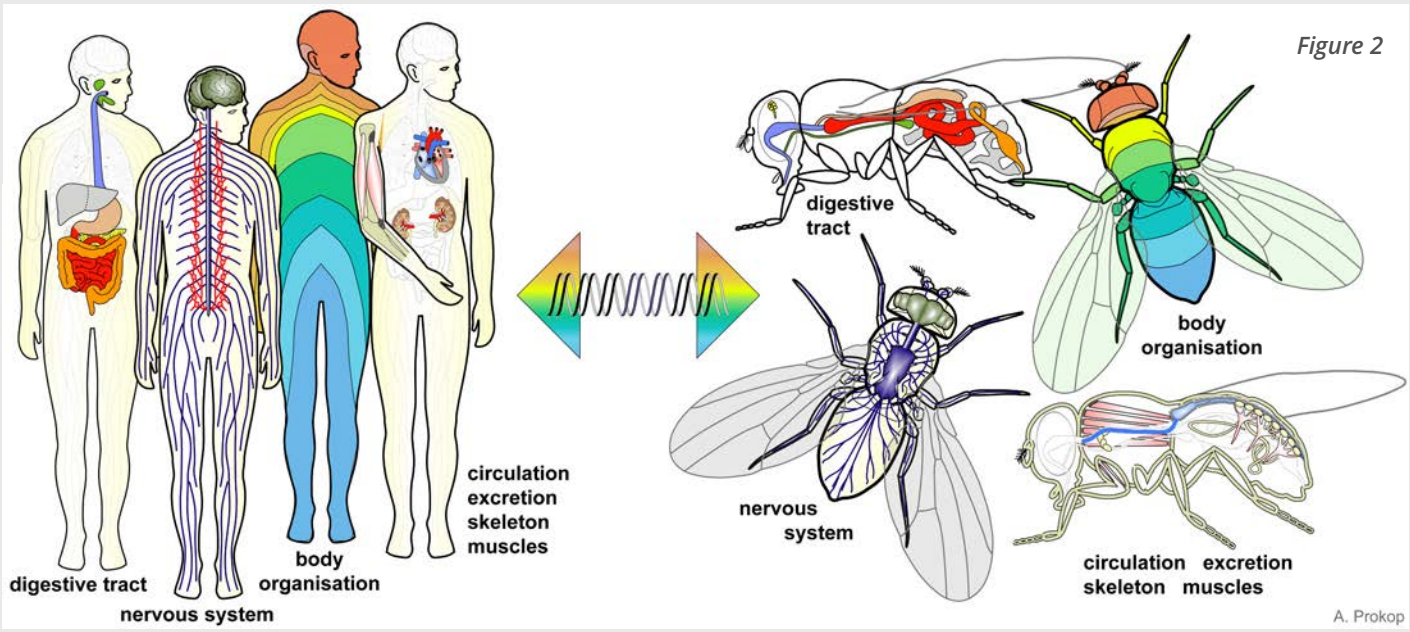



Image: © A. Prokop

*Figure 2*

← *Continued from page 23*

ing that can instruct cures to contain these aberrant cells, comes from DB research. Tissues keep so-called stem cells which can be re-activated in orderly manners to divide and grow replacement tissues. There are high hopes from stem cell research, for example, to replace cartilage in arthritis or damaged discs, or brain cells in dementia, much of which is guided by the vast knowledge gained through DB.

> "Most DB research does not use human embryos, but covers the breadth of the animal and plant kingdoms. This ambition might seem to bear the risk of over-stretching our research capacities, but it is, in fact, a great strength of DB and gold mine for discovery."

The applications of DB go far beyond biomedical research. For example, understanding plant development provides a means to speed up breeding processes, such as optimising root systems, plant size or flowering time, thus contributing to the efforts of achieving sustainable food security in times of over-population. Furthermore, understanding environmental influences on development, such as temperature-dependent sex determination in turtles, has enormous importance for conservation biology, especially in times of increasing pollution and global warming.

In conclusion, DB may appear as a mere academic discipline, but its value for society is enormous. This should make us think about a carefully balanced system of science funding. Current trends seem to favour clinical or industrial research performed to translate biological knowledge into an economic or societal benefit. But we must not overlook that fundamental research, such as in the field of DB, lays the long-term foundations for such developments. ■

The author would like to thank Ottoline Leyser and Aidan Maartens for helpful comments on this manuscript. Andreas Prokop is Professor of Cellular and Developmental Neurobiology at the Faculty of Biology, Medicine & Health (The University of Manchester) and communication officer of the British Society for Developmental Biology.

**Andreas Prokop**
**Professor of Cellular & Developmental Neurobiology**
BSDB – British Society for Developmental Biology
Tel: +44 (0)161 275 1556
Andreas.Prokop@manchester.ac.uk
http://bsdb.org/
www.twitter.com/Poppi62/status/932523941033316352

# All about the adult long-tailed knifefish S. macrurus

Graciela A. Unguez and Chiann-Ling C. Yeh from New Mexico State University explain that sarcomere disassembly is a naturally occurring event during tail regeneration in the adult long-tailed knifefish S. macrurus

Perhaps the most characteristic feature of skeletal muscle invertebrates is its regular pattern of striations, comprised of many hundreds of identical repeated units called sarcomeres[1]. How so many proteins come together so eloquently to form each of these highly organised myofibrillar structures present in vastly different muscles in very different animal phyla remains a central question in muscle biology. Many (>100) of the protein components that make up a sarcomere invertebrate have been identified[2] and the spatial distribution of these proteins within the sarcomeric unit has been well characterised[3].

Sarcomere proteins are compartmentalised into functional regions that include the Z-disk, which flanks the sarcomere and anchors thin filament proteins (such as actin) in the I-band. Thin filaments interact with the thick filament proteins (such as the myosin heavy chain, MHC) of the A-band and these myosin structures are crosslinked with the proteins of the M-line (such as myomesin) [2-3].

How these proteins are localised in different regions of the sarcomere and which proteins are necessary for sarcomere integrity are topics of intense investigation with several groups formulating different models by which the spatial and temporal sequence of sarcomere assembly takes place[3-5]. Although these models diverge in how sarcomeres are formed, they all propose that sarcomere assembly is a well-ordered stepwise process.

In contrast to the efforts on understanding sarcomere formation, relatively few studies have characterised the sarcomere disassembly process – a process that occurs under atrophy conditions and muscle loss following trauma or degenerative disorders such as sarcopenia, muscular dystrophy, or amyotrophic lateral sclerosis[6]. These studies have largely been under conditions of induced changes in specific sarcomere gene expression using genetic animal models[7-10].

Whether sarcomere structures get dismantled in a temporal sequence that is in the exact reverse order of that followed in their assembly remains unknown. Remarkably, sarcomere disassembly occurs in the gymnotiform Sternopygus macrurus as part of the process by which some muscle cells convert into electrocytes, i.e., the non-contractile electrogenic cells of the electric organ, during tail regeneration[11]. After tail amputation, myogenic precursors in the regeneration blastema give rise to multinucleated muscle cells and some of these myotubes proceed to fuse, disassemble sarcomeres and downregulate many sarcomeric proteins to form electrocytes[11].

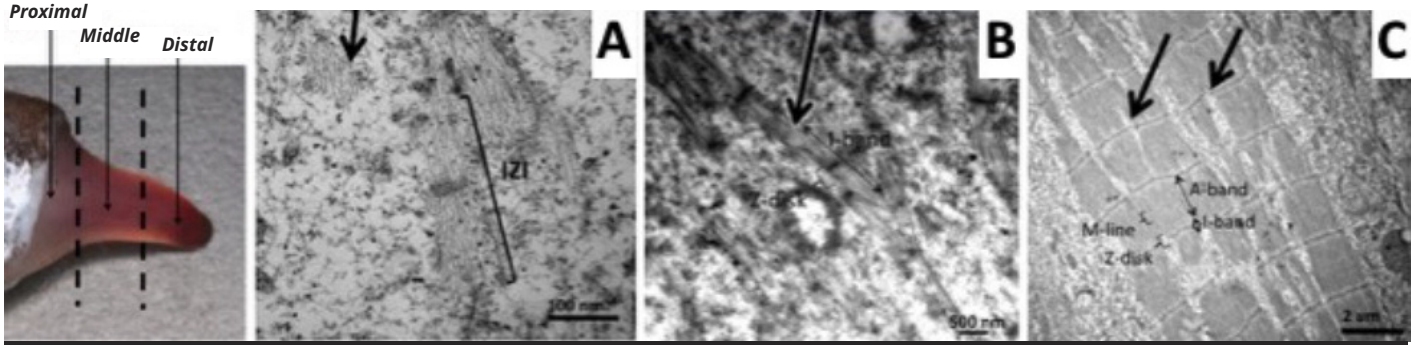



*Figure 1. A) Proximal region: Thick filaments are no longer visible; I-Z-I brushes detected; thin filaments disperse throughout the electrocyte (arrow). B) Middle region: M-band is no longer visible at the midpoint of sarcomere (arrow). Thick filaments begin to disappear, and thin filaments appear misaligned. C) Distal region: Many myofibrils are detected. Z-disks begin to pull apart in early electrocytes (arrows)*

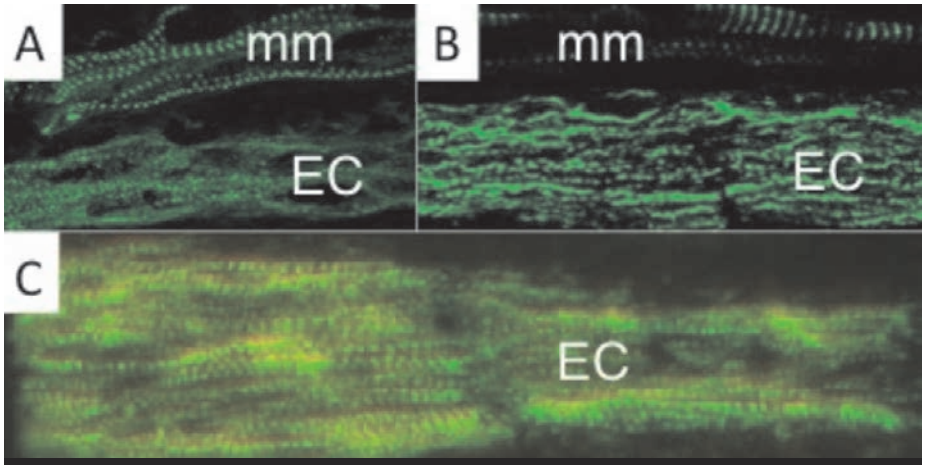



*Figure 2. Portions of regenerating electrocytes (EC) following fusion of myofibrils (mm) and during the disassembly of sarcomeric structures. A: alpha-actinin in Z-disks. B: tropomyosin in I-bands. C: MHC in A-bands*

Using a combination of ultrastructural and immunolabeling approaches, we have begun to analyse changes in sarcomere structures and sarcomeric protein expression at different stages of the muscle cell-to-electrocyte conversion within each regeneration blastema two weeks after tail amputation (Fig. 1). These data confirm the proximal-to-distal cell differentiation gradient where regenerating electrocytes most proximal to the tail amputation site are more differentiated (i.e., less sarcomeric structures) than those regenerating electrocytes most distal (more striations) to the amputation site (Fig. 1). Moreover, the breakdown of sarcomeres during the formation of electrocytes was found to occur in a step-wise manner.

This temporal sequence of sarcomere disassembly correlated with the changes detected in protein expression obtained with immunolabeling (Fig. 2). First, Z-disks misaligned to form smaller striated myofibrils (Fig. 1C and 2A) followed by the disappearance of the M-line (Fig 2B). The A-bands with MHC were removed (Fig. 1B and 2C) causing sarcomeres to break into IZI components (Fig. 1A). These I-bands (Fig. 1A and 2B) then dispersed throughout the electrocyte and some remained visible in adult electrocytes.

These data suggest a disassembly of sarcomeres that closely follows the reverse order of the model for sarcomere formation proposed by Sparrow and Schock[5]. Although it remains premature to conclude the characterisation of the molecular and cellular processes that underlie the striking phenotypic conversion of muscle cells into the highly specialised electrocytes, this work clearly extends the application of S. macrurus to studies relevant to sarcomere stability and homeostasis.

References

1 Huddart H. and Kerkut G.A. (1975). The fine structure of skeletal muscle. In: The comparative structure and function of muscle. Pages 4-48. ISBN: 978-0-08-017845-5. Elsevier Inc.

2 Gautel M. and Djinovíć-Carugo K. (2016). The sarcomeric cytoskeleton: from molecules to motion. Journal of Experimental Biology 219: 135-145.

3 Ehler E. and Gautel M. 2008. The sarcomere and sarcomerogenesis. Advances in Experimental Medicine and Biology 642: 1–14.

4 Sanger JW, Wang J, Fan Y, White J, Mi-Mi L, Dube DK, Sanger JM, and Pruyne D. (2017). Assembly and Maintenance of Myofibrils in Striated Muscle. Handbook of Experimental Pharmacology. 235:39-75.

5 Sparrow JC, Schöck F. (2009). The initial steps of myofibril assembly: integrins pave the way. Nature Review Molecular Cell Biology. 10:293-8.

6 Burd, N.A., Gorissen, S.H., Loon, L.J.V., 2013. Anabolic Resistance of Muscle Protein Synthesis with Aging. Exercise and Sport Sciences Reviews 41, 169–173.

7 Nishii, K., Morimoto, S., Minakami, R., Miyano, Y., Hashizume, K., Ohta, M., Zhan, D.-Y., Lu, Q.-W., Shibata, Y., 2008. Targeted disruption of the cardiac troponin T gene causes sarcomere disassembly and defects in heartbeat within the early mouse embryo. Developmental Biology 322, 65–73).

8 Peng, J., Raddatz, K., Labeit, S., Granzier, H., Gotthardt, M., 2006. Muscle atrophy in Titin M-line deficient mice. Journal of Muscle Research and Cell Motility 26, 381–388.

9 Perkins, A.D., Ellis, S.J., Asghari, P., Shamsian, A., Moore, E.D., Tanentzapf, G., 2010. Integrin-mediated adhesion maintains sarcomeric integrity. Developmental Biology 338, 15–27.

10 Weinert, S., Bergmann, N., Luo, X., Erdmann, B., Gotthardt, M., 2006. M line–deficient titin causes cardiac lethality through impaired maturation of the sarcomere. The Journal of Cell Biology 173, 559–570.

11 Unguez, G.A., Zakon, H.H., 1998. Phenotypic conversion of distinct muscle fiber populations to electrocytes in a weakly electric fish. Journal of Comparative Neurology 399, 20–34.

12 Holtzer H, Hijikata T, Lin ZX, Zhang ZQ, Holtzer S, Protasi F, Franzini-Armstrong C, Sweeney HL. (1997). Independent assembly of 1.6 microns long bipolar MHC filaments and I-Z-I bodies. Cell Structure Function 22:83-93.

Funding Source: This research supported by NSF CISE/CNS and BIO/IOS INSPIRE Award and Howard Hughes Medical Institute's 2010 Science Education grant 52006932.

**Graciela A. Unguez, PhD**
**Professor of Biology**
New Mexico State University
Tel: +1 (575) 646 7963
gunguez@nmsu.edu
https://bio.nmsu.edu/

# 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

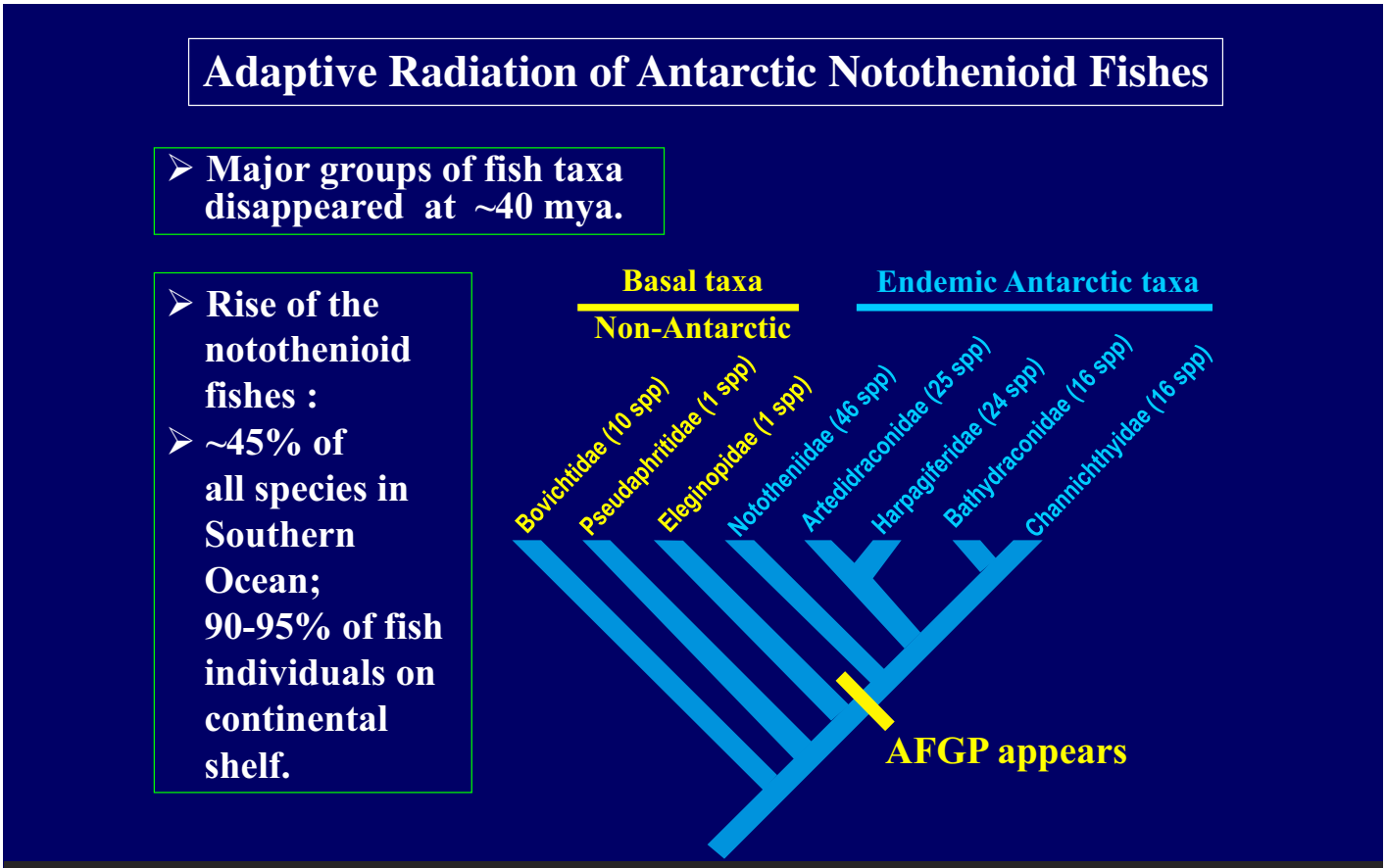



*Figure 1. Cladogram of Antarctic fishes of the Suborder Notothenioidei and characteristics of the group*

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.

**Arthur L. DeVries**
Department of Animal Biology,
University of Illinois
Tel: +1 217 333 4245
adevries@life.illinois.edu

# The role of geography in addressing global health needs

**Senior Research Advisor from the American Association of Geographers, Yonette Thomas discusses the important role that geography can play in addressing global health needs, both in research and in practice**

The American Association of Geographers (AAG) is a non-profit scientific and educational society, founded in 1904. For over 100 years the AAG has contributed to the advancement of geography and added to this, its members come from nearly 100 countries and share interests in the theory, methods and practice of geography.

Introducing the fascinating subject of health geography, the AAG's senior research advisor, Yonette Thomas points out that human geography involves the interaction between human beings and their environments in place, time and spatially defined areas. Having said that, the subject of health adds to this type of geography because where people reside and live impacts their health and wellbeing. Thomas then goes on to expand this fascinating point in her own words, such as what diseases impact upon people, how their physical environment impacts their health.

"Geography and health, have a long conceptual and methodological history. Medical geographers focus on the interaction of health and geography and bring these two areas together. This focus on the geography of health and disease is multi-disciplinary because, for example, medial sociologists and social epidemiologists study people in context from an ecological perspective and engage health geographers in such studies. We know and have evidence for understanding how where people live and reside directly impacts their health, what kind of food they eat and how active they are. This is a multi-disciplinary effort requiring shared conceptualisations and methodologies."

"More specifically, examining broader perspectives in terms of environments and physical location, or country-by-country right down to municipalities and

neighbourhoods, is where the action really happens. If we look at the City of London during the time of John Snow, people were fetching water from the Broad Street pump when the cholera epidemic was raging. John Snow, the father of modern epidemiology, is famous for removing the Broad Street pump and halting the cholera epidemic.

"When you look at lower and middle-income countries (LMICs) in the world today – such as in Bangladesh and other countries where people are moving into urban areas or forced into migration because of wars or famines – the knowledge and tools of health geography help us understand and implement strategies for dealing with the consequences of these events. So geographers play a significant role in using tools such as geographic information systems (GIS) to map out water resources, sanitation control points, food sources, where crops are better grown in relation to where population groups are and where people are at risk."

Having looked at these intersecting pieces, Yonette then underlines that health geography does not only inform issues affecting populations in low and middle-income countries, but in developed countries such as the United States as well. In the United States an opioid epidemic is significantly affecting certain population groups. For example, people in working class communities like Kennett, Missouri, a state in the Midwestern United States, who worked in the factories, are white, and experienced privilege are bearing the brunt of the opioid crisis, Yonette explains before telling us about this point further.

"The factories have moved from those areas, so people are out of work and are not only on pills, but suffer chronic conditions such as diabetes, metabolic syndrome and cardiovascular disease. The fact that there are few doctors to provide care to the affected in many of these towns has created an access to care issue. This presents an example of a collaboration opportunity for public health researchers, health professionals, and health geographers to work with state and local entities.

Geographers play an important role in collaborating with epidemiologists, public health professionals and researchers, professionals in sectors such as the transportation sector, or with those who focus on water and food security. Geographers add spatial understanding to public health challenges. Context and environment are fundamentally important, particularly how they impact health."

Having looked at the significance of health geography in the world today, Yonette is keen to share her thoughts on the important role that geography can play in addressing global health needs, both in terms of research and practice and impacting policy. When it comes to understanding the dynamics of global health, we are witnessing the rapid movement of people from rural into urban areas and new urban areas are being established whether the infrastructure is ready for them or not, Yonette tells us.

"We see this happening in places such as China, Bangladesh, India and Africa and so geography can help policymakers and those at the national, sub-national and municipality levels to prepare for and respond to the dynamic movement of population groups and to identify, for example, where key sources of sanitation and water should be located. They play a role in helping global and urban health professionals map out and locate where infrastructure needs to be to respond to this movement of people and related health issues.

If you look at Sustainable Development Goals 3 and 11, for example, they rely on fundamental tools of geography in helping us to understand the dynamic movement of people and how we respond. Infrastructure informed by research and practice should, therefore, be put in place to prevent, intervene and treat disease conditions and maintain health."

The conversation then moves towards Yonette's thoughts on the priorities for research in the field of health geography. She explains that much research is taking place today, indeed this is the bread and butter of academics such as Yonette. She underscores that: "where we are falling short is in the active translation of that research into practice and policy".

In closing, Yonette firmly underlines that now is a very exciting time for health geography and that journals such as Open Access Government can make a call for action to policy-makers, researchers and people on the ground to actively translate what we already know into both practice and policy.

"Practitioners and other professionals are out there implementing phenomenal programmes – but what really needs to happen in the 21st century is a specific focus on how we are translating what we know into programming, practice and infrastructure development and policymaking on the ground.

"If you use the example at the country level, the minister of health is not as important as the minister of finance. Health issues can get lost in the mix because other things take precedence. So, we need to target health from a policy-making, infrastructure development and economic value perspective, so a prime minister must realise that the health of her/his population will ensure the economic health of the country and vice-versa." ■

**Yonette Thomas, PhD**
**Senior Research Advisor**
American Association of Geographers
Tel: +1 301 758 4407
ythomas@yfthomasdr.com
www.aag.org
www.twitter.com/theaag

# For malaria progress: The bottom line IS the bottom line

David H Peyton. Ph.D., Professor of Chemistry at Portland State University explores the progress being made on malaria in the world today

The annual report issued by the World Health Organization (WHO) that tracks malaria worldwide came out at the end of November 2017 and it was not reassuring to those of us working against malaria. This report gave a picture that indicated progress has stalled (a word taken from WHO's website). This is a sobering introduction to the report, especially for an organisation that has been, in this person's estimation, optimistic about the state of malaria over the last few years.

**"New data from national surveillance systems suggests that we may be underestimating the burden of malaria and WHO will embark on a detailed review of national data and estimation methods in 2018. Even with the current conservative estimates, however, globally, the fight against malaria is at a crossroads."** *(From the World Malaria Report 2017, page 61)*

### What has stalled in malaria control?

To answer this, I turn to the Malaria Report itself. Firstly, the number of cases of malaria has increased, as enumerated in the report. This metric is greatly important because it reflects not only deaths, but also other burdens on the local economies, as well as effects on families, health systems and so on. Not only is the relatively modest increase in this number important – especially because the number has not decreased – but it is admitted being a conservative estimate by the compilers of the report.

Thus, the situation may be worse. These numbers are also somewhat biased in earlier years by the introduction of more rapid diagnostic tests for malaria, that has allowed more accurate numbers – rather than just presumption from a fever presentation: it may be that some of the earlier years' declines in malaria cases are not entirely accurate.

Secondly, the number of deaths from malaria has remained constant from 2015, instead of decreasing. Given the increase of cases, this might be taken as a minor victory, but remember – these numbers are conservative, so caution would be advised in any celebration.

Thirdly, the rate of distribution of insecticide-treated nets (ITNs) has decreased since 2014. This is particularly disturbing because the nets are not durable and holes in them can be viewed as analogous to drug resistance. If a mosquito can fly through a little hole, the net may reduce the frequency of biting, but still not (eventually) prevent the transmission of malaria.

The distribution of ITNs is primarily to those who are 'underserved' (have no nets, or not enough nets), so those with nets that are damaged or have an insecticide that has worn off or expired need net replacements. Yet the accounting for these cases is not clear.


Also, the mosquitos are becoming more resistant to the most common insecticides on the nets.

Fourthly, the intermittent preventative treatment of pregnant women (IPTp) is still far below the rates hoped for by the policy-makers. The same can be said for IPT of children.

Fifthly, access to appropriate drugs has improved over the last seven years, as has the application of rapid diagnostic testing. Yet even here, the overall coverage remains uneven, with some countries still not providing good access. Counterfeit drugs also remain a problem, especially in the private markets.

**What is at the heart of the lack of progress that we are seeing?**

We must look to the budgets, as much as we might wish to think that problems might be solved elsewhere. Realistically, problems like malaria, having a global reach and demanding both technological and implementation aspects to solve them over decades, must have sufficient funding to have any chance at success.

The World Malaria Report 2017 provides graphs on page five – demonstrating that the funding for the entire malaria enterprise has remained at about $2.8 billion ($2016-U.S., from 2010 – 2016). In fact, 2013 was the high-funding year (about $3 billion), followed by 2010 & 2012 (which had nearly the same funding amounts).

So, this is the situation that WHO optimistically terms, "stable." The major amount of funding comes from the U.S., yet the future of support from the U.S. for international projects may not be stable. For example, in 2017 an early draft budget from the President did not provide for the continuation of the Fogarty International Center of the National Institutes of Health and a large tax 'restructure' (cut) has just been enacted by Congress.

The message of the World Malaria Report is clear – that the financial underpinning for malaria needs to increase substantially – but whether this will be a realistic expectation from the U.S. and other sources is quite another matter.

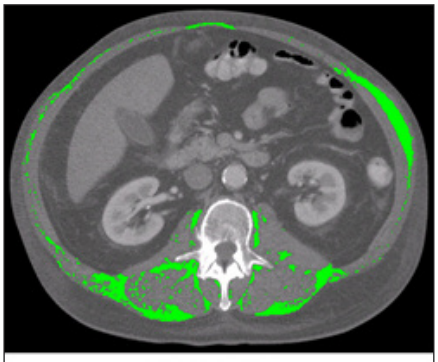
Portland State UNIVERSITY

**David H Peyton. Ph.D.**
**Professor of Chemistry**
Portland State University
Tel: +1 503 725 3875
peytond@pdx.edu
www.pdx.edu/chemistry/profile/dr-david-h-peyton
www.twitter.com/dmi_doc

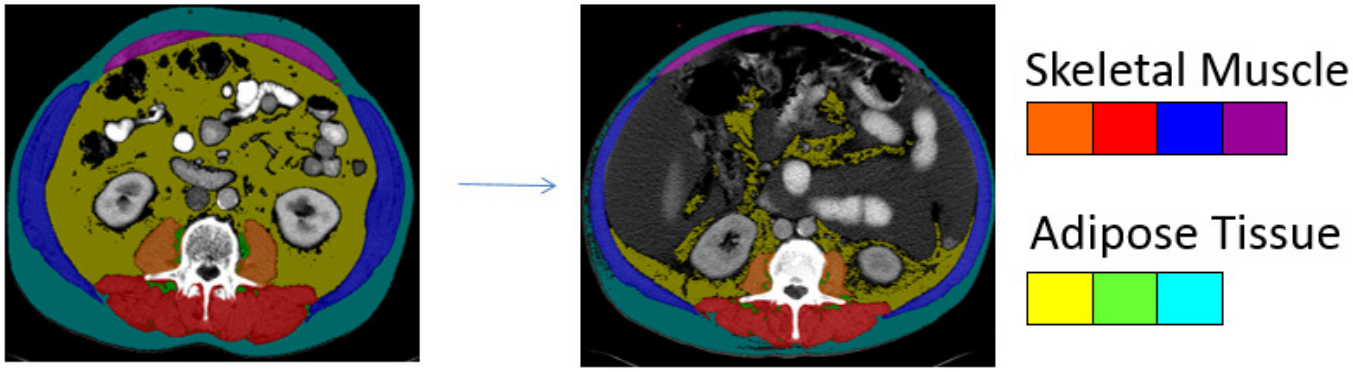
# Disease-associated myosteatosis in people with cancer: Can it be treated?

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

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

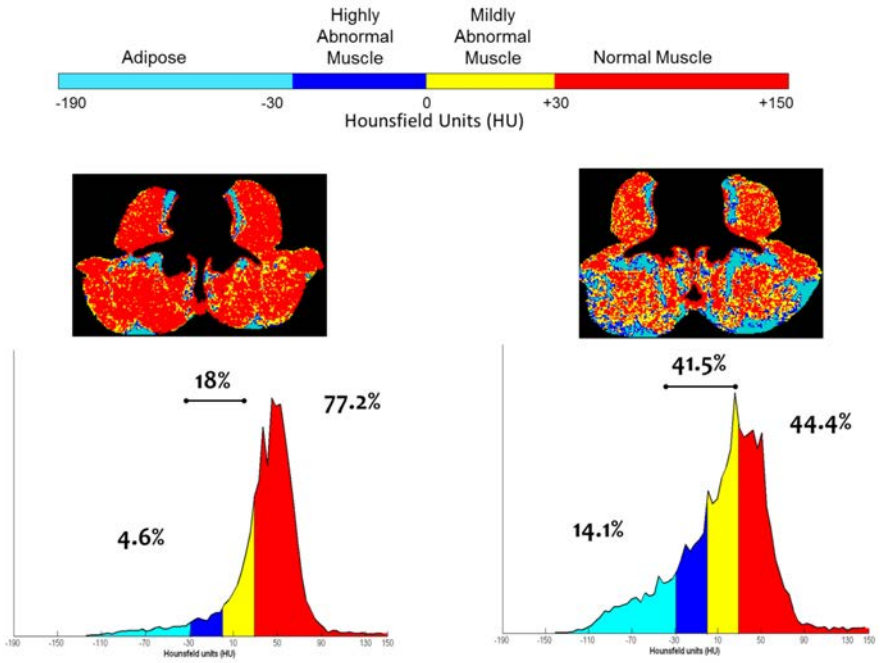


*This slide shows a CT image from a cancer patient who underwent 16 weeks of first line platinum doublet chemotherapy for lung cancer. Only the intramuscular adipose tissue is shown in color*




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

**Illustration of Variation in Muscle Radiodensity**




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

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

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

UNIVERSITY OF ALBERTA

**Dr Vera Mazurak**
University of Alberta
www.afns.ualberta.ca/StaffProfiles/AcademicProfiles/Mazurak.aspx

# AAV: From almost a virus to an awesome vector for human gene therapy

Dr. Arun Srivastava, George H. Kitzman Professor of Genetics, from the University of Florida describes the rationale and strategies for the development of next generation (NextGen), generation X (GenX) and optimised (Opt) recombinant AAV vectors for human gene therapy

Recombinant AAV vectors have been, or are currently being, used in 165 Phase I/II clinical trials (and one recent Phase III trial) in humans and thus far, no serious adverse events have ever been observed or reported. AAV2 vectors have shown clinical efficacy in three human diseases: Leber's congenital amaurosis (LCA), aromatic L-amino acid decarboxylase deficiency (AADC) and choroideremia. In the past decade, at least 12 additional AAV serotype vectors have also become available. AAV1 vectors have successfully been used in the gene therapy of lipoprotein lipase deficiency (LPL) and $\alpha$1-antitypsin deficiency (AATD); and AAV8 vectors have shown clinical efficacy in haemophilia B; AAV5 vectors in haemophilia A; and AAV9 vectors in spinal muscular atrophy (SMA) and Pompe disease. The AAV1-LPL vector was approved as a drug, designated as Alipogene tiparvovec and marketed under the trade name Glybera®, in Europe in 2012.

In 2017, an AAV2 vector expressing retinal pigment epithelium-specific 65 kDa protein (RPE65) was licensed as a drug, Voretigene Neparvovec (Luxturna), in the USA. Additional Phase I/II clinical trials are currently being pursued with AAV1, AAV2, AAV3, AAV5, AAV6, AAV8, AAV9 and AAV10 vectors for the potential gene therapy of a wide variety of human diseases.

Despite these remarkable achievements, it has become increasingly clear that the full potential of AAV vectors composed of the naturally occurring, wild-type (WT) capsids and genomes is unlikely to be realised for the reasons outlined below.

## AAV capsid is targeted for degradation by the host cell enzymes

Since the wild-type [WT] AAV did not evolve for the purposes of delivery of therapeutic genes, recombinant AAV vectors composed of naturally occurring capsid are unlikely to be optimal in human clinical trials. Dr. Srivastava's laboratory made the original observation that following infection of cells, only ~20% of the input AAV2 vectors gain entry into the nucleus, whereas ~80% fail to escape the endosome in the cytoplasm. It was subsequently reported that AAV2 capsids become ubiquitinated in the cytoplasm, where they are targeted for degradation by the host cell proteasomal machinery, thereby negatively impacting the transduction efficiency of the first generation of AAV vectors.

The WT AAV2 capsid contains specific amino acid residues (7 tyrosines {Y}, 17 serines {S} and 15 threonines {T} that are surface-exposed and are targeted for phosphorylation by the host cell protein kinases. In addition, AAV2 capsid also contains seven surface-exposed lysine (K) residues, which are ubiquitinated. These modifications render a large fraction of first generation of AAV vectors for degradation by the host cell proteasome machinery. Each of these surface-exposed Y, S, T and K residues were mutagenised in Dr. Srivastava's laboratory to generate the next generation (NextGen) of AAV vectors with improved intracellular trafficking to the nucleus and consequently, high-efficiency transduction.

Interestingly, most, if not all, of the surface-exposed Y, S, T and K residues are highly conserved among all 10 commonly used AAV serotype vectors and most of these residues have also been mutagenised in each of the 10 AAV serotype vectors. Thus, the capsid-modified next generation of AAV vectors, as schematically illustrated in figure 1, overcome some of the limitations associated with the first generation of AAV vectors.

In this context, it is important to point out that three Phase I/II clinical trials with one of these tyrosine-mutant AAV2 vectors have been initiated and the initial results appear very promising. In one trial, 13 of 14 patients with Leber's hereditary optic neuropathy (LHON), who were administered this vector intravitreally, showed improvement in visual acuity up to 24-month follow-up, without any loss of vision or any serious adverse events. Thus, the capsid-modified next generation of AAV serotype vectors will prove to be

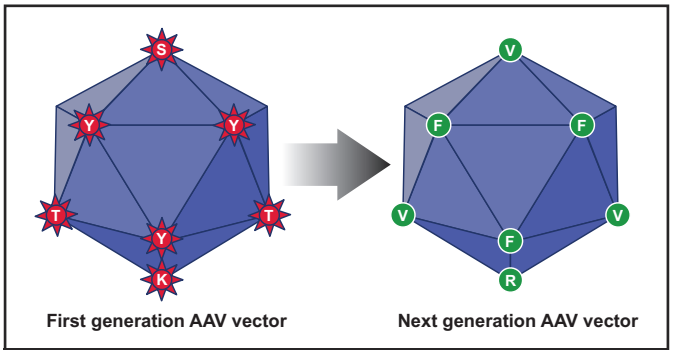



*Figure 1. Surface-exposed tyrosine (Y), serine (S), threonine (T) and lysine (K) residues in the first generation AAV vectors are mutagenised to phenylalanine (F), valine (V) and arginine (R) residues, respectively, in the next generation (NextGen) AAV vectors that are more efficient and less immunogenic.*

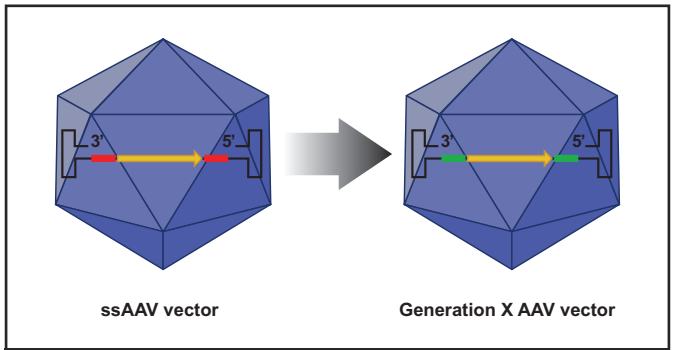



*Figure 2. The D-sequence in the ssAAV genome (depicted in red) is replaced by a substitute sequence (depicted in green) in the generation X (GenX) AAV vectors that mediate more efficient transgene expression. Encapsidation of the GenX genome into the NextGen capsid leads to the generation of more efficient optimised (Opt) AAV vectors.*

far more efficacious than their WT counterparts in human gene therapy.

## The single-stranded AAV genome is transcriptionally-inactive

The WT AAV genome is a single-stranded DNA and single-stranded DNA of both [+] and [-] polarities are encapsidated into separate mature virions with equal frequency. While inconsequential for the WT AAV, which remains latent in host cells, the single-stranded DNA of a therapeutic gene in an AAV vector is problematic, since single-stranded DNA is transcriptionally-inactive and viral second strand-DNA synthesis is a rate-limiting step during AAV vector-mediated transgene expression.

Dr. Srivastava's laboratory identified that FKBP52, a well-known cellular chaperone protein that binds the immunosuppressant drug FK506, interacts specifically with the single-stranded sequence of 20 nucleotides, termed the D-sequence, within the AAV inverted terminal repeat (ITR) at the 3' -end of the viral genome and strongly inhibits the viral second-strand DNA synthesis, resulting in impaired transgene expression. In nearly all clinical trials performed thus far have utilised ssAAV vectors and yet clinical efficacy has been observed in several human diseases, as outlined above.

Dr. Srivastava hypothesised that substitution of the D-sequences from the viral genome would allow more efficient viral second-strand DNA synthesis and consequently high-efficiency transgene expression. However, both D-sequence-substituted AAV genomes failed to undergo encapsidation. Interestingly, when only one of the two D-sequences was substituted from the AAV genome, successful encapsidation ensued and the efficiency of transgene expression from the D-sequence-substituted AAV genomes was significantly higher than that from their unmodified counterparts. These genome-modified vectors, designated generation X (GenX) AAV vectors are depicted schematically in figure 2.

Further studies revealed that the D-sequence at the 5' -end in the viral ITR contains the binding site for a cellular NF-κB repressing factor (NRF), which inhibits viral transgene expression. Thus, the genome-modified GenX AAV vectors partially overcome the limitation associated with the conventional ssAAV vectors.

More recent studies from Dr. Srivastava's laboratory have documented that when the modified AAV genomes are encapsidated into the modified capsids, the resulting optimised (Opt) AAV vectors transduce cells and tissues significantly more efficiently at 20-30–fold further reduced doses. Thus, the NextGen, GenX and Opt AAV serotype vectors circumvent the problems associated with the first generation of AAV vectors, in addition to being far more efficacious, less immunogenic and more cost-effective.

Plans are currently underway to use one of these NextGen AAV vectors to initiate a Phase I clinical trial in humans in a three-way collaboration among Christiann Medical College in India, and Emory University and University of Florida in the USA.

**Dr. Arun Srivastava PhD**
George H. Kitzman Professor of Genetics
University of Florida
Tel: +1 352 273 8259
aruns@peds.ufl.edu
http://research.pediatrics.med.ufl.edu/researchers/research-faculty/arun-srivastava/

# An emerging environmental health concern: Impacts of air pollution on the brain

Anthony S. Wexler and Pamela J. Lein from the University of California share their expert views on the impacts of air pollution on the brain

Air pollution is a complex mixture of gases and particles in the atmosphere. Air pollutants are defined as compounds known to be deleterious to human health and welfare. In the United States, air pollutants are categorised as criteria and hazardous pollutants. The criteria pollutants generally derive from combustion processes in motor vehicles, electric generating stations and industrial processes.

Criteria gases include carbon monoxide (CO), sulphur dioxide ($SO_2$), nitrogen dioxide ($NO_2$) and ozone ($O_3$); criteria particles are denoted by their size range, with $PM_{10}$ and $PM_{2.5}$ denoting the mass concentration of particles smaller than 10 micrometres (millionths of a metre) or 2.5 micrometres, respectively. Hazardous air pollutants are toxic chemicals, for example, benzene and arsenic.

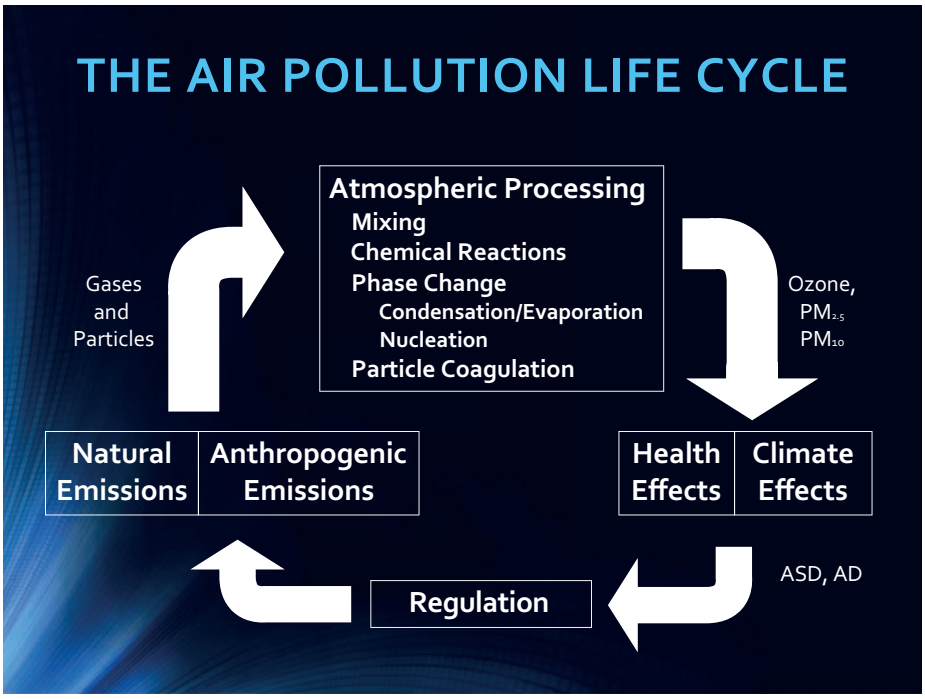
In a comprehensive review of the worldwide disease burden of pollution, recently published by The Lancet ("The Lancet Commission on Pollution and Health", published online October 19, 2017, www.thelancet.com), air pollution was identified as the predominant cause of pollution-associated morbidity and mortality. While the link between air pollution and respiratory and cardiovascular disease is well-established, more recent studies have raised concerns about the potential impact of air pollution on the brain, particularly the developing and the aging brain.

Air pollution and especially traffic-related air pollution have been associated with increased risk of neurodegenerative disease, in particular, Alzheimer's disease (AD) and diverse neurodevelopmental disorders, including autism spectrum disorder (ASD), attention deficit hyperreactivity disorder (ADHD), learning and intellectual disabilities and schizophrenia. These conditions exact a tremendous cost on the affected individual, their families and society motivating support for research that determines whether these associations are causal and if so, what components in air pollution are responsible and what individual factors (gender, age, nutritional status, genetic makeup, etc.) determine whether exposure to air pollution will result in neurological disease?

Researchers employ two complementary disciplines – epidemiology and toxicology – to study possible links between air pollution and health. Epidemiologic studies use statistics to test the strength of correlations between increased exposure to a given pollutant and higher incidence of disease. Epidemiologic studies can identify associations in the human population; however, they have a key weakness, often summarised as "correlation does not establish causation". Let us take for example living near heavily trafficked roadways, which has been associated with an increased incidence of ASD and AD. Is the effect due to the higher concentration of air pollutants near the roadway or due to the higher level of noise and vibration, or because housing is less expensive near busy roadways so people with lower incomes and possibly poor diet live near these roadways? And even if air pollution is the cause, which pollutant(s) cause the effect?

Another challenge arises from the fact that many neurological diseases, including AD and ASD, result from complex interactions between environmental factors and genetic susceptibilities: The wider the range of genetic susceptibilities within a population, the more challenging it is for epidemiology to identify clear associations between exposure and disease state.

Toxicology is a tool for unravelling these complex questions. To assess the health impact of air pollution, toxicologists use models ranging from cell cultures to laboratory animals and these can be engineered to express known human genetic susceptibilities to disease. In contrast to epidemiology, in toxicology, exposures can be controlled, and extraneous factors can be eliminated as variables, such as noise or diet in the near-roadway example above. In this way, toxicolo-




gists can determine if air pollutants cause an adverse health effect.

But toxicology faces the challenge of accurately mimicking human exposures. Think about the complexities of near-roadway air pollution, which is composed of incomplete combustion exhaust, brake wear, tire wear and road wear as well as derived from a mix of vehicles ranging from motorcycles to heavy duty trucks. At the University of California, Davis, we are addressing this challenge by locating animal exposure facilities adjacent to heavy traffic, so that the animals breathe the same mixture as people who live near busy roadways. In addition to assessing neurological outcomes in these animals, we are characterising the chemical composition of the air so future studies can assess the health effect of individual components within the polluted air to identify the disease-causing pollutant(s).

Why are we focusing on the near roadway example? While regulations promulgated to reduce emissions have significantly improved air quality in cities across North America and Western Europe, improved air quality in geographic locations close to sources of air pollution, such as roadways, power plants and industrial facilities, have lagged behind. People living in these locations have a higher incidence of disease, including neurological disease. Since individuals in lower socioeconomic strata are more likely to reside in more highly polluted neighbourhoods, the problem of near-source air pollution exposure is not just a public health issue, but also an environmental justice issue.

In conclusion, epidemiologic studies have identified a number of neurological diseases associated with air pollution. But questions still remain: Is the association causal or is there another intervening factor that underlies the observed association? What are the cellular and molecular mechanisms linking air pollution exposure to neuropathology? What components of the air pollution are causing neurological disease – Gases? Particles? Which ones? And what are the sources of neurotoxic air pollution? This last question is critically important because it is the sources that can be controlled by regulation. Answers to these questions, which will require toxicology in addition to epidemiology, are required to identify air pollution emissions control measures that effectively minimise neuropathological risks.

UCDAVIS VETERINARY MEDICINE

**Pamela J Lein**
**Professor and Vice-Chair**
Department of Molecular Biosciences
**Director, UC Davis CounterACT Center of Excellence**

**Anthony S Wexler**
**Distinguished Professor**
Department of Mechanical and Aerospace Engineering
Department of Civil and Environmental Engineering
Department of Land, Air and Water Resources
**Director, Air Quality Research Center**

University of California
Davis, CA 95616 USA
Tel: +1 530 752 1970
pjlein@ucdavis.edu
http://www.vetmed.ucdavis.edu/faculty/results.cfm?fid=19369
http://www.vetmed.ucdavis.edu/lein-lab/index.cfm

# Ground-breaking results for Huntington's Disease (HD) research

**Svein Olaf Olsen and Maiken Arnesen from the European Huntington Association reveal their thoughts on a recent and significant breakthrough concerning Huntington's Disease (HD) research**

The 11th December 2017 will probably go into history along with the discovery of the Huntington gene in 1993. On this date, IONIS Pharmaceuticals announced the results from the first Huntingtin lowering trial in humans. The result exceeded all expectations and represents a significant step towards a possible treatment for the hereditary – Huntington Disease (HD).

Huntington's Disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities during their prime working years and until now there has been no cure. HD is known as the quintessential family disease because every child of a parent with HD has a 50/50 chance of carrying the faulty gene (www.hdsa.org).

In Europe, we see a prevalence of 7-12 patients per 100,000. This means that in The European Union you find between 36,000 and 52,000 people with HD. In addition, you have more than 250,000 affected as children or grandchildren of an HD patient, says Astri Arnesen, President of The European Huntington Association (EHA).

Firstly, to find a drug that can slow down the development of the disease or even stop the progression is important for the affected human being and her/his family, is the best news, Astri Arnesen continues.

But it will also have enormous benefits on the health budgets. Studies from UK (European Journal of Neurology published by John Wiley & Sons Ltd on behalf of European Academy of Neurology 2016) show that the annual cost per person with HD was £21,605. The largest proportion of this cost (65%) was due to informal care (£14,085), Astri Arnesen says.

## Best Christmas gift ever for the Huntington community

For all of us involved in HD, the lowering results was: "The Best Christmas gift ever for the Huntington Community!", Astri Arnesen underlines

The compound has so far proven the ability to lower the expression of mutant huntingtin considerably. "This gives us reason to believe that the root cause of HD can be targeted and influenced," Astri Arnesen says. The treatment might slow down the progress of Huntington's and improve symptoms.

"I almost cried when Kristina Bowyer, the Executive Director, Patient Advocacy in Ionis, informed me about the amazing results," Astri continues.

"Huntington's Disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities during their prime working years and until now there has been no cure. HD is known as the quintessential family disease because every child of a parent with HD has a 50/50 chance of carrying the faulty gene."

## What is Huntingtin lowering?

'Switching off' the cause of Huntington's Disease was the first thought that appeared when the HD gene was discovered in 1993. Huntingtin lowering drugs – previously called 'gene silencing' drugs – reduce the activity of the HD gene.

The drug tells the cells to delete the 'message' from the 'sick' gene causing the disease. In other words: it 'shoots the messenger'. The first major progress in achieving this came around a decade ago, when several studies in HD mice reported success in reducing the activity of


the gene. And now the trial has been carried out in humans – with positive results.

The date of 11th December will therefore probably go into history along with the discovery of the HD gene in 1993. It's a milestone and big breakthrough.

### What is the next step?

There is still a huge job to be done and there may be setbacks, in recent weeks we have celebrated, and hope is raised among all HD affected families. We needed this great news and it encourages us to continue the hard work ahead of us, Astri states.

The pharma company Roche will now take over further development. Planning of the third phase of the trial has already started. This phase requires several hundred participants.

Astri comes with an appeal to the Huntington community: "We encourage potential participants to contact the HD clinics that Roche will choose for the trial. It is not yet known where and when the Phase III trial will be, but Roche announces that they want to act as soon as possible", says Astri Arnesen, President of the European Huntington Association.

"And the best part of it all – this is only the beginning. There are several other very exciting Huntingtin Lowering trials being done right now – or planned to start soon. I hope all HD affected enter 2018 with the reassurance that we are moving closer to our goal", Arnesen concludes. ■

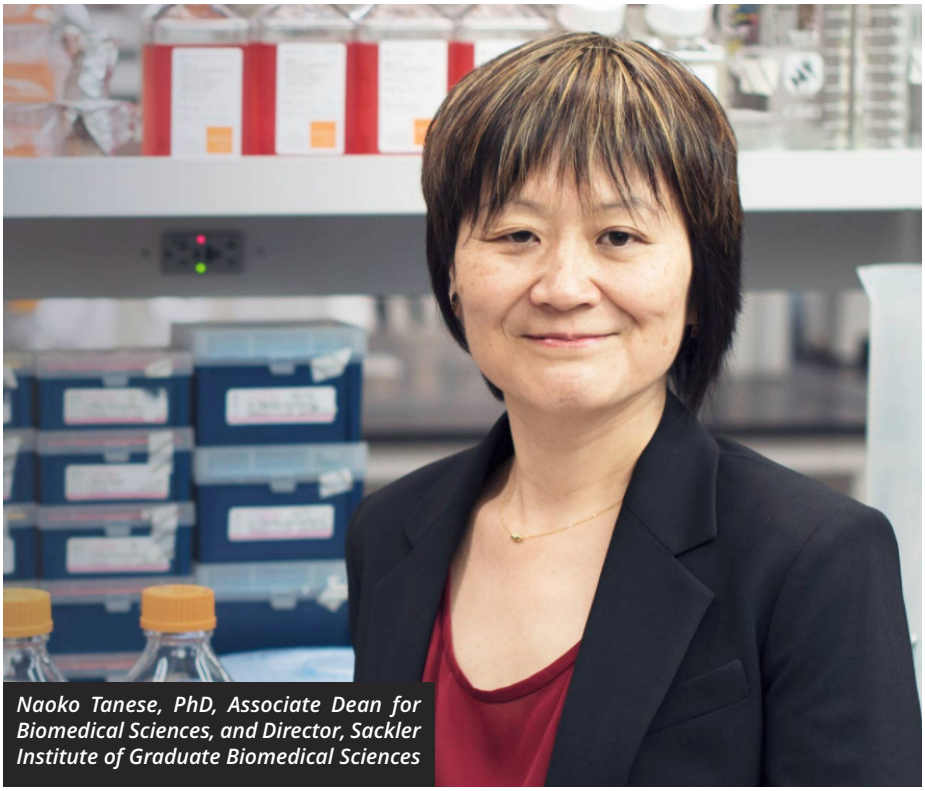
**Svein Olaf Olsen**
**Member at large**

**Maiken Arnesen**
**Web editor**
European Huntington Association
Tel: +47 90 20 20 31
astri@eurohuntington.org
http://eurohuntington.org/
www.twitter.com/eurohuntington

# 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.

**Naoko Tanese, PhD**
**Associate Dean for Biomedical Sciences, Director, Sackler Institute of Graduate Biomedical Sciences**
New York University School of Medicine
Tel: +1 212 263 8945
tanesn01@med.nyu.edu
https://med.nyu.edu/faculty/naoko-tanese
www.twitter.com/nyuschoolofmed
http://sackler.med.nyu.edu

# Technology interventions to address dyspnoea: Point-of-care lung ultrasonography

**Cecilia Van Cauwenberghe from Frost & Sullivan's TechVision Group highlights technology interventions that address dyspnoea – focussing on point-of-care lung ultrasonography**

The Murray and Nadel's Textbook of Respiratory Medicine (Schwartzstein and Adams, 2016), etymologically defines dyspnoea from the Greek dys (painful, difficult) and pneuma (breath). Clinically, dyspnoea constitutes a medical expression related to the awareness of breathlessness or shortness of breath experienced by both normal subjects and patients suffering, from either respiratory or cardiovascular disease, such as chronic obstructive pulmonary disease (COPD), heart failure, advanced cancer and interstitial lung diseases, among many others.

It is important to remark that breathlessness or dyspnoea is generally defined subjectively (Bolzani et al., 2017a). The experience of breathing discomfort involves qualitatively individual perceptions that may vary in intensity. Just to make a small but important difference, breathlessness indicates the patient's perspective according to daily experience; dyspnoea applies to the vital signs of the underlying medical condition. Such a patient's perspective or experience also entails interactions among multiple physiological, psychological, social and environmental factors, intervening all together in the form of a secondary physiological and behavioural response.

Due to its causes may derive from multiple sources, no precise data on the prevalence of dyspnea is available (Bolzani et al., 2017b). Meta-analyses insinuate a worldwide prevalence of 10% for COPD in adults older than 40 years exhibiting dyspnea as a cardinal symptom. Dyspnea in children, on the other hand, has been reported including its psychosocial impact (Lands, 2017).

Such a subjectivity of dyspnoea is precisely one of the main challenges faced in both diagnosis and treatment. Its causes fall into three broad categories: respiratory system dyspnea, cardiovascular system dyspnea and dyspnea due to atypical causes. Moreover, different types of dyspnea can be cited according to its duration: acute (sudden appearance and persistence over hours to days) and chronic (gradual appearance and persistence during weeks or months.

Different types of dyspnea are also observed in terms of activity: physical exertion dyspnea (unpredicted dyspnea at rest indicating a potentially serious medical disorder), intermittent dyspnea (usually due to cold air or allergy suggesting asthma), work-related dyspnea (potentially indicating occupational asthma), upper respiratory tract infections dyspnea (suggesting COPD), orthopnoea (when lying down, usually in the supine position, typically associated with heart failure), paroxysmal nocturnal dyspnea (also indicating heart failure), trepopnoea (associating shortness of breath with lying on the left or right side) and platypnoea (only in the upright position), among other types.

Therefore, determining the cause of dyspnea is a task of vital importance in which first symptoms appearance, onset, character, duration, interval, periodicity and acuteness of the symptoms play all distinctive roles.

## Clinical interventions of dyspnoea

### Primary assessment

Primary assessment starts with a physical examination. Hence, when receiving a case of dyspnea, important clues about its underlying causes can be provided by assessing vital signs. Tachycardia or accelerated pulse, for instance, may indicate anemia, heart failure, or pulmonary embolism. Peripheral edema or distention of the jugular veins may be also associated with heart failure, as well as, cardiac whispers may be related to cardiac valvular disorders. Conversely, decreased breath sounds and wheeziness may suggest COPD.

Conventional testing implies pulse oximetry, complete blood count, basic metabolic panel, chest radiography, electrocardiography (ECG) and spirometric studies, which either reveal or discharge the existence of signs of heart failure, arrhythmias, pneumonia and interstitial lung disease or lung tumour. Evidence of asthma and pulmonary embolism may exhibit normal radiographic findings; however, spirometry is a supportive study for detecting airflow obstruction. Additional studies comprise echocardiography, computed tomography (CT scan), ventilation-perfusion scanning, ultrasound and stress testing.

Primary measures in blood analysis may involve brain natriuretic peptide (BNP), a cardiac neurohormone secreted by the myocardium and its prohormone, N-terminal pro-BNP, which in patients with dyspnoea due to heart failure, their concentrations are increased, thus helping physicians to discern between respiratory and cardiovascular causes of dyspnoea. Another biomarker frequently used in D-dimer, associated with fibrin degradation in the blood and pulmonary emboli.

## Multidimensional diagnostics approaches

Dyspnoea can be defined as a multidimensional experience. Therefore, there is no a comprehensive, validated instrument capable of embodying the multidimensional nature of dyspnoea (Banzett and Moosavi, 2017). Now, there are two multidimensional instruments: the Dyspnoea 12 (D-12) and the Multidimensional Dyspnea Profile (MDP) intended to address this challenge.

D-12 was designed to provide a single global score embracing the affective dimension. This approach is easy to apply to a variety of patient groups and accessible for patients waiting to be seen in a clinic. It attempts to avoid under- or over-medication based on unidimensional scales that ignored the affective aspect of dyspnoea.

MDP was elaborated to deliver a better characterisation of the complex dyspnoea experience, also matching laboratory and clinical. Patients first of all, rate the overall breathing as a scale indicator of discomfort or

unpleasantness and then rate the intensity of a set of individual sensory descriptors. The approach also comprehends a measurement model for pain and a list of negative emotions, in addition to the synonymous sensory descriptors and sensation categories for clustering and principal components analyses.

### Breathlessness management

Suitable management to relieve breathlessness in advanced diseases may require both pharmacological and non-pharmacological interventions (Bolzani et al., 2017c). Some pharmacological interventions refer to opioids, benzodiazepines and oxygen. Nevertheless, the use of drugs to treat breathlessness, especially if the underlying cause is not deeply understood, is limited due to potential adverse side effects and the extreme care needed for doses titration.

> "It is important to remark that breathlessness or dyspnoea is generally defined subjectively. The experience of breathing discomfort involves qualitatively individual perceptions that may vary in intensity. Just to make a small but important difference, breathlessness indicates the patient's perspective according to daily experience; dyspnoea applies to the vital signs of the underlying medical condition."

Non-pharmacological interventions for the relief of breathlessness may be focused on three categories: respiratory, related to inefficient breathing observed due to dysfunctional breathing patterns and increased respiratory rate; cognitive-emotional, associated with patient feelings around the sensation of breathlessness generating anxiety, distress, feelings of panic and thoughts about dying; and physical, related to deconditioning of limb, chest wall and accessory muscles as a result of dyspnoea.

Non-pharmacological interventions focused on respiratory approaches attempt to relieve breathlessness through breathing training, handheld fan and chest wall vibration, among many other resources (Bolzani et al., 2017a). Non-pharmacological interventions concentrated on cognition or emotion to relieve breathlessness use distractive auditory stimuli (music), meditation/relaxation (e.g. visual or guided imagery; progressive muscle relaxation), biofeedback, mindfulness-based stress reduction, yoga therapy and psychological therapy (e.g. cognitive behavioural therapy) (Bolzani et al., 2017b). Non-pharmacological interventions based on physical functioning may involve pulmonary rehabilitation and nutrition support (Bolzani et al., 2017c).

## Technology interventions of dyspnoea

### Point-of-care lung ultrasonography

The influence of age, multimorbidity, cognitive and motor impairment is essential for the accurate diagnosis of dyspnea (Vizioli et al., 2017). In fact, lung ultrasound (LUS) has been widely recognised as a relevant study in the differential diagnosis of dyspnea in internal medicine (Perrone et al., 2017). Being dyspnoea one of the most recurrent causes of admission in internal medicine wards (Wang et al., 2017), LUS at the bedside provides high sensitivity and specificity, thus helping clinicians to manage medical resources. In fact, a wider use of a portable technique in the internal medicine wards is significantly gaining attention. Bedside LUS has demonstrated to notable contributions to the differential diagnosis of dyspnoea, exhibiting higher sensitivity and specificity than any other technique. Its application not only is restricted to emergency rooms, but also to sub-acute internal medicine areas.

Radiologic and laboratory results may cause disproportionate delay previously adequate therapy is indicated. Therefore, the use of an integrated point-of-care ultrasonography (PoCUS) approach may represent the ideal solution by offering shorter time needed to formulate a diagnosis, while preserving an appropriate safety profile (Zanobetti et al., 2017).

This non-invasive intervention may involve the ultrasound evaluation of the lung, heart and inferior vena cava, in addition to conventional tests, which can be performed in parallel.

PoCUS has shown results for the diagnosis of acute coronary syndrome (ACS), pneumonia, pleural effusion, pericardial effusion, pneumothorax and additional causes of dyspnea, with remarkable accuracy when compared to conventional examinations. Indeed, PoCUS may result significantly more sensitive, especially when the cause of dyspnea is associated with heart failure.

Furthermore, patients can be stratified for a more detailed assessment, in which PoCUS denotes a feasible and reliable diagnostic approach to the patient with dyspnea, additionally involving a considerable reduction in time to diagnosis. In agreement with these approaches, adjacent technologies such as wearables, microfluidics, emerging sensors and artificial intelligence, are converging toward the development of new products focused on the complexity around dyspnoea.

## Brief market landscape considerations

According to Frost & Sullivan investigations (Das, 2016), point-of-care testing (POCT) constitutes an integral part of the healthcare market. Indeed, POCT is promptly evolving into a preferred testing mode in Europe and North America. Frost & Sullivan found that POCT, a particularly PoCUS, displays unparalleled growth opportunities for a cross-section of players, ranging from original equipment manufacturers (OEMs) to data integrators to technology vendors.

The stakeholders need to be well-informed about the challenges posed by the industry to design intelligent growth strategies - to innovate their business models and capitalise on the transformation that the market is undergoing and principally, to deliver real-world solutions to unmet medical needs such as dyspnoea. Different technological building blocks are smartly contributing to the better clinical translation and functionality of powerful tools to diagnose dyspnoea. ■

Acknowledgements

I would like to thank all contributors from industry involved with the development and delivery of this article and Frost & Sullivan's staff from the TechVision Group.

Further reading

Banzett, R.B. and Moosavi, S.H., 2017. Measuring dyspnoea: new multidimensional instruments to match our 21st-century understanding.

Bolzani, A., Rolser, S.M., Kalies, H., Maddocks, M., Rehfuess, E., Swan, F., Gysels, M., Higginson, I.J., Booth, S. and Bausewein, C., 2017a. Respiratory interventions for breathlessness in adults with advanced diseases. The Cochrane Library.

Bolzani, A., Rolser, S.M., Kalies, H., Maddocks, M., Rehfuess, E., Hutchinson, A., Gysels, M., Higginson, I.J., Booth, S. and Bausewein, C., 2017b. Cognitive-emotional interventions for breathlessness in adults with advanced diseases. The Cochrane Library.

Bolzani, A., Rolser, S.M., Kalies, H., Maddocks, M., Rehfuess, E., Gysels, M., Higginson, I.J., Booth, S. and Bausewein, C., 2017c. Physical interventions for breathlessness in adults with advanced diseases. The Cochrane Library.

Das, R., 2016. Western Europe Point-of-Care Testing (POCT) Market – Integration, Miniaturization and Consumerization will Accelerate Growth in the Future. Frost & Sullivan Market Engineering. http://www.frost.com/mc01.

Lands, L.C., 2017. Dyspnea in Children: What is driving it and how to approach it. Paediatric Respiratory Reviews.

Perrone, T., Maggi, A., Sgarlata, C., Palumbo, I., Mossolani, E., Ferrari, S., Melloul, A., Mussinelli, R., Boldrini, M., Raimondi, A. and Cabassi, A., 2017. Lung ultrasound in internal medicine: A bedside help to increase accuracy in the diagnosis of dyspnea. European journal of internal medicine, 46, pp.61-65.

Schwartzstein, R.M. and Adams, L., 216. Murray and Nadel's Textbook of Respiratory Medicine, Sixth Edition.

Vizioli, L., Forti, P., Bartoli, E., Giovagnoli, M., Recinella, G., Bernucci, D., Masetti, M., Martino, E., Pirazzoli, G.L., Zoli, M. and Bianchi, G., 2017. Accuracy of Lung Ultrasound in Patients with Acute Dyspnea: The Influence of Age, Multimorbidity and Cognitive and Motor Impairment. Ultrasound in Medicine & Biology.

Wang, Y., Shen, Z., Lu, X., Zhen, Y. and Li, H., 2017. Sensitivity and specificity of ultrasound for the diagnosis of acute pulmonary edema: a systematic review and meta-analysis. Medical Ultrasonography.

Zanobetti, M., Scorpiniti, M., Gigli, C., Nazerian, P., Vanni, S., Innocenti, F., Stefanone, V.T., Savinelli, C., Coppa, A., Bigiarini, S. and Caldi, F., 2017. Point-of-care ultrasonography for evaluation of acute dyspnea in the emergency department. Chest.

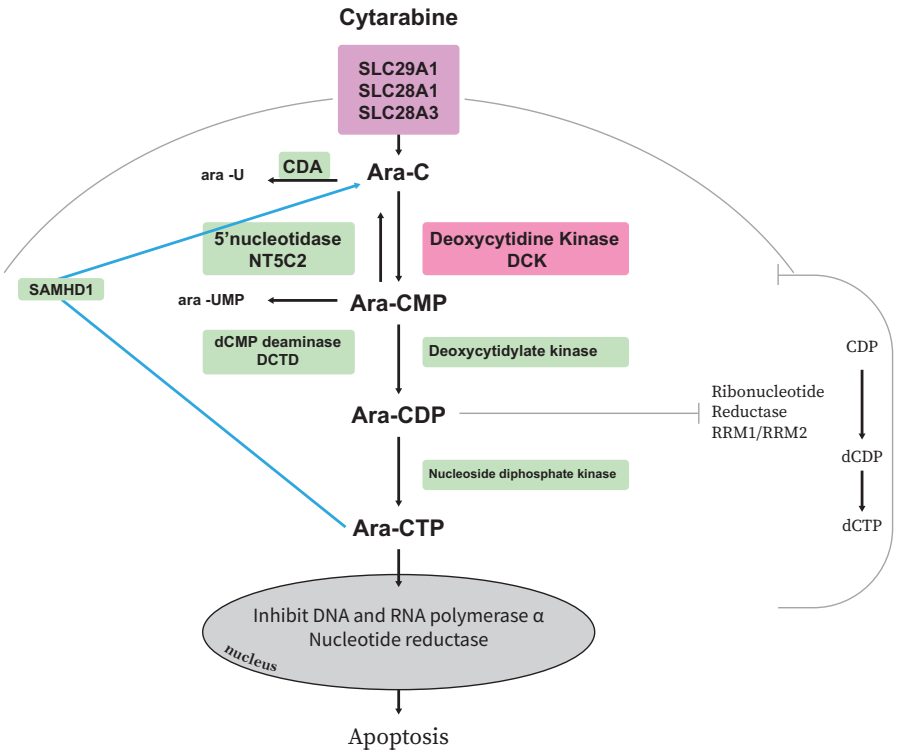
**Cecilia Van Cauwenberghe, Ph.D., MSc, BA**
**Associate fellow and senior industry analyst**
TechVision Group, Frost & Sullivan
Tel: +1 210 678 3623
Cecilia.VanCauwenberghe@frost.com
www.frost.com
www.twitter.com/Frost_Sullivan

# Acute myeloid leukaemia (AML) and cytarabine pharmacogenomics

Professor Jatinder Lamba from the Department of Pharmacotherapy and Translational Research gives an in-depth perspective on acute myeloid leukaemia (AML) and cytarabine pharmacogenomics

Acute myeloid leukaemia (AML) is the cancer of the myeloid precursor stem cells characterised by the appearance of immature, abnormal myeloid cells in bone marrow and other organs. AML is a very heterogeneous disease with various subtypes classified based on the morphology, immnuophenotype and cytogenetics.

Despite advances in recent years, the 5-year survival rates for AML are ~68% for children younger than 15 years and ~57% for children between 15-19 years. The utilisation of multiple clinical, cytogenetic and other molecular features that are associated with the response has helped in identification of patient's more/less likely to respond.




Additionally, minimal residual disease (MRD) after induction 1 has been identified as a powerful predictor of poor outcome. The nucleoside analog, cytarabine (ara-C), has been the mainstay of AML chemotherapy for more than 40 years[1,2]. The most common treatment strategy includes induction therapy, which consists of 3+7 regimen with daunorubicin (45 mg/m$^2$ per day for 3 days) and cytarabine 100mg/m$^2$ for 7 days). This induction regimen has been shown to induce remission in 60-70% of patients. Cytarabine, in combination with varying doses of anthracycline and addition of a third agent (cladribine, clofarabine and more recently CD33 targeted therapies such as gemtuzumab ozogamicin etc.), has been the standard of practice for a few years now.

However, despite the major advances in AML drug combination strategies and treatment options, resistance and disease remission represent our major obstacle to reach the desired outcomes[3,4]. Although a significant proportion of patients achieve complete remission after initial therapy, most of these experience relapse which has a significant impact on long-term survival rates[5].

One of the most common and severe toxicities associated with cytarabine is myelosuppression. Cytarabine is a prodrug requiring activation to ara-CTP through series of phosphorylation steps and this triphosphate form of ara-C inhibits DNA polymerase-α and β and competes, with deoxycytidine triphosphate (dCTP) for incorporation into DNA and RNA thereby inhibiting DNA synthesis and triggering leukaemic cells[6-8]. Thus, intracellular levels of the active ara-CTP are critical for achieving significant leukaemic cell death. Previous *in vitro* studies have shown that the intracellular concentrations of ara-CTP are higher in ara-C sensitive cells, than in resistant cells.

Further, leukaemic cells from patients with chronic myelogenous leukaemia

(which is not responsive to ara-C), have only half the ara- CTP levels, as compared to leukaemic cells from patients with AML (which is responsive to ara-C)[4].Thus, one of the mechanism underlying ara-C resistance is insufficient intracellular levels of the active triphosphate metabolite ara-CTP, which may be due to:

- Inefficient cellular uptake due to low levels of the transporters (SLC29A1, SLC28A3 and SLC28A1);
- Reduced activation due to alterations in enzymes as DCK, CMPK1;
- Increased inactivation rates due to NT5C2, CDA, or DCTD and more recently identified enzyme SAMHD1[9]; and/or
- Increased cellular dCTP pools, that can compete with DNA incorporation of ara-CTP and inhibit DCK activity which, in turn, are regulated by the enzyme ribonucleotide reductase (consisting of RRM1 and RRM2 subunits). Figure shows metabolic pathway and thus key players that might impact cytarabine activation and thus its therapeutic benefit.

Single nucleotide polymorphisms (SNPs) in genes involved in transport, activation and inactivation of cytarabine can influence the intracellular ara-CTP levels by influencing the expression and activity of these genes and this, in turn, can also influence the clinical outcome of the patients treated with ara-C.

Several studies so far have investigated some of the key players and have shown an association of SNPs within key candidate cytarabine metabolism genes and clinical response in AML patients, or with cytarabine in vitro chemosensitivity[10]. Our group has previously reported an association of SNPs in DCK, NT5C2 and RRMs with intracellular levels of ara-CTP in leukaemic cells, as well as clinical response to AML[11-15].

Despite these efforts, one of the biggest gaps in the literature is that most of the previous studies have focused on selective genes and so far, no study has performed a comprehensive and integrated analysis of genetic variation in the complete cytarabine metabolic pathway. It is important to note that simultaneous contribution of multiple genes can impact the drug activation and thus response, so it is very critical to the field of pharmacogenomics around AML/paediatric and AML is still in its infancy.

In summary, AML is a very heterogeneous disease, with multiple subgroups that impact the therapeutic outcome. Pharmacogenomics has the potential to improve the clinical outcome in AML, although there are limited studies, results so far indicate the potential for SNPs in activating, inactivating enzymes, as well as drug transporter to be of clinical relevance. The integration of pharmacogenetic markers with prognostic markers in larger clinical cohorts can advance our ability to designed personalised therapy for patients to achieve greatest therapeutic benefit.


1. Braess, J. [Acute myeloid Leukemia]. Dtsch Med Wochenschr 141, 1748-1751 (2016).
2. Short, N.J. & Ravandi, F. Acute Myeloid Leukemia: Past, Present, and Prospects for the Future. Clin Lymphoma Myeloma Leuk 16 Suppl, S25-9 (2016).
3. Rowe, J.M. AML in 2016: Where we are now? Best Pract Res Clin Haematol 29, 315-319 (2016).
4. Abraham, A. et al. RNA expression of genes involved in cytarabine metabolism and transport predicts cytarabine response in acute myeloid leukemia. Pharmacogenomics 16, 877-90 (2015).
5. Ravandi, F. Relapsed acute myeloid leukemia: why is there no standard of care? Best Pract Res Clin Haematol 26, 253-9 (2013).
6. Major, P.P., Egan, E.M., Beardsley, G.P., Minden, M.D. & Kufe, D.W. Lethality of human myeloblasts correlates with the incorporation of arabinofuranosylcytosine into DNA. Proc Natl Acad Sci U S A 78, 3235-9 (1981).
7. Major, P.P., Sargent, L., Egan, E.M. & Kufe, D.W. Correlation of thymidine-enhanced incorporation of ara-C in deoxyribonucleic acid with increased cell kill. Biochem Pharmacol 30, 2221-4 (1981).
8. Yates, J. et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood 60, 454-62 (1982).
9. Schneider, C. et al. SAMHD1 is a biomarker for cytarabine response and a therapeutic target in acute myeloid leukemia. Nat Med 23, 250-255 (2017).
10. Bhise N., C.L., and Lamba J.K. Genome-Wide Association Studies – From polymorphisms to Personalized Medicine, Chapter 19: Pharmacogenetic studies in pediatric acute myeloid leukemia, (Cambridge University Press, 2016).
11. Cao, X. et al. RRM1 and RRM2 pharmacogenetics: association with phenotypes in HapMap cell lines and acute myeloid leukemia patients. Pharmacogenomics 14, 1449-66 (2013).
12. Lamba, J.K. Pharmacogenomics of cytarabine in childhood leukemia. Pharmacogenomics 12, 1629-32 (2011).
13. Mitra, A.K. et al. Genetic variants in cytosolic 5'-nucleotidase II are associated with its expression and cytarabine sensitivity in HapMap cell lines and in patients with acute myeloid leukemia. J Pharmacol Exp Ther 339, 9-23 (2011).
14. Lamba, J.K. Genetic factors influencing cytarabine therapy. Pharmacogenomics 10, 1657-74 (2009).
15. Lamba, J.K. et al. Pharmacogenetics of deoxycytidine kinase: identification and characterization of novel genetic variants. J Pharmacol Exp Ther 323, 935-45 (2007).


Lamba Lab members involved in the cytarabine pharmacogenomics research include AbdelRehman Elsayed, Dr. Roya Rafiee and Salma Bargal

UF Department of Pharmacotherapy and Translational Research
College of Pharmacy


**Professor Jatinder Lamba**
Department of Pharmacotherapy and Translational Research
Tel: +1 352 273 6425
jlamba@cop.ufl.edu
jatinderklamba@ufl.edu
http://ptr.pharmacy.ufl.edu/


# Are we ready for a blockchain world?

## Marta Pierkarska, Director of Developer Ecosystem, Hyperledger asks if we are ready for a blockchain world in the future

Blockchain, the hype, the buzzword of the decade, the fairy dust that is supposed to solve all our problems. Technology that underlies Bitcoin and most other cryptocurrencies and is often confused with it. However, the umbrella of distributed ledger technology has applications beyond cryptocurrency.

Today, we see adopters in business environments in nearly every industry, ranging from financial and banking, through manufacturing and supply chain all the way to intellectual property, healthcare or real estate. Blockchain brings a promise of a secure, cost-efficient, transparent and easily auditable way to track any asset. Physical goods can be tokenised, traded and tracked through virtual peer to peer, distributed business networks without requiring a centralised point of control.

Hopefully, with the excitement around it, this technology can become pervasive in enterprises, government agencies and perhaps even the public sector. Why? Because, at any time a community of organisations need to have a common system of record and build useful automation on top of it, so a blockchain will make sense. It cannot solve the issues of authenticity – we still need auditors to verify what is put on a blockchain but distributed blockchains in business settings will probably become the invisible backend piping that helps almost any industry. Most industries use transactions to get work done. Most industries have trust challenges. Most industries suffer from contracts being manually executed and assets being opaque.

Also, we find that most industries are looking for cost savings. We observe some fields being particularly eager to jump in and others are more in observation mode, but even the less brave ones have early adopters. The biggest challenge is lack of technical talent that can help with defining the use cases and deploy production system. This is a skill that will be highly relevant for many years to come.

What this all means for consumers is anyone's guess. Blockchain most probably will be completely invisible technology that just improves the systems we have today. Today, most users do not know that mobile devices include several chips and 2 operating systems. Many consumers don't even know what an operating system is.

Similarly, they should not be expected to know that the sustainably caught fish they ordered in a restaurant was tracked and certified with the use of distributed ledger technology, which meant it became affordable to them. The prospect for using this tech to go beyond a common system of record, to create actual digital assets on a chain (an insurance contract, an options contract, shares in a company, etc.) is very real and people are already piloting this.

We're encouraged to see so many regulators, banks, governments and others working to build up their own competencies in this space so that as industries start to implement their business processes as blockchain applications, the regulatory and statutory hurdles can be addressed. At Hyperledger, we're focused on creating an open framework for a cross-industry distributed ledger that can revolutionise the way we do business, increasing trust, accountability and transparency, while simultaneously streamlining business processes.

As with any technology, young or mature, we have challenges we are facing every day. There are issues around regulations and adaptability of the solutions – how do we plug new solutions into the existing legacy systems, even if we know that there are huge benefits to it, the technical questions still need to be answered. What stops many enterprises from moving from POC to deployment is performance, scalability and interoperability.

We need mature stable technologies and techniques for scaling transactions across chains. This is true even in a consortium chain setting, where you can achieve much higher transaction rates than on the public chains. Getting to tens of thousands of transactions per second across geographically diverse networks with non-trivial validation logic running on each node will be an architectural and design challenge for developers working in this space.

The good news is there are many use cases requiring lower transaction rates (land titles, medical records for a small country, supply chain flows for a given industry) and developers at Hyperledger are working on solutions for addressing scalability. This is just a function of time. This technology is still very young and we're still addressing the management, monitoring and design challenges – what you might call the "DevOps of blockchain." We'll expect substantial progress in 2018, but these are still early days.

So, are we ready for a world powered by blockchain? Are we ready to usher in a new trustless paradigm, where people no longer need to trust organisations but instead trust the software? I think so – it's not too crazy to think that in the next 5 years, nearly every Fortune 500 company will have a distributed ledger as part of their back-end system somewhere. However, let's remember – blockchains are based on a peer-to-peer network, so you need peers to build that a common system of record. In this space, we need to collaborate and interoperate.

It also means that anywhere where a company participates in a network of trading partners, a supply chain, a regulated market, etc., then they likely will see an operational and strategic investment in blockchain tech. I have some personal wishes. I wish to be able to manage my personal healthcare records through a "wallet" of some sort. I wish to have inter-bank or even international payments settle immediately rather than over the course of days.

I hope that the provision of government services – particularly when it comes to property registry, permits, voting registration and other process/transactional touch points – will dramatically change. Most of all I hope that blockchain will bring people closer than before – collaboration and cooperation for the better of mankind and especially that we will not have just a single blockchain to rule them all. ■

**Marta Pierkarska**
**Director of Developer Ecosystem**
Hyperledger
info@hyperledger.org
www.hyperledger.org
www.twitter.com/hyperledger

# Distributed ledger Blockchain technology for the financial services industry

**We interviewed R3's Chase Gordon to learn about cutting-edge distributed ledger technology for businesses in the financial services industry today**

R3 builds cutting-edge distributed ledger technology for businesses. Corda, an enterprise-grade, blockchain-inspired DLT platform was designed by and for the financial industry, with input from over 100 banks, financial institutions, regulators, trade associations, professional services firms and technology companies.

This blockchain-inspired DLT platform was designed to meet the highest standards of the financial services industry, one of the most complex and highly regulated industries in the world, which also means it can be applied to all other areas of commerce. Applications of this blockchain-inspired DLT platform will in 2018 include, collateral lending, FX matching, syndicated lending and open account trade finance.

Chase tells us that other areas of application for such distributed ledger technology include insurance, reinsurance, healthcare and many more as the interview begins. He offers his thoughts on the role of Blockchain in the financial services world, first of all, in his own words.

*Chase Gordon, Associate at R3*

"There are many benefits of using Blockchain in the financial services industry. The industry is known for using financial systems that date back 30 years or more, so it's not surprising that it has embraced Blockchain widely to improve upon such legacy systems. Blockchain enables the financial services industry to create better efficiencies and save money in the process.

"One of the key areas of financial services that blockchain can enhance is settlement of trades, which in some cases can take as long as a week, which is completely inappropriate for today's operating environment. Blockchain can reduce this time to minutes or even seconds.

"In addition, blockchain can help the industry move closer towards full automation with the use of smart contracts that execute automatically once pre-set conditions are met. Our Corda platform uses smart contracts that link business logic and data to associated legal prose to ensure that the financial agreements on the platform are rooted firmly in law.

"This blockchain-inspired DLT platform is the foundation of a vibrant ecosystem of interoperable applications for finance and commerce. These apps are built by a growing network of partners, harnessing the power of DLT to overcome the specific challenges faced by their customers."

The conversation then moves to how one would explain distributed ledger technology to somebody with little or no knowledge of it, something that Chase is eager to explain to us.

> "There are many benefits of using Blockchain in the financial services industry. The industry is known for using financial systems that date back 30 years or more, so it's not surprising that the it has embraced Blockchain widely to improve upon such legacy systems. Blockchain enables the financial services industry to create better efficiencies and save money in the process."

"Distributed ledger technology is essentially an immutable record of an agreement, which is secured cryptographically through hashes and keys, and it has an audit trail which is evaluated by separate nodes.

"On a traditional blockchain, each entity has its own node and information is shared to each of these nodes to validate a transaction. Corda tweaks this approach to data privacy and security by only sending data to those who have a "need to know."

"This unique feature of Corda emerged from the requirements of financial institutions which need to ensure the confidentiality of trades and agreements, while also capturing the benefits of a distributed ledger infrastructure."

In closing, Chase underlines the vital role that research and development (R&D) plays in the field.

"Back in September 2015, we launched an architectural working group with our members, which was the largest collaborative R&D effort in the industry. The learnings from this helped us to build Corda. We currently have around 60 R&D projects on the go and continue to use the findings from these as we ready Corda for commercial roll-out." ■

**Chase Gordon**
**Associate**
R3
www.r3.com
www.twitter.com/inside_r3

# The Oceans Protection Plan is transforming marine safety in Canada

**Canada's Minister of Transport, The Honourable Marc Garneau explores the Oceans Protection Plan and how this is transforming marine safety in Canada today**

Prime Minister Justin Trudeau's announcement in November 2016 of the $1.5 billion Oceans Protection Plan marked the largest ever investment to improve marine safety and protect Canada's coasts.

Since then, the government has launched more than a dozen innovative initiatives as part of the Oceans Protection Plan and, in the coming years, will continue to dedicate resources to improve Canada's marine safety system, build and enhance emergency response capacity and protect the marine environment. This is the government's most comprehensive plan to protect our coasts and the most ambitious investment in our oceans ever made by the Government of Canada.

Several methods to better protect Canada's coasts are being explored. Among challenges faced by our coastal communities are managing marine traffic congestion and improving local understanding of the activity taking place in their waters. The Anchorages and Enhanced Maritime Situational Awareness initiatives, under the Oceans Protection Plan, address this need directly.

## Addressing marine traffic congestion in Canada

In Canada, the right to anchor a vessel is part of the common law right of navigation. A vessel is also free to anchor temporarily and for a reasonable period of time in any appropriate location, unless specifically prohibited by laws or regulations. However, Canadian port authorities assign and manage anchorages within their boundaries. When a port's anchorages and terminals are full, vessels must anchor elsewhere until space becomes available.

The Government of Canada is working with the marine industry, Indigenous peoples, community organisations and stakeholders to develop a process to identify anchorages. Analysing and responding to environmental, economic, cultural, safety and security concerns and drafting a manual of best practices for ships at anchor is part of this initiative. It is also proposing oversight and management options for these anchorages.

Image: © CdC-HoC

*The Honourable Marc Garneau, Canada's Minister of Transport*

By working closely with those who are most affected, we are taking action to make maritime information more available and to reduce marine traffic congestion. This will help ensure marine shipping in Canada is safe, responsible and better prepared to protect the environment and coastal communities.

# CANADA

**Improving local maritime situational awareness**
Canada's Indigenous peoples and coastal communities need user-friendly local data on marine traffic for several purposes. In response, the Canadian government is developing a new maritime awareness information system that will provide a user-friendly tool to increase access to local maritime information, including vessel traffic, for Indigenous partners, coastal communities and stakeholders.

> "The Government of Canada is working with the marine industry, Indigenous peoples, community organisations and stakeholders to develop a process to identify anchorages. Analysing and responding to environmental, economic, cultural, safety and security concerns and drafting a manual of best practices for ships at anchor are part of this initiative. It is also proposing oversight and management options for these anchorages."

This new system will enable Indigenous peoples and coastal communities to work hand-in-hand with safety authorities. It will integrate existing and new sources of information, including support from space-based Automatic Identification System (AIS) data services.

Collectively, we'll be better able to understand maritime activity in local waters, improve communication and collaboration between all parties. This innovative system will lead to stronger marine safety planning, pollution prevention and emergency response capabilities.

Strong collaboration and state-of-the-art technology will result in a more comprehensive and coordinated response to marine emergencies and better safeguarding of our coastal environment.

We need the participation of Indigenous peoples, coastal communities and industry to make sure that the solutions developed to solve the challenges we face. There will be several opportunities to provide input into decisions and there is much more to come as players collaborate in finding solutions to protect our coasts.

https://www.tc.gc.ca/en/campaigns/protecting-coasts.html

**The Honourable Marc Garneau**
**Minister of Transport**
Office of the Honourable Marc Garneau
Tel: +1 613 991 0700
http://www.tc.gc.ca/eng/menu.htm
https://pm.gc.ca/eng/minister/honourable-marc-garneau

# Agenda 2030 and international aviation

**Dr. Fang Liu, Secretary-General of the International Civil Aviation Organization, explores how international aviation contributes to Agenda 2030 by empowering local sustainable development through global connections**

Every 24 hours, some 10 million global travellers are being carried around the world on just over 100,000 flights.

Commercial aircraft also carry over half of the world's 1.4 billion tourists to their destinations annually and many readers may be surprised to learn that these numbers are all presently forecast to double in just 15 years' time.

With the importance of aviation connections to local economic vitality and prosperity becoming much better appreciated, most especially in the context of the 17 UN Sustainable Development Goals (SDGs) adopted under Agenda 2030, it's critical that governments continue to work through ICAO today to ensure that future air transport growth is effectively managed and that air services expand sustainably and equitably.

## ICAO Compliance: A key enabler of sustainable development

To help assure this, the United Nations agency for civil aviation, ICAO, has been continuing to help States cooperate on the basis of more than 12,000 standards for global air transport adopted under the Convention on International Civil Aviation (Chicago Convention).

These ICAO provisions serve as an important foundation upon which governments can develop their local aviation infrastructure, operations and other capacities, consistent with other States' expectations and the existing global alignment of our network.

This greatly aids governments related ambitions to leverage, on behalf of their local citizens and businesses and the sustainable future of their civil societies, the distinct socio-economic benefits which derive from global aviation connectivity.

Today those benefits generate many positive impacts for the global economy, with our sector, directly and indirectly, employing some 63.5 million people, contributing over 2.7 trillion dollars annually to global GDP and moving over 3.8 billion passengers and one-third of world freight by value each year.

## The challenges of modernising a dynamic transport sector

When we talk about effectively managing the forecast growth in air transport, our sector is focused most intently on improving upon our current metrics for ICAO Strategic Objectives such as aviation safety, security and capacity/efficiency.

Some have likened this challenge to try to repair an automobile while it's still moving, and the task is further intensified by the fact that global aviation governance is so consensus-based. Forging common ground is never simple, but it's especially complex when you're serving 192 Member States characterised by greatly varying civil aviation and socio-economic needs.

ICAO, States and industry groups focus on capacity and efficiency in aviation because the speed by which modern commercial aircraft can move passengers and freight globally is the core value offering of international air transport.

Safety and security provisions complement this essential rapid transit attribute, establishing an overall foundation of speed, breadth, confidence and dependability which no other form of transport can equal.

ICAO also places a determined focus on the sustainability of our sector, as represented by our additional Strategic Objectives for the economic development and environmental performance of civil aviation.

*Dr. Fang Liu, Secretary-General of the International Civil Aviation Organization*

Environmental goals and challenges are especially urgent today given the current global context and we have been grateful for our States' leadership in helping our sector to achieve some key world firsts, whether in terms of new aircraft $CO_2$ emissions standards or the landmark international emissions offsetting solution represented by our recent CORSIA agreement.

## The pressing need for globally-coordinated aviation development

One thing we know for certain is that our network needs both new and modernised infrastructure established, especially if we're to manage future growth while still improving upon our sector's admirable safety and security results.

To help address these issues, whether, through our ICAO World Aviation Forums or other events and missions we undertake, ICAO is expanding global awareness at the highest levels on aviation's unique ability to connect cities and countries to the world.

We are stressing to ministers and state planners everywhere that, to optimise aviation's significant socio-economic benefits, their aviation infrastructure and related development needs should be incorporated into their national development plans and strategies.

We also, of course, wish to engender higher levels of investment for the large-scale air transport infrastructure modernisation now needed, whether in developed or developing States. To that end, our World Aviation Forums are essentially designed to forge new partnerships among aviation, finance, donor and development communities and to help our Member States realise business plans consistent with investor expectations for transparency and accountability.

Our expectation is that this work will foster sustainable economic growth for governments which make the necessary commitments and follow through successfully on both their projects and investments.

This, in turn, will greatly expand local access to foreign markets and producers, amplifying business opportunities and engendering more dependable and positive employment and tax base impacts, permitting further staged growth.

And another important piece of this puzzle will be the numbers of skilled young men and women available to operate our technologically, logistically and politically complex global network.

Just this year we hosted our first Global Summit for Next Generation Aviation Professionals and initiated an ICAO Gender Equality Programme, both of which help to address our future aviation workforce and human development challenges in league with ICAO's Global Aviation Training office.

Aviation is now poised to usher in a 21st-century air transport network which will serve as a key enabler of local economic vitality and sustainable development by optimising global connections. This role is directly consistent with the convention which established us and a testament to the vision of its drafters. ■

**Dr. Fang Liu**
**Secretary-General**
International Civil Aviation Organization (ICAO)
Tel: +1 514 954 8219
icaohq@icao.int
www.icao.int
www.twitter.com/icao
www.twitter.com/icaoFangLIU

# Reinforcing the foundations in Canadian teacher education

**Both the Canadian Association of Foundations of Education and Canadian History of Education Association examine the fundamentals of teacher education in the country today**

The foundations of education, usually including the fields of educational history, philosophy and sociology, have held a central place in most teacher education programmes in Canadian universities. Traditionally, these subjects were taught as a means for teacher candidates to understand their place within their profession and the larger society.

Over the past two generations, the foundations have gone through profound changes in perspective that reflect the cultural, legal and philosophical shifts of this country's populace: based on its roots in the humanities, the foundations' content, methodology and pedagogy now offer vital, critical perceptions and approaches to understanding and teaching in our pluralistic globally-oriented society.

In the most recent wave of educational reform discussions, however, arguments have been made that treating foundational fields as isolated disciplines is an outdated approach, ineffective in a post-modern, integrated world. This assault has taken on two facets that have become all too common: the desire to eliminate the "foundations" configuration altogether in teacher education to be replaced with more 'practical' study; or, the appropriation of the term "foundations" by fields not heretofore associated with this area of study.

## Prioritising educational research and teaching

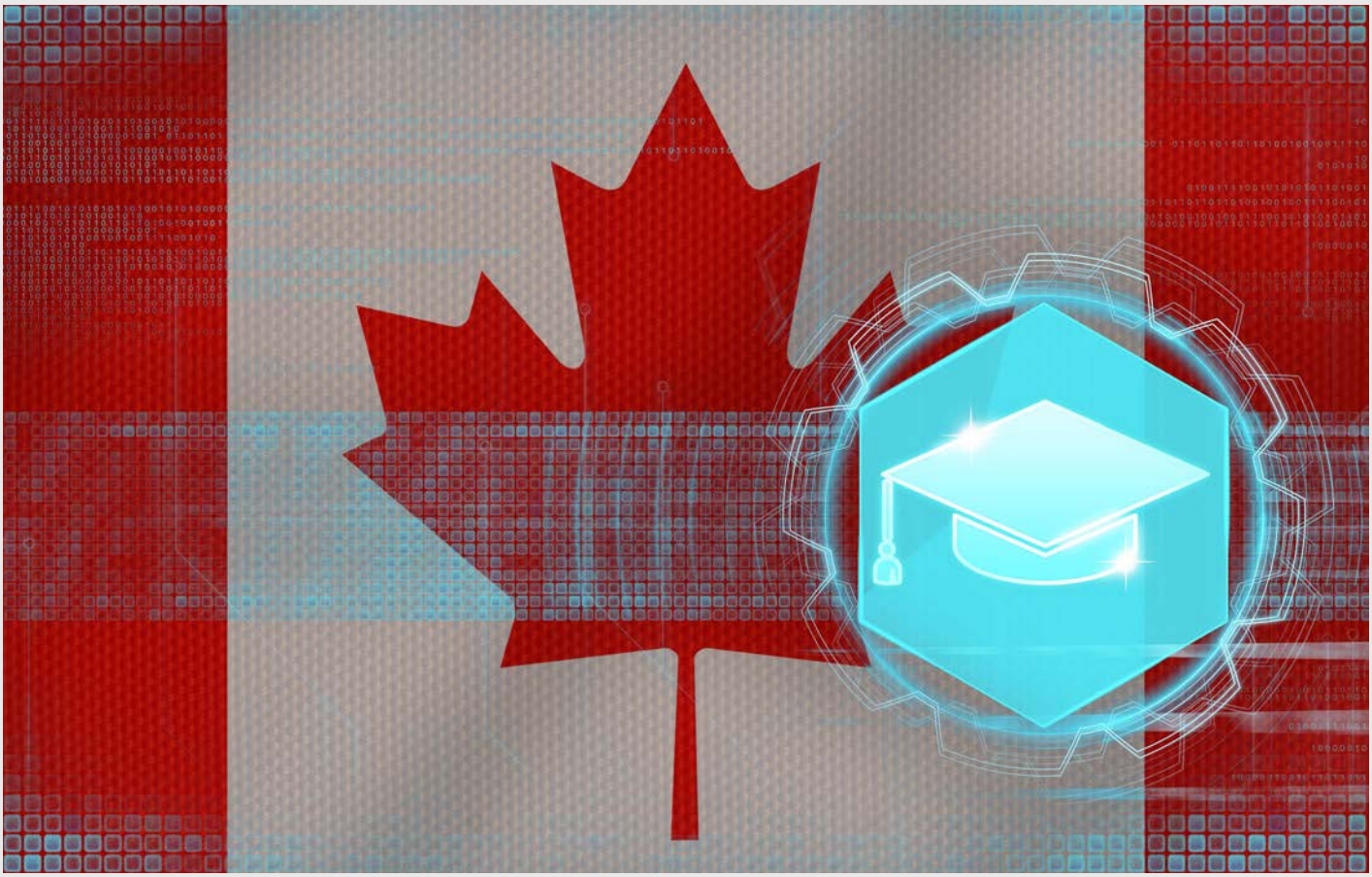
As Faculties of Education reassess and redistribute their programme content, a host of more practical subjects (e.g., educational technology, classroom management and instructional methodologies) have tended to take expanding roles in the newest courses of study, while educational foundations fight rear guard actions, arguing only for its preservation in some form. In more stark cases, such as the recent decision at the Ontario Institute of Studies in Education, whole Departments related to the foundations have been shuttered, with researchers being redeployed into other areas.

Of course, this does not represent the path of all scholarship and university programmes across the country. Nevertheless, we are very concerned that the undermining of the foundations will have a grave effect on the possibility of improving educational understanding in our country. We argue that teacher education must be more than merely training for classroom practice – the offering of tips and tricks. Rather than separating the theoretical from the practical, choices of practice must be underpinned by critical and creative thinking arising from holistic understandings. The study of classroom management, for example, can only be properly understood when revealed through a wider philosophical, historical and sociological framework. Here, students may be able to balance promising practices with such larger issues of power, context and anti-racist/anti-oppressive education.

## Arrogation

Other stakeholder groups within the debate concerning teacher education argue that research and teaching in the foundational areas need to be expanded to include additional fields such as anthropology, Indigenous studies and gender and sexual diversity studies and that these studies be taken up in integrated ways. As such, a number of new courses not traditionally associated with the foundations have appeared in various programmes, as well as on government research grants.

Overall, this is part of the ongoing debate within any discipline. What we argue, however, is that the foundations should not be viewed as a simple body of knowledge to be memorised, with more content being added in a snowball effect. Rather, the field must come together as an integrated perspective that can aid both



teachers and citizens as they confront the plethora of complex questions and concerns they will face in the 21st century. Splintering the foundations into a loosely connected umbrella of courses would not help achieve the needed deeper understandings.

## Challenges that lie ahead

While recent attempts to dislodge the "foundations" have shaken confidence, we posit that the single greatest challenge to improving education in Canada arises out of the taken-for-granted assumptions of techno-rationalism and neo-liberalism. If Canadian educators and educational researchers focus on the logic of 'efficiency and effectiveness', simply preparing individuals for the 'world of work', then how can we expect teachers and citizens at large to take up and engage in holistic and more profound ways of thinking?

We believe that teaching and research in educational foundations should take on greater significance as success in society will depend on knowledge and learning about the historical context of educational/societal assumptions, theories and practices; about how knowledge is put together and ethical decisions made; about school systems as social structures embedded in communities; and about the disparities that existed and continue to exist in society and schools, including those based on race, ethnicity, class, gender, abled-ness and so on.

This means, of course, that the foundations must be more than museum-work. Like any other living entity, it must grow and adapt to the changing world around it. This involves breaking the old rigid disciplines into more integrated, flexible shapes, more accepting of new ideas and forms. If educational foundations can grow, adapt and integrate, this area of teaching and research will contribute in deep and meaningful ways to improving education in Canada. As such, bolstering foundational studies is an important part of the way ahead in bettering education in Canada. ■

**Kurt Clausen**
**President, Canadian Association of Foundations of Education**
cafe.acefe@gmail.com
www.cafe-acefe.com

**Lynn Lemisko**
**Past-President, Canadian History of Education Association**
www.ache-chea.ca
www.twitter.com/chea_ache

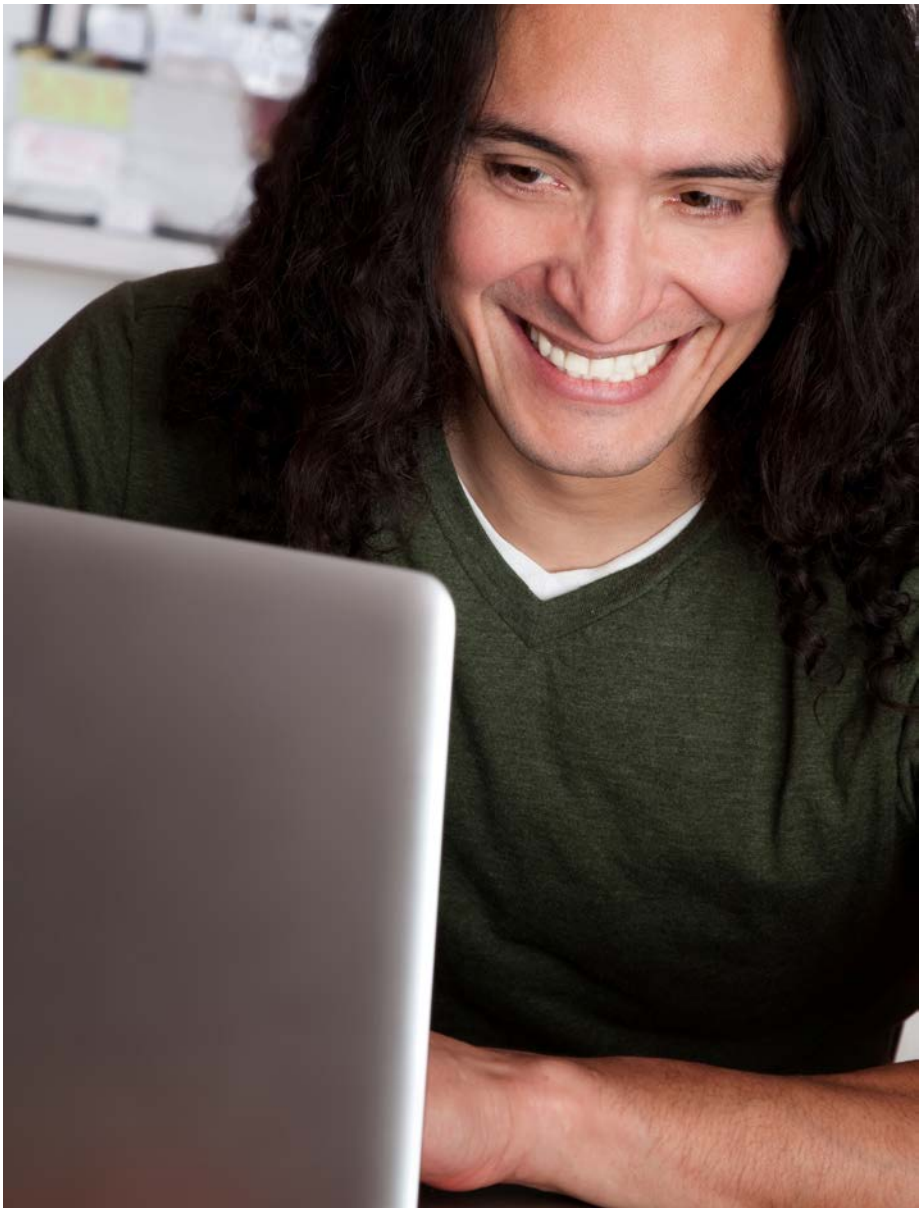
# Non-Indigenous individuals' responsibilities within higher education contexts

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.

**Dawn Zinga**
**Associate Professor and Chair**
Department of Child and Youth Studies
Brock University
Tel: +1 905 688 5550 ext. 3152
dzinga@brocku.ca
https://brocku.ca/social-sciences/departments-and-centres/child-and-youth-studies

# INDEX

# TAILOR-MADE PROMOTION

**As part of our package of information services, Open Access Government are proud to present the option of a bespoke publication.**

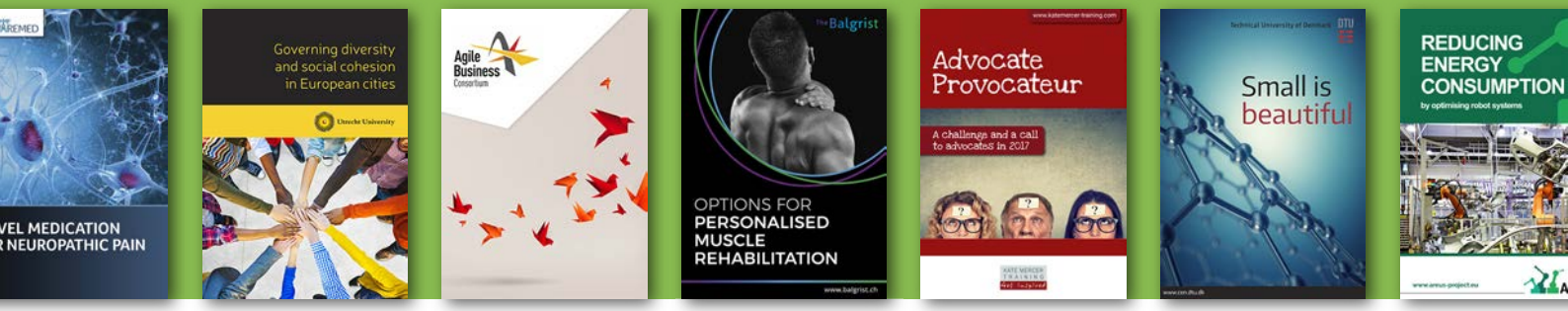
Our ebooks can be used by you to target a specialised readership with informative content. They can be 8, 12 or even 16 pages promoting your profession and services.

Our production, editorial and design teams will work with you to identify and develop your message before delivering it electronically to a targeted audience using the latest digital publishing technology for ease of reading.

We have access to an extensive database of contacts within specialised areas, so you can be confident that your message will be delivered to the right people at the right time.

**Get in touch today to plan your communication strategy.**

Tel: **0843 504 4560**




www.openaccessgovernment.org

OPEN ACCESS GOVERNMENT

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