

International INNOVATION

Disseminating science, research and technology

ISSUE
192



**LEAVING
FOOTPRINTS**

THE RESEARCHERS MAKING
THEIR MARK ON SOCIETY

POLICY

Stephan Kuster underscores the connection between science policy and excellent research.

Science Europe recognises the need for the right framework conditions to reflect the complexity of science systems

PRACTICE

ResearchImpact is adopting a fresh approach to technology transfer and industry liaison. Michael Johnny, David Phipps and Krista Jensen highlight the importance of knowledge mobilisation

RESEARCH

A selection of contributors share their experiences of how the rising prolificacy of social media has impacted on their day to day lives in this issue's **Research Roundtable** discussion

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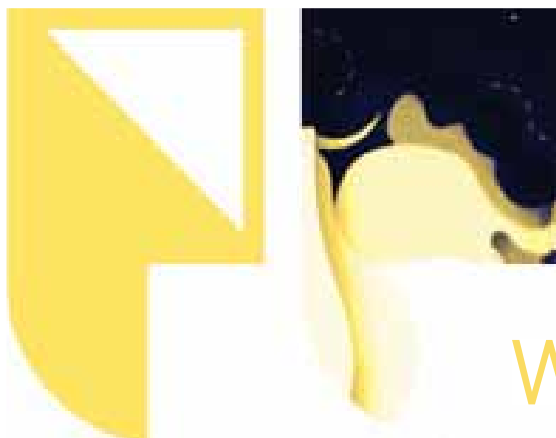
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*Of those who replied to the follow-up client feedback questionnaire



Welcome to *International Innovation*

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LITTLE DID INVENTOR Otto Frederick Rohwedder knew, when he introduced the first commercial bread-slicing machine, that this would set a proverbial benchmark for future ideas. The concept itself may seem simple, but this belies the complexity of the contraption. It took Rohwedder over a decade to create the device, beginning in 1912 when he first toyed with the idea of producing a machine to slice bread. In 1917 a fire destroyed his factory, with his prototype machine and blueprints going up in flames. Ten years later he had finally amassed sufficient funds to start over.

Beginning with a problem and/or goal, the process of innovation is arduous. Similarly to Rohwedder, scientists inevitably encounter barriers on their journey from idea to invention. Hurdles may emerge in the form of funding, silos and time commitments, for example, rendering the enterprise stressful and prolonged. But these challenges are par for the course and pale in comparison with the notion of arriving at a breakthrough. This discovery may positively impact on future generations and, well, might even be the best thing since sliced bread.

Whether streamlining research on electroporation, or developing a standardised dental diagnostic terminology system, the researchers presented in this edition of *International Innovation* are furthering their disciplines and, ultimately, making a mark on society. We provide complementary commentary from the Science Council and Science Europe, whose respective emphasis on maintaining a strong and stable science base, and producing and managing a healthy basic research ecosystem, is geared towards fostering innovation.

Here at *International Innovation*, we showcase exciting scientific developments from across the research and policy landscape. Feel free to visit www.internationalinnovation.com where you can browse our most recent editions and register to receive our newsletter, or follow us on Twitter (@IntlInnovation) to discover our latest talking points.

For now...enjoy the issue!

LAUREN HAIGH

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August 2015

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I think we need to tell more of the story of what scientists do, why they do it and what sort of people they are

Diana Garnham, Science Council

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Science systems are highly complex by nature and the policies enacted to provide the right framework conditions for them to thrive will reflect that complexity; especially in a very diverse multilevel system such as Europe

Stephan Kuster, Science Europe

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Researchers should make their research available and searchable, and highlight their area of expertise. This involves creating strong profiles on social media (LinkedIn is great for this) and niche websites like Academia.edu. [...] A social media presence is as basic as having a business card

Anton Tsvetov,
Russian International Affairs Council

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To find out how you can feature in *International Innovation*, please contact Josh Carpanini: jcarpanini@researchmedia.com

For more information about the contributors in this issue:

www.sciencecouncil.org

www.scienceeurope.org

www.researchimpact.ca

Register

Keep up to date with the latest content and register for the weekly *International Innovation* newsletter:

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Mapping global mental health

The latest edition of the World Health Organization's *Mental Health Atlas* has enabled the progress of its Mental Health Action Plan 2013-2020 to be assessed

Mental health disorders are estimated to affect one in 10 people worldwide, yet, shockingly, almost half of the global population lives in a country where there is less than one psychiatrist per 100,000 people. To combat this issue, World Health Organization (WHO) launched a comprehensive mental health action plan that outlines four key objectives: supporting mental health authorities; reinforcing community-driven mental health and social care services; increasing initiatives to prevent mental health issues and promote awareness of its prevalence and importance; and strengthening research into disorder pathology and treatment.

The *Mental Health Atlas* series contains the most detailed information on the global mental health situation, providing an excellent framework to further the advancement of the Action Plan. Data collected from nearly 90 per cent of WHO's Member States in 2014 indicated that many countries are updating mental health policies and creating new laws. A worldwide increase of 35 per cent in the number of nurses working in mental health is also a measure of improvement.

In spite of progress, huge inadequacies remain in low- and middle-income countries. The latest *Atlas* reveals that these countries continue to lack mental health resources and access to mental health workers. The publication also highlights that the implementation of recently developed mental health plans is often weak and not in accordance with international human rights laws. Unequivocally, much more remains to be done if WHO is to achieve the goals of its Action Plan.



Japan to cut emissions

According to the Emission Database for Global Atmospheric Research, Japan accounts for 2.65 per cent of global emissions, making it the sixth largest greenhouse gas producer in the world. However, the country has promised to cut emissions by 26 per cent from 2013 levels by 2030

Although these reductions appear steeper than US (18-21 per cent by 2025) and EU (24 per cent by 2030) targets, analysts at Climate Action Tracker claim the cut is in fact less ambitious than first thought, due to the 2013 baseline. Measuring from 2005 levels, the goal equates to a 25.4 per cent cut, which is less than current European and American targets.

Recent record highs of carbon emissions in 2014 reflected the shift from nuclear power to gas and coal following the Fukushima nuclear disaster in 2011. These trends are echoed in Japan's 2030 power generation plan, which aims to provide 20-22 per cent of the country's electricity needs from nuclear energy (a near 10 per cent drop from pre-Fukushima levels), 20-22 per cent from renewables, and 26 and 27 per cent from coal and gas, respectively. Thus, many environmental authorities remain sceptical of Japan's climate pledge.



First drone delivery in the US

The US moves one step further towards authorising everyday deliveries as the first government-approved drone transported 4.5 kg of medical supplies to a health clinic

Constructed by Australian drone manufacturer, Flirtey, the drone completed three three-minute flights from Lonesome Pine Airport, Virginia, to the clinic at the Wise County Fairgrounds. The demonstration served as proof that drones could be useful in everyday transportation scenarios, especially in remote locations. Chief Executive Matt Sweeny stated: "Proving that unmanned aircraft can deliver lifesaving medicines is an important step toward a future where unmanned aircraft make routine autonomous deliveries of everyday purchases".

Although limited flight times and current laws that only allow drone flight to occur well away from built-up areas have restricted their commercial use, it is thought that these outdated policies will soon be upgraded to enable safe and viable drone flights.



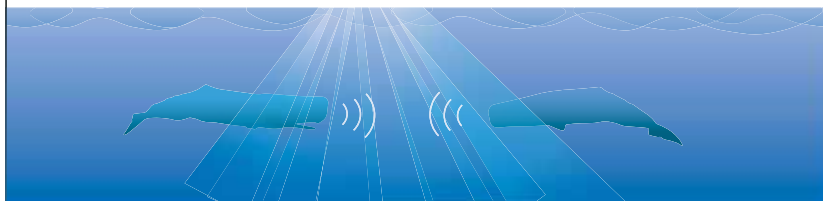
Race for renewables

Sir David Attenborough is the latest to announce his support for an innovative 'Apollo-style' research programme that seeks to make renewable energy cheaper to lessen dependence on fossil fuels

Attenborough joins a group of leading scientists, business executives, policy



makers and naturalists who together propose that the only way to effectively manage global fossil fuel consumption is to ensure renewable energy is a cheaper alternative. The programme also plans to improve green energy storage and transport capacities. In order to achieve these ambitious goals, Attenborough calls for the same 'extraordinary' problem solving that saw man safely land on the Moon.



Underwater culture

Intriguing results recently published in *Nature Communications* have added to a growing body of literature proving that animals have their own cultures. The study reports that not only do sperm whales exist in social communities, they also communicate with each other using learned, cultural dialects

It reveals that sperm whales acquire different dialects from one another in the same way human children pick up accents from their parents. The published findings explain it is not that whales are born with different vocal chords depending on their geographical location, but rather their social upbringings cause them to learn a dialect unique to their community.

Whales live in clans – groups of extended families. The researchers have concluded that the observed differences between whale clans cannot be explained without considering culture. Indeed, the results suggest that cultural difference is the best way to explain why sperm whales live in multilevel societies; something that would not be possible without a unique dialect.

2014: Warmest year on record

An international study has analysed several climate change markers from across the globe to confirm that 2014 was Earth's warmest year on record

The *State of the Climate in 2014* report compiled by the National Oceanic and Atmospheric Administration's Center for Weather and Climate gathered data from over 400 scientists in 58 countries around the world. Detailed information on global climate indicators, such as land and ocean temperature, sea levels and greenhouse gas emissions, as well as data on notable weather events, were collected by environmental monitoring stations on land, water, ice and in space.

Four independent datasets indicated that 2014 was the warmest year on record in terms of temperatures near the Earth's surface. Unsurprisingly, sea surface temperatures also reached historic highs coinciding with the maximum greenhouse gas concentrations ever documented and the most elevated sea levels since records began. These data demonstrate the worrying trends of global warming and confirm the need for unified action.



Community

Keep in touch with the latest in research dissemination



Calendar

28 September – 1 OctoberBerlin, Germany
10th International Conference on Behaviour, Physiology and Genetics
of Wildlife
www.izw-berlin.de/welcome-234.html

7-10 OctoberTampa, USA
2015 Biomedical Engineering Society Annual Meeting, 25th Anniversary
www.bmes.org/annualmeeting

13-15 OctoberBirmingham, UK
Solar Energy UK
<http://bit.ly/SolarEnergyUK>

31 October – 5 NovemberSantiago, Chile
22nd World Congress of Neurology
www.wcn-neurology.com

1-4 NovemberBarcelona, Spain
Global Cleaner Production and Sustainable Consumption Conference
www.cleanerproductionconference.com

5-7 DecemberAhmedabad, India
International Conference on Cognition, Brain and Computation
www.cogs.iitgn.ac.in/cbc2015

Funding calls

Wellcome Trust – Translation Fund

Boundary pushing, innovative and groundbreaking are just a handful of characteristics the Wellcome Trust's Translation Fund aims to nurture in this exciting new funding call. The Fund endeavours to support individuals or teams to accelerate product development in the biomedical arena. Eligible projects must have already demonstrated proof of principle, supported by experimental data.

Deadline: 16 October 2015
See more at: <http://bit.ly/TranslationFundWT>

Natural Environment Research Council – Green Infrastructure Innovation Projects

The Natural Environment Research Council (NERC) can offer up to £1 million for innovation projects with the potential to accelerate impact on green infrastructure. Proposals must address the issues and opportunities around green infrastructure in the planning and investment decisions that are made by local policy makers, local planners and organisations responsible for developing the built environment. This opportunity is open to applicants based in UK higher education institutions, NERC research centres and independent research organisations approved by the Council.

Deadline: 22 October 2015
See more at: <http://bit.ly/NERCGreenIIP>

Keeping in touch



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Online

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What our researchers are talking about



Claude Turmes, Member of the European Parliament for Luxembourg's Green Party @ClaudeTurmes

Self-generation of energy is a basic right for prosumers and must be enforced all over EU
#EnergyUnion #SummerPackage



Science Council @Science_Council

Several of our members have signed a #climatechange communiqué ahead of the COP21 Paris summit in December
<http://bit.ly/GuardianClimateAction>



EuroNanoForum 2015 @ENF2015

The winners of awards at #ENF2015 @ENF2015 http://bit.ly/ENF2015_winners
Congratulations to all the winners!



Science Europe @ScienceEurope

Read the latest SE Working Group brochure, entitled 'Seven Reasons to Care about Integrity in Research':
http://bit.ly/SE_integrity

ResearchImpact @researchimpact

Today's ResearchSnapshot: Groundbreaking programme helps make York Region more inclusive
<http://bit.ly/1oCWGYu>



What are we doing



Last year, *International Innovation* publisher Research Media pitched and won the tender to produce EUREKA's 30th anniversary report. Now complete, the 80-page report celebrates EUREKA's past, present and future, while conveying the organisation's know-how in innovation, funding and support. EUREKA is a major intergovernmental group, specialising in market-driven industrial R&D. The beautifully crafted report was officially launched at EUREKA's 30th anniversary celebrations in Lugano, Switzerland – an event which also marked the handover of chairmanship to Sweden. Visit Research Media's website to preview the finished article:

www.researchmedia.com/portfolio-view

Formula E is leading a new futuristic racing series. *International Innovation* takes a look under the car's bodywork to showcase its sleek design and cutting-edge technology.

Check out this powerful infographic on Research Media's Flickr stream:
<http://www.flickr.com/photos/researchmedia/17329192475/>



SCI-COMM SPOTLIGHT: THE DIGITAL BUSINESS CARD



As the onus falls increasingly on scientists to engage with the public, Media and Government Relations Manager **Anton Tsvetov** advises them to embrace social media and trust that audiences can understand complex thought

Could you briefly explain your responsibilities at the Russian International Affairs Council?

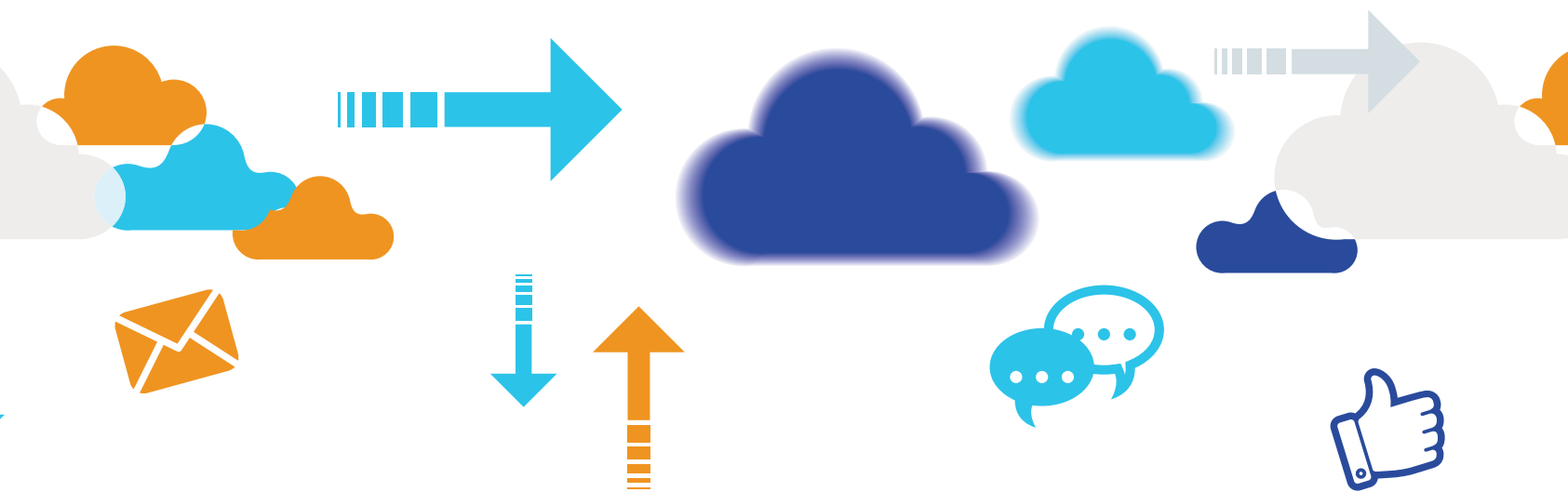
My job is to connect the Council's vast expert community with the media, make our research available and inform the public of the outcome.

When connecting media representatives with scientists, how do you decide who to call?

The first thing I think about when considering which researcher to contact is past experience. Do I know of an expert who has already

commented on the issue at hand or a similar issue? If I have a good relationship with a journalist she or he usually gives some feedback on whether they found the expert's comments useful. I have a virtual portfolio [of sorts] of people who will comment on a certain topic from a certain angle.

It gets a bit more complicated if I can't respond to a journalist's specific request straight away – the topic may be more unusual, for example, or none of my 'first choice' experts are available. This is where the Council's research projects come in useful; I start checking our authors' profiles and event participation lists.



As a last resort, there's our large database of about 12,000 experts, searchable by topic and discipline. In a perfect situation I would ask project managers if they have worked with a certain expert to find out how comfortable he or she is talking to the media.

All of this must happen very fast as I try to get back to the journalist within half an hour or so.

What should researchers be doing to promote their work?

First of all, they should make their research available and searchable, and highlight their area of expertise. This involves creating strong profiles on social media (LinkedIn is great for this) and niche websites like Academia.edu. This might be passive promotion, but it increases your chances of being discovered by relevant media contacts. A social media presence is as basic as having a business card.

It's also important to regularly ask yourself who might be interested in this research. Approaching the media directly, or via a communications professional, with research results may help spread the news, gather new opinions and influence the public agenda.

The language used by the media is very different to that of researchers. Should scientists be using media-friendly terms?

Academic language puts a premium on precision, while news and views favour simplicity and effect. Both styles have their flaws – scholarly texts are often filled with clutter (see Steven Pinker's *Why Academics Stink at Writing*), and the media tends to strip an idea down to distortion. In the end, I think we should settle for a certain level of complexity. There are audiences within the general public who are more than capable of consuming complicated ideas and concepts. But if we want to go beyond that, we should probably get used to our ideas being translated with some loss of accuracy. Any professional interpreter will tell you that a 100 per cent precise translation is impossible.

How possible is it to translate complex ideas into simple messaging without distorting or misinterpreting the original concept?

I really think there is a consensus point somewhere and it may be reached by a frank and detailed discussion between the researcher and

the media outlet and/or communications professional. Sensationalism can happen quite often, but from what I gather, there is a renaissance in public interest towards science and readers are increasingly well informed. This is improving the quality of science journalism, thus giving hope for high-quality scientific translation.

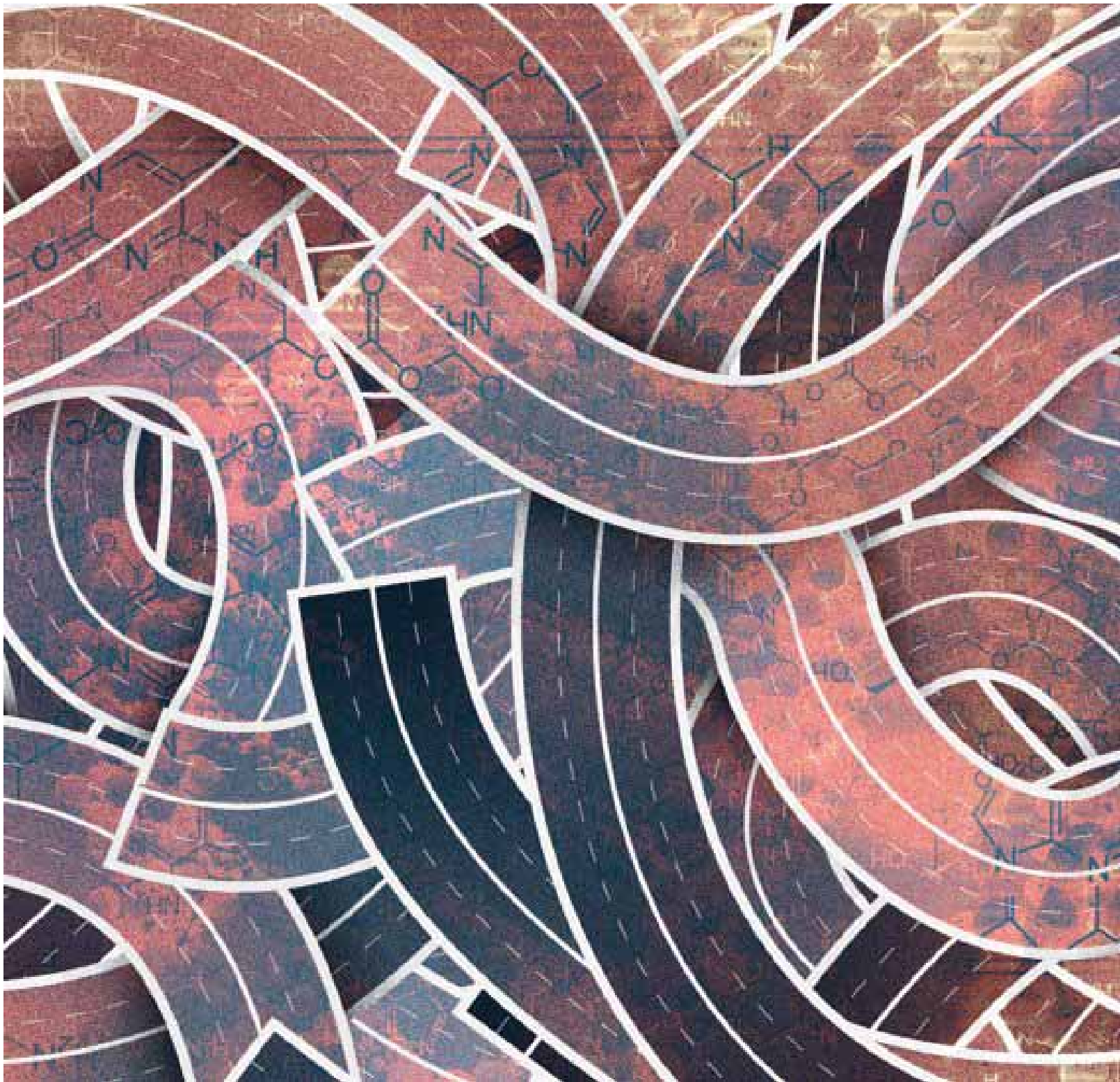
Is it really that important for scientists to spend time communicating their research when they could be working on the next breakthrough?

It is important that academics don't let the communications activity affect the research itself. Ideally, they should have access to counsel within the research organisation. A communications professional can help package research content in a media-friendly manner, find relevant impact targets and deliver the information to them. In this relationship, the communicator becomes an interpreter of scholarly findings and the researcher is the expeditor. However, this kind of perfect 'marriage' is very rare, even more so in Russia.

If you had just one science communication tip to give to the research community, what would it be?

Get on social media. As an aspiring researcher myself I have found this very useful for my studies in addition to dissemination of publications. Social media really broadens the scope of information sources; it helps you to get to know the community better. Twitter is perhaps the best choice to start with. I understand it may be intimidating at first, but you will get used to it very soon.

Anton Tsvetov is the Media and Government Relations Manager for the Russian International Affairs Council.

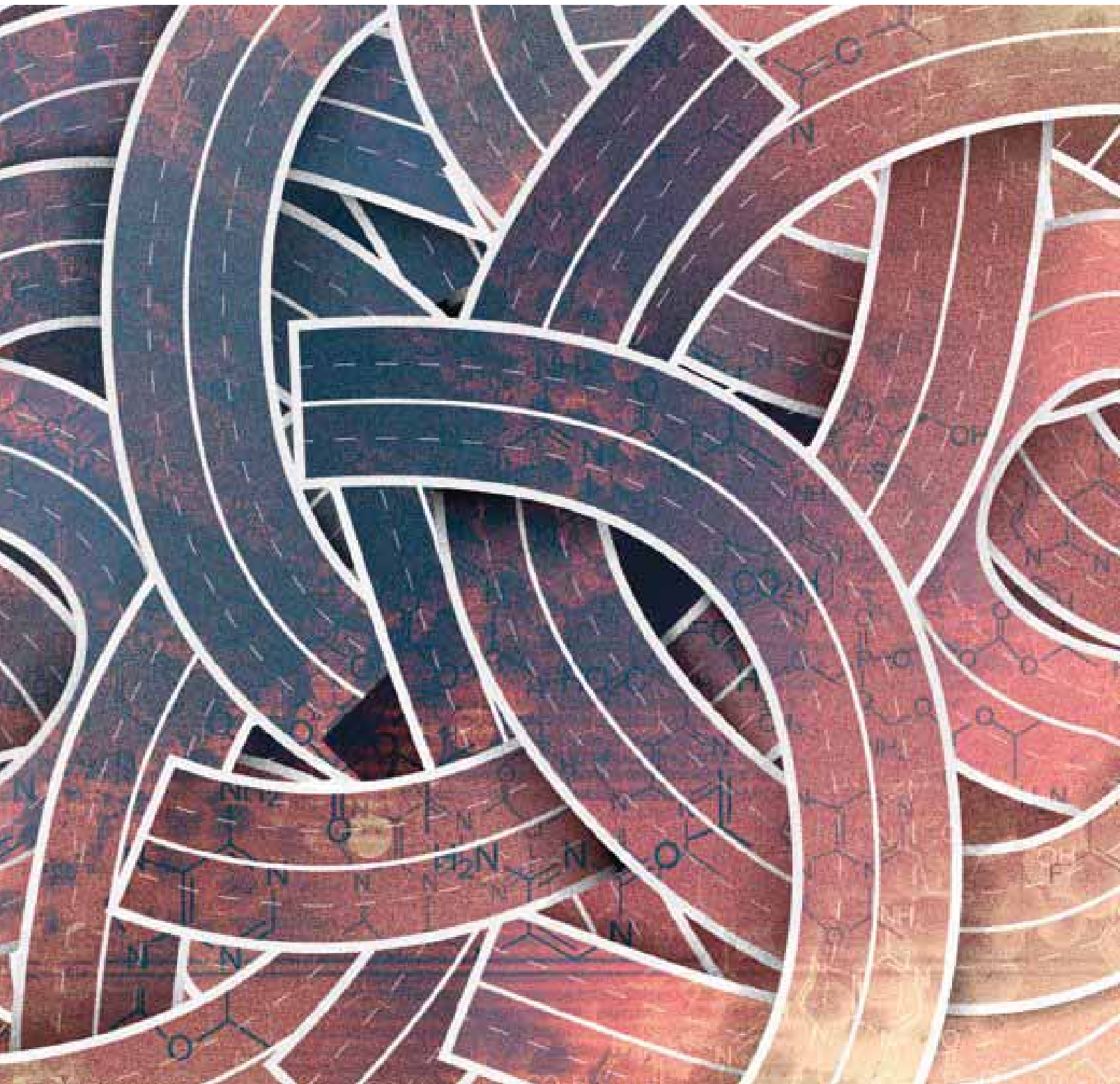


THE MANY ROADS INTO SCIENCE

DIANA GARNHAM

CHIEF EXECUTIVE, SCIENCE COUNCIL

Science Council's Chief Executive Diana Garnham opens the book on the current state of the UK's science workforce. She explores the need to increase diversity, improve education and offer alternative career routes in order to strengthen this workforce and, in turn, attract global investment



Could you reveal why you wanted to be a part of the Science Council?

I joined the Science Council in 2006, during its early stages, and was excited to be part of shaping and developing its role to support the UK science workforce. In my previous roles, I had done a great deal of work around public engagement with science and realised that the public did not relate to the scientists at all. There was little understanding of the role of the scientist, and the focus and discussion had always been about research rather than the application of science. It was extremely different to medicine and health where there is a much greater appreciation of the skills needed to apply medical science.

What aspects of your role as Chief Executive do you most enjoy?

Our sector is one of widely differing stakeholders with a diversity of passions and views about science. I enjoy the challenge of bringing them together, knowing that if the sector works collaboratively it will be more effective in every area of endeavour, from research to policy. The key has been to build understanding and respect between the differing perspectives – both single disciplines and broader subjects, research and academic views with applied scientists, public and commercial sectors, and so on.

When I was appointed, the founding President, Sir Gareth Roberts, charged me with developing 'science councilness' in the organisation, which I think we have now achieved. Member organisations say that they get a buzz from working together to tackle common concerns, and all those who attend our meetings are amazed by the breadth of our discussions.

Can you outline the key policy issues affecting the UK science community at present?

We are primarily interested in the UK maintaining a strong and stable science base that creates an attractive environment for investment in science and technology businesses. We also seek to ensure that the nation is a global leader in the way it attracts and retains its science workforce. The quality of UK science education from primary through to degree level is a priority; for example, we have concerns about secondary and pre-graduate level science qualifications, particularly for the technical workforce. The UK is lagging behind other leading science economies in the way it develops these non-graduate, vocational routes to science careers and the science community has leant towards a 'one-size-fits-all' science degree route.

There is also a need to tackle diversity in the science workforce. This is not only with regard to gender, but also social and economic characteristic and ethnicity. Many areas of science are currently facing skills shortages, but there is clear evidence that they are not recruiting from across society – we must improve this quickly.

Related to this is the need to raise awareness of science-based careers. Evidence suggests that young people enjoy the science they are taught at school and also see being a scientist or engineer as valuable work, but for the most part they do not want to be a scientist (see http://bit.ly/KCL_ASPIRES). That's the key perception we need to understand and change. I think we need to tell more of the story of what scientists do, why they do it and what sort of people they are.

At the Science Council we take a thematic approach in our careers work (see www.futuremorph.org) and provide information about numerous science-based careers available in various employment sectors. Projects like '10 types of scientist' and '100 leading professional scientists' help us to illustrate the range of careers available. At present, careers awareness, information, advice and guidance is underfunded and fragmented in the UK; for a number of years we have been calling on successive governments to commit to addressing the issue.

Finally, one of the biggest policy issues we are dealing with is the UK's future role in Europe, and how this will affect UK science. We have benefited greatly from attracting global talent over the years, so we need to remain at the heart of Europe. This runs alongside the need for a measured and balanced immigration policy to ensure the UK remains an open and welcoming place to do science.

What activities does the Council conduct to support the science workforce?

A key area has been to better understand the UK science workforce and how various employment sectors draw down on science skills and knowledge at different levels. We have identified 10 types of scientist as a way of illustrating the range of knowledge and skills that are needed to enable science to maximise its impact for the benefit of society and the economy. Our research found that 20 per cent of the UK workforce (5.6 million workers) uses science in their role, with 1.2 million people in jobs that are primarily science based. This is set to grow: if the UK achieves its ambition to be a leading science- and technology-based economy, we predict that as many as one-quarter of jobs will involve science.

The types of roles and level of science knowledge and skills needed varies for different sectors. A relatively small number of graduates now enter the science workforce having studied a single science discipline. Outside of research and academia there has been growing demand for



students with a broader base of knowledge and skills, perhaps topped up with specialist Masters' degrees. Alongside the core science disciplines such as physics and chemistry, there is a demand for graduates with broader biological science, environmental science and Earth science qualifications. Across the economy there is a need for workers with a good level of science and maths knowledge, combined with softer business-related skills such as marketing and project management.

How does the Council inform and influence science policy?

In a variety of ways. We have organisational and individual points of contact with UK government departments and Parliament and in Europe. With 41 member organisations we have many different entry points and, more importantly, listening and intelligence gathering opportunities with other science policy organisations and industry. A key part of our role is to respond to policy consultations as and when they happen. Over the past decade, this has given us a good bank of evidence and views to draw upon: everything from school science curricula to science-based funding through to homeopathy. We seek to develop a broad approach as it is clear that it is not just science funding issues that impact the UK science base: skills, education, regulation and regional strategy investment are all areas in which we have developed positions and sought to influence UK and European policy.

Can you outline the current challenges facing society and the best approach to overcoming them?

Global challenges include food security, ageing populations, disease prevention and the need to develop sustainable low-carbon economies. The Science Council believes the UK has a responsibility to actively work with its global partners to tackle these issues. These are overlapping issues for the UK as well; we need to confront existing obstacles related to the health and wellbeing of our population.

What are the Council's key objectives regarding policy over the coming years?

Key policy goals include enhancing local and regional science and innovation capacity; there is a great deal more that can be done to unlock the potential of science to drive growth and job creation across the country.

Public engagement is a hot topic right now and, when done well, performs a great service. We need to involve the public in discussions on where we are taking science. It is also important for us to consider the public's concerns and anxieties on certain science issues, such as genetically modified foods, and meet these concerns in a humble and modest way.



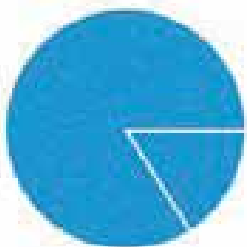
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STEPHAN KUSTER

Head of Policy Affairs, Science Europe



STRENGTHENING THE RESEARCH ECOSYSTEM

Stephan Kuster gives an insight into Science Europe's top priorities when it comes to science policy, highlighting the need for evidence-based policy that will enhance Europe's capacity for excellent research

Could you give an insight into your background and how you came to occupy the role of Head of Policy Affairs at Science Europe?

I first came to do research policy work while at a research institute in Switzerland, where I was involved in capacity building projects in the southern Balkans and the Caucasus. I then moved to Brussels as an advisor on European research affairs for the Swiss National Science Foundation (SNSF). It was in that role that I was seconded by SNSF to be part of the Science Europe Pilot Office in 2011. In April 2012 I followed our Director, Amanda Crowfoot, to become the second official member of staff of the newly established Science Europe Office, as Head of Policy Affairs. Since then the policy team has grown to include three senior policy officers, and the Office now counts 18 staff working as a secretariat for our Members in Brussels.

What are Science Europe's main policy priorities?

Science systems are highly complex by nature and the policies enacted to provide the right framework conditions for them to thrive will reflect that complexity, especially in a diverse multilevel system such as Europe. Science policy is about producing and managing what is probably the most crucial public good produced with public funding in Europe: an excellent and healthy basic research ecosystem with direct pathways to innovation, public health, societal wellbeing, economic growth and so on.

One of our top priorities when it comes to science policy is that it should be evidence based, and guided by the overarching vision of maintaining and enhancing Europe's capacity to produce excellent research. In order to have the most impact, Science Europe focuses on the issues where our members are collectively responsible and therefore can act by doing and leading.

We structure our policy work along four strategic objectives, which build the basis of the Science Europe Roadmap: our long-term action plan. These are broad enough to provide a stable strategic vision for collective science policy making in a context that is otherwise undergoing fast and constant change.

What is the Science Europe Roadmap and the role of policy within this?

The Roadmap is the strategic plan for Science Europe for the coming years. It was developed and adopted by our Members in 2013. It lays out the long-term strategic goals for the organisation, its vision for the European Research Areas, and defines nine Priority Action Areas, each with specific objectives. Working towards attaining these objectives constitutes the main policy priorities for Science Europe and its Working Groups.

How does the organisation contribute to the continuous development of research policy in Europe?

The Roadmap objectives guide our policy priorities in our day to day policy work with our Members. We have set up a structure of collaboration among the Member Organisations. This allows us to efficiently fulfil the three roles for which Science Europe was set up: being a platform of collaboration among large research performing and research funding organisations in Europe; acting as a think tank on science policy issues; and representing the interests of our Members.

We do this by bringing together 50 of the major public research organisations in Europe and facilitating direct conversations between their governance levels in our General Assembly, their technical experts in our policy Working Groups and the wider scientific community represented by our Scientific Committees.

The first contribution of value to research policy in Europe is in the mutual learning that takes place when our Member Organisations share their experiences, because it directly contributes to the dissemination and upscaling of models that have proved successful in a given country or organisation.

The biggest impact, however, comes when the sharing of information leads to collective action. For instance, currently high on the agenda is the transition to an open access system for scientific publications. To ensure a fast and effective transition, the Members of Science Europe



- Ensuring the efficiency and effectiveness of the research system and fostering research potential
- Improving the scientific environment and the institutions at which researchers perform and build their careers
- Ensuring that research results are utilised in the best possible way, by opening and sharing them within and beyond scientific communities
- Supporting 'borderless science' to ensure that researchers and research organisations throughout Europe can collaborate on projects, programmes and facilities





Access to Research Data

Cross-Border Collaboration

Gender and Other Diversity Issues

Open Access to Research Publications

Research Careers

Research Infrastructures

Research Integrity

Research Policy and Programme Evaluation

Science in Society

agreed on two sets of common principles which they use to develop their own open access policies. This directly contributes to open access policy in the European Research Area, complementing European Union (EU) initiatives such as the open access rules in Horizon 2020.

Can you discuss the organisation's role in the EU research policy debate?

Science Europe has recently renewed its membership in the European Research Area partnership, together with four stakeholder organisations representing the university sector, research and technology organisations and the European Commission. We see great potential for substantial discussions among these partners on the design, implementation and monitoring of European Research Area actions.

The association regularly participates in expert roundtables and responds to public consultations on science-related topics. It is in these occasions that the long-term work of defining and consolidating common positions among our Members pays off.

We keep close contacts with the European Parliament and have briefed their Members on the impact on the research system of various legislative initiatives. For instance, the potentially negative implications of a narrow Data Protection Regulation on the capacity of biomedical researchers to use vital patient data in their search for new treatments.

Another very relevant debate taking place right now is the reform of the EU Copyright system. The current system is outdated: not providing exceptions for scientific research potentially undermines important scientific techniques such as text and data mining (TDM) and risks blocking entire paradigm shifts currently taking place and often described as 'open science'.

What are Science Europe's Research Funding and Research Performing Organisations and how do they contribute to managing national public research investments in Europe?

The 50 Member Organisations that make up Science Europe are national public bodies whose primary role is either to allocate public funding to scientific research or to use public resources to perform scientific research. In order to fulfil the membership criteria they need to be not-

for-profit public bodies with a significant scientific and budgetary impact on their national research landscapes, and be scientifically independent.

As such, they are not only among the leading science organisations worldwide, they also play an important policy role nationally and at European level. They are involved in the design and implementation of national research policy in close interaction with their national ministries and other counterparts.

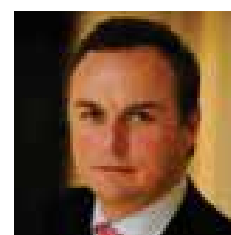
Collectively they account for a substantial portion of the public investment in science and research in Europe. They are also directly involved in European projects through their successful participation in the EU Framework Programmes such as Horizon 2020.

Can you describe Science Europe's roles in the Global Research Council (GRC) and how it contributes to global debate on science policy?

Science Europe is a regular participant of the GRC annual global summits alongside many of our Member Organisations. As an association that includes European research funding councils, Science Europe has also actively supported the regional activities of the GRC, for instance by co-organising regional meetings in the past and facilitating collective input from European participants to documents and declarations adopted by the GRC.

Although the two organisations are very different in scope and aims, the experience of setting up Science Europe has allowed us to pass on some valuable insights and advise to the GRC in the development of its structures and processes.

www.scienceeurope.org





This article was written by Michael Johnny, Manager, Knowledge Mobilization; David Phipps, Executive Director, Research and Innovation Services; and Krista Jensen, Knowledge Mobilization Officer, all of whom are based at York University, Canada

SCIENCE FOR SOCIETY

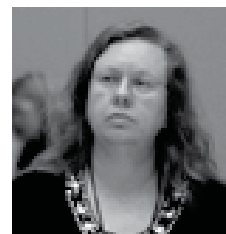
The Government of Canada's new science, technology & innovation strategy means universities must adopt a fresh approach to complement technology transfer and industry liaison. **ResearchImpact-RéseauImpactRecherche**, a network of 11 Canadian universities, is working hard to support this new approach through knowledge mobilisation

Writing in *Canadian Government Executive*, Chad Gaffield, former President of the Social Sciences & Humanities Research Council of Canada, re-imagined Canada's innovation systems. "An international consensus is now emerging around a people-centred model of innovation for successful change in businesses, government and communities. [...] The new model calls upon us to re-kindle the relationship between knowledge and society; to re-imagine and renew the historic covenant between campuses and the public; and to exploit all the ways of knowing about the past and present to tackle the world's toughest challenges."

Canadian innovation is driven by the priorities of the Government of Canada and has traditionally been based on four pillars: science, technology, engineering and mathematics (STEM). However, Canada's recent science, technology and innovation (ST&I) strategy, released in December 2014, includes focus areas that derive inputs from across the social sciences, humanities, health, natural sciences and engineering. Examples of these broad focus areas include mental health, healthy ageing, food and food systems, water security, disaster mitigation, responsible development in the North and gaming.



David Phipps



Krista Jensen



Michael Johnny

A NEW MODEL OF INNOVATION

Most universities in Canada have a Technology Transfer office to support technology licensing, marketing, patenting and ultimately revenue generating activities. It is through these traditional concepts of university-industry liaison working primarily in STEM disciplines that universities have engaged with industry partners to support previous federal ST&I priorities. However, traditional concepts of technology transfer and industry liaison are not sufficient to support the engagement of university research in these broad focus areas of the 2014 ST&I strategy, which do not rely on patenting and start-up companies but require a people-centred model of innovation. Features of this model include engagement, collaborative research and dissemination to private, public and non-profit organisations.

Knowledge mobilisation helps address this gap. Knowledge mobilisation actively engages university research and researchers with non-academic partners working to support these broader notions of innovation. Knowledge brokers support collaborative research projects that engage

RESEARCHIMPACT-RÉSEAUIMPACTRECHERCHE PUTTING RESEARCH INTO PRACTICE: SELECTED EXAMPLES INCLUDE:

- RIR-University of Guelph brokering services have helped inform effective transportation system planning for the City of Guelph, Ontario
- RIR-Memorial University brokers have created a robust online tool – yaffle.ca – to help rural communities engage in collaborative research
- RIR-Kwantlen Polytechnic University brokers are supporting a bio-regional food system
- In Toronto, the cooling policies for a city of 2.5 million people were informed through an internship project brokered by RIR-York University
- Knowledge brokers at Université du Québec à Montréal and Université de Montréal are creating innovative knowledge products to disseminate research to social service sector leaders

A NETWORK OF 11 UNIVERSITIES

Memorial University of Newfoundland, Université de Montréal, Université du Québec à Montréal, Carleton University, York University (lead), McMaster University, Wilfrid Laurier University, University of Guelph, University of Saskatchewan, Kwantlen Polytechnic University, University of Victoria

academic researchers with non-academic organisations to address real world problems. This co-production model of collaborative research has proven effective in enabling academic research and expertise to have impacts on those areas that have been identified as important to Canadians.

MAXIMISING RESEARCH IMPACT

ResearchImpact-RéseauImpactRecherche (RIR) is Canada's knowledge mobilisation network. Started in 2006, RIR is a growing pan-Canadian network of 11 universities that is investing in university-based knowledge brokers who provide knowledge mobilisation supports to faculty, students and partner organisations. The vision of RIR is to maximise the social, cultural, economic, environment and health impacts of academic research across local and global communities. The network believes that academic research can make a significant contribution to society by partnering academic expertise with expertise from community, industry and government organisations.

Under the leadership of our Executive Lead Committee (usually Vice Presidents Research), the pan-Canadian network is a community of practice of knowledge brokers allowing us to share and exchange information easily and effectively, ensuring knowledge brokers across the country can improve their local knowledge mobilisation practices. We practise knowledge mobilisation in a variety of institutional structures including: community service learning; a research shop model; a living lab model; a public engagement model; and professional knowledge brokers fully integrated into the research enterprise. Since we operate as a community of practice seeking the best from different models, this diversity is our strength.

RIR members are also making important contributions to the scholarship of knowledge mobilisation through local, national and international collaborative, peer reviewed publications such as a recently published paper on knowledge brokering at RIR-York University. Using ResearchSnapshot, we synthesise this knowledge into clear language knowledge products and use social media platforms to share this broadly. This is one example of how we walk the talk in knowledge mobilisation by making our own scholarship accessible to broad audiences.

LOOKING BACK TO LOOK FORWARD

As we enter into our 10th year of operation, three themes have emerged as underlying principles:

- Impact is measured at the level of our non-academic partners who produce the products, make the policies and deliver the services that have an impact on end beneficiaries. Academic impact from

traditional scholarship remains the foundation of academic research but a consideration of impacts beyond the academy are increasingly required by funding organisations in grant applications. Our experience shows that impact takes time, often expressed three to five years after the end of the research project. Impact expressed over time by non-academic research partners has implications for funding, evaluation and communication

- Meaningful engagement among collaborators requires mutual respect and shared ownership from inception to impact. We have abandoned the knowledge 'supply and demand' model and now seek to support authentic partnerships between complementary academic and non-academic expertise. This means we don't 'bridge the gap' (a knowledge transfer paradigm that reinforces academic and non-academic silos) but 'close the loop' between research and its use by creating shared spaces for collaborative research. Dissemination is necessary but not sufficient for knowledge mobilisation
- Successful knowledge mobilisation requires sustained investments in professional knowledge brokers. Knowledge mobilisation activities are frequently funded as a component of research projects, often as part of a graduate student or research employee's many other duties. Investing in dedicated and professional knowledge brokers, in the way that our universities hire technology transfer professionals, creates a high standard of knowledge mobilisation service excellence

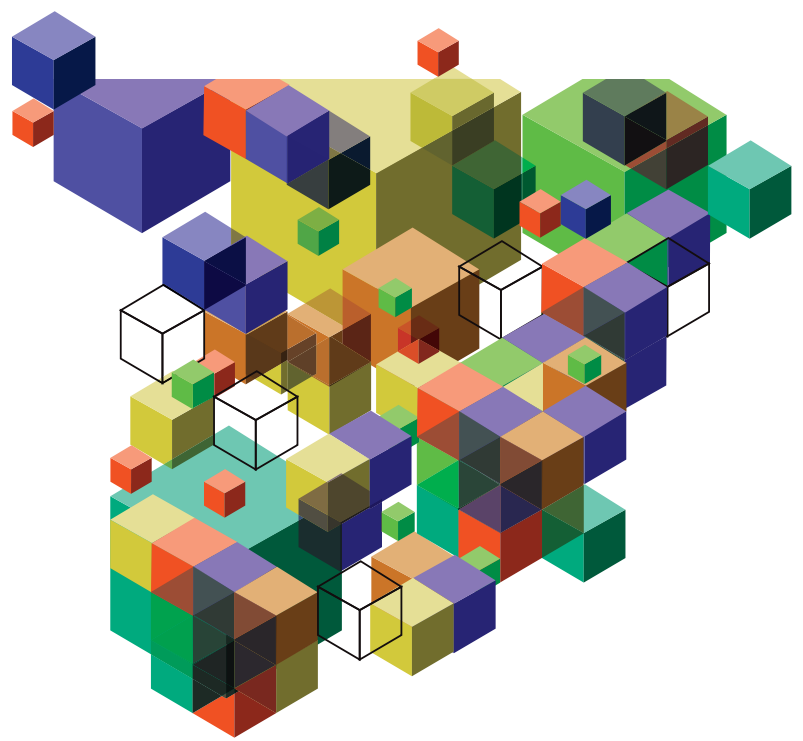
RIR is the only Canadian network focused on supporting university-based knowledge brokers who are working to maximise the economic, social and environmental impacts across all research disciplines. Canadian universities can extend the impacts of over \$3 billion invested every year in academic research by investing in knowledge mobilisation. Maximising the impacts of research in areas of critical importance to Canada's economy, society and environment will help universities become full partners in Canada's future.

WWW.RESEARCHIMPACT.CA

research impact
turning research into action



THE BASQUE COUNTRY: INDUSTRIAL REVOLUTION



Over the past 30 years, Spain's Basque Country has become a model of successful industrial transformation. Indeed, according to the European Commission, the autonomous region is currently the wealthiest in the country. Despite this, in trying economic times there is a need to further boost the area's global competitiveness, and the question remains as to how this relatively small region can achieve this revolution. Technology Transfer Manager **Miryam Asunción** from the CIC nanoGUNE research centre gives her take on the situation

DESPITE THE OVERALL success of the Basque industrial sector, and the importance of its role in the economy, the region's industry activity has declined since the 2008 financial crisis. It currently amounts to less than 21.3 per cent of the gross domestic product (GDP) compared to 24.5 per cent in 2008, and its gross value added (GVA) has decreased annually by 1.5 per cent. The Basque Country therefore finds itself at a critical moment of reflection and change; there is a need to transform its industry through innovation and stem the de-industrialisation processes of recent years.

SMART SPECIALISATION

To address this challenge, the Basque Government plans to build a strong, competitive economy based on R&D in the health and biosciences, advanced manufacturing and energy sectors. The plans are outlined in a smart specialisation strategy (RIS3) currently being implemented, which forms an integrated, region-specific agenda for economic transformation. It will achieve this by using a unique, knowledge-based system that seeks to focus resources and investments in areas where there can be clear synergies with the existing and potential business capacities of the region. The Basque Country has thus begun a transition from a model of incremental industrial advancements toward one that consolidates knowledge from industrial, scientific, political and social stakeholders.

Key to achieving this conversion is the application of a cluster strategy to develop a concentration of interconnected businesses, suppliers and associated institutions in the three fields outlined by RIS3. The Basque Country has long been at the forefront of the design and implementation of cluster methodology, which was first introduced by competitive strategy expert Michael Porter in the 1990s, when the region embarked on a plan to transform its economy in response to deep economic crisis and high levels of unemployment. The success of this policy as part of a broader economic strategy can be seen in the GDP growth experienced

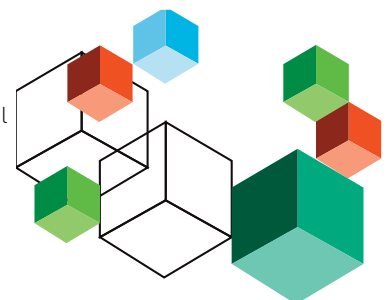
over the last 30 years, which places the Basque Country in the top 5 per cent of European regions today in GDP per capita.

BUILDING COMPETITIVENESS

In 1997, the Basque Technology Network (RVT) was established to facilitate and coordinate the transfer of scientific and technological knowledge to production industries. The Basque Government's Department of Industry has provided over 50 per cent of R&D support to members of the Network, now known as the Basque Science, Technology and Innovation Network (RVCTI). The RVCTI has three subsystems: science and university, technological development and innovation, and support to innovation.

The nanoBasque Agency was launched to shape territorial competitiveness through nanoscience, micro- and nanotechnologies. Its strategy is an open and integrative proposal that covers three main action areas: business development, knowledge generation and enhancement of sector dynamism. However, the economic expansion of nano- and microtechnologies in the Basque Country is not yet a reality, as the gap between scientific and technological capabilities and their economic exploitation by companies seems more marked than in other advanced regions.

It appears that the nanoscientific field is very detached from the traditional world and that companies have a distinct lack of ability to absorb and exploit the scientific-technological capabilities that are created. Compared to more traditional technological areas, entering into the nano world requires businesses to have greater access to infrastructure and collective amenities (public



facilities/equipment), as well as greater policy support. The nanoBasque Agency aims to respond to these needs with a plan for identifying and providing connections to micro-nano infrastructures and equipment, as well as a new model for forging relationships. Finally, the Agency also studies how to find answers to niche market demands of nanotechnology in combination with the core Basque sectors and clusters.

NANO KNOWLEDGE

To increase knowledge generation, the Basque's strategy facilitated the creation of Cooperative Research Centres (CICs) dedicated to health and biosciences, advanced manufacturing and energy. CIC nanoGUNE, of which I am Technology Transfer Manager, is one such centre, coordinating nanoscience and technology research to promote competitive growth. The Centre's research programme is carried out by nine research groups centring on different areas of nanoscience. The CICs play an important role in the Government's strategy to direct innovation based on scientific knowledge, working closely with companies within the manufacturing industry to bridge the gap between science and industry, and tailoring collaborations to meet the requirements of the companies involved.

When the worlds of science and industry collide there is a need for intermediaries and translators to ensure a common understanding and successful path from research to commercialisation. Scientists need to work with business individuals who are 'on the same wavelength', and who can guide them through the commercial process. Conversely, businesses must have the ability to determine how the research that public institutions have to offer can be of commercial benefit. The commercialisation of scientific breakthroughs is something that has become more formalised in recent years. There are many routes for this technology transfer, including licensing, royalties, incubation and in-house development. Beneath all this activity, there are complex issues

regarding the potential value locked up in these intellectual assets, and how they can best be developed to generate value without straying too far from the original ideals.

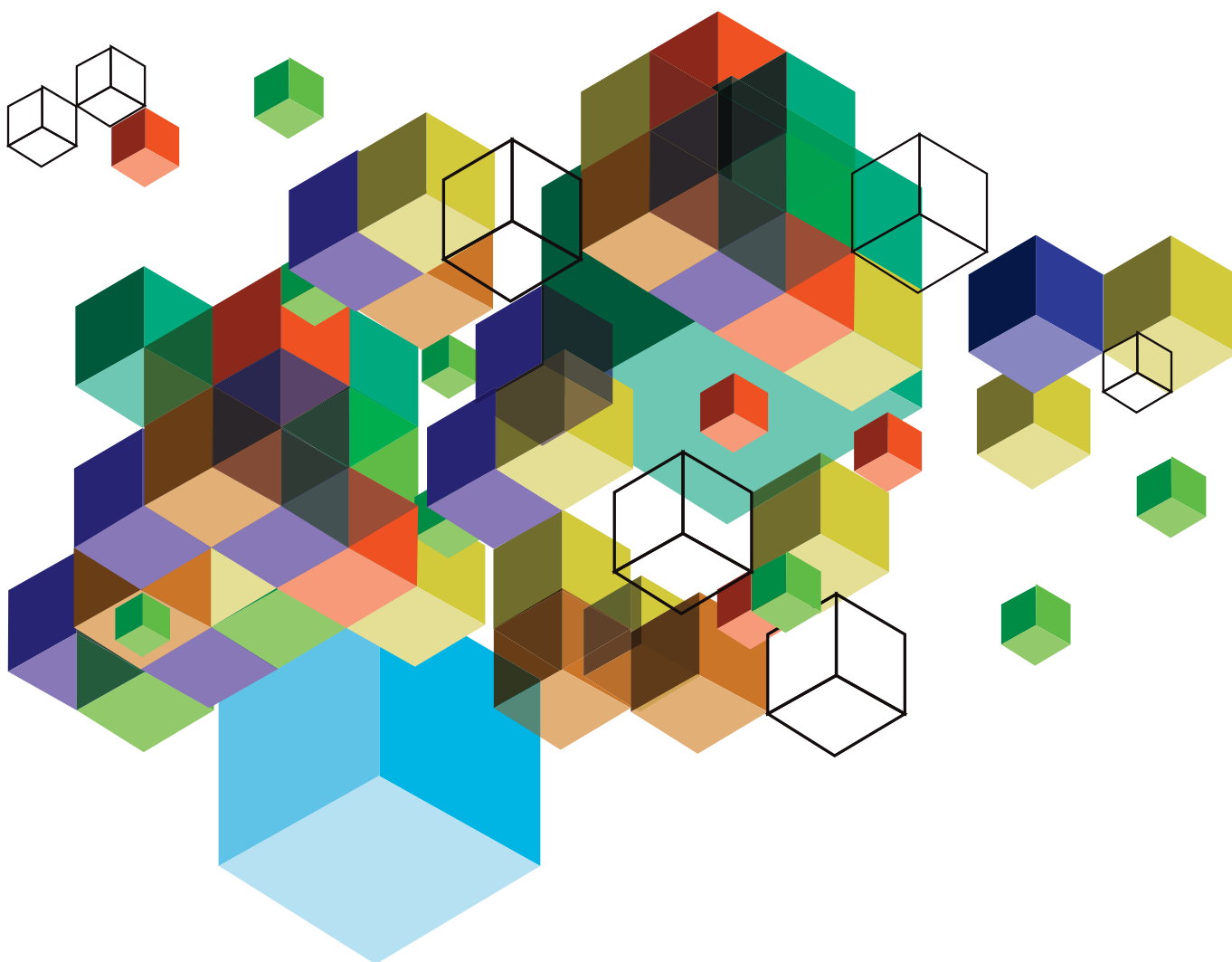
The conclusion is that there is no single path to commercialisation. Every technology transfer process has its own requirements and each path must be adapted accordingly.

A WORD OF ADVICE

Scientists intending to proactively share their knowledge with industry must find the proper communication or means to facilitate their goals. In my experience, the difficulty is that scientists are required to change their communication style when interacting with industry in the first instance. Simultaneously, it is necessary for industry to progress into a more scientific arena when conversing with researchers.

It is a misconception that scientific principles are important when starting to build connections with industry; in fact, the researcher should be 'less precise' during their first approach, instead focusing on the potential applications of the research, addressing market demand with their competitive technology. Conversely, industry players should build a more technical understanding of scientific concepts that will enable them to differentiate a final product from other contenders. The desired outcome is for scientists to become experts in the market of their research result or product, and for businesses to gain a more scientific understanding of the value of research.

www.nanogune.eu





EURONANOFORUM 2015

Riga in Latvia was the proud host of this year's EuroNanoForum, which united industry, policy makers, academia and innovative SMEs. The event provided a forum for sharing expertise and discussing key challenges facing nanotechnology and advanced materials

THE FOCUS OF EuroNanoForum (ENF) 2015, the seventh ENF event, was on promoting European reindustrialisation and creating new markets for advanced technology. Organised by the University of Latvia and Spinverse, the Nordic leader in innovation consulting, in cooperation with the European Commission's Directorate-General for Research and Innovation, the theme of this year's conference was 'Nanotechnology for European competitiveness'.

Coinciding with the Latvian presidency of the council of the European Union (EU), ENF 2015 took place on 10-12 June and offered an outlook of European and global developments, trends and innovation demands in nanotechnologies and advanced materials industries. Across the three-day event, attendees participated in plenaries, sessions and workshops

that focused on advanced materials and new production technologies within the healthcare, energy, chemical and automotive industries.

Representatives from industry, along with SMEs, investors and policy makers, were afforded the opportunity to debate pressing topics, spanning education and entrepreneurship. In addition, participants were privy to first-hand knowledge on initial activities launched under Horizon 2020 and expert insight for coming calls during sessions on specialisation and public-private partnership initiatives. Alongside the conference, the event also featured a Nanotech Europe Exhibition, Brokerage Day, Poster Session, Best Project Award, FutureFlash! and Latvian Salets.

HIDDEN POTENTIAL

Clara de la Torre, Director of Key Enabling Technologies and Directorate General for Research and Innovation at the European Commission, outlined key opportunities for nanotechnology

"Europe has always been celebrated for its excellent science and industrial innovation; though today, more than ever before, we need growth. We need to keep finding new collaboration models and new ways to support our creativity. This conference serves as a perfect example of how, by joining forces, we can put our great traditions and excellence to the service of Europe's reindustrialisation. Nanotechnologies and advanced materials have potential to lead to unforeseen advances and new markets, as well as find fresh solutions to our problems in health, energy, climate and the environment, turning those into real opportunities for growth in Europe."

ENF 2015 brought together
1,200 delegates, including 150
speakers from 50 countries

TOWARDS LOW CARBON ENERGY SOLUTIONS

Looking at the EU Energy Triangle, Dr Fabrice Stassin, Managing Director at the Energy Materials Industrial Research Initiative (EMIRI), outlined his company's work driving forward research and innovation in the advanced materials for low carbon energy applications in order to meet Europe's energy and climate change challenges.

EMIRI in numbers:

- €4 billion sales of advanced materials for energy
- €400 million investment in R&I on advanced materials for energy
- 20,000 direct jobs in manufacturing of advanced materials for energy
- 4,000 researchers: human resources for R&I on advanced materials for energy

<https://emiri.eu>

MANUFACTURING MATTERS

Speaking at the conference, Rudolf Strohmeier, Deputy Director-General of Research Programmes, highlighted the importance of manufacturing industries in Europe

"In the EU, manufacturing is responsible for 80 per cent of total exports and for 32 million direct jobs and another 20 million indirect jobs in the related supply sector. In addition, manufacturing is responsible for three-quarters of private sector R&D expenditure and half of the innovation expenditure. If we lose manufacturing in Europe, we also lose R&D and, as a final consequence, growth and jobs.

We cannot allow this to happen. We must reindustrialise Europe and the Commission has set the ambitious goal to raise industry's share of the GDP to 20 per cent by 2020. Industry is on the verge of a new industrial revolution, sometimes called Industry 4.0, or cyber-physical systems, where the progress in information and communication technologies is shaking up the landscape of industry and manufacturing.

The reason I wish to address Industry 4.0 in this nano and materials conference is that although ICT is driving the developments, Industry 4.0 is more than 'digital'. Linking the 'physical' with the 'digital' world through 'cyber-physical systems' has the power of making our industrial system truly flexible, resilient, resource efficient, human centred and highly competitive. It also enables new intelligent products – based on nanotechnologies and advanced materials – to reach the market place and provide the needed innovation to address societal challenges.

Making Industry 4.0 work for Europe therefore requires a holistic and systemic approach. Digitalisation alone will not reindustrialise Europe."

FutureFlash!

- Best project competition – the 10 best projects launched under the EU funding instruments
- Demo area – showcasing the 10 best projects in nanotechnology and advanced materials

REALISING POTENTIAL

Patrick Boisseau, Chairman of the European Technology Platform on Nanomedicine and the French Atomic Energy Commission-Laboratoire d'électronique des technologies de l'information, provided an overview of nanomedicine in Europe

Exploiting the physical, chemical and biological properties of materials at the nanometre scale, nanomedicine has the potential to enable early detection and prevention, and essentially improve diagnosis and treatment processes. In Europe there are more than 1,500 academic teams and over 500 SMEs working in the various fields of nanomedicine, such as *in vitro* diagnostics, medical imaging, therapy, regenerative medicine and patient monitoring.

With more than €600 million of European Commission funding invested in nanomedicine projects between 2007 and 2014, and 122 products under clinical trial, Europe has the potential to become a future world leader in nanomedicine. However, European patients are still missing the innovative nanotherapeutics under development compared with the US market.

The European Technology Platform on Nanomedicine identified several bottlenecks, which required coordinated public actions to create a favourable ecosystem in Europe for the blooming of the most promising SMEs or startups, and possibly the relocation of large companies. Now at a turning point, Europe could soon create a profitable nanomedicine sector, thus contributing to an industrial renaissance on the continent.



The vesicle vehicle

Presenting a novel diagnostic strategy, **Dr Juan M Falcon-Perez** details the potential impact of his research on overcoming liver disease, which claims more lives per annum than diabetes and road traffic accidents combined

What are exosomes, and how is your group furthering understanding of this subject?

For many years, cell biologists were focused on what was happening inside cells, without paying too much attention to the reactions and processes that were happening in the intercellular space. A revolution of this intracellular view followed the discovery of small biological vesicles observed outside cells and circulating in the bodily fluids. In the past decade, it has been shown that most of the cell-types forming the body synthesise

and secrete small vesicles, exosomes, which interchange materials and signals with the adjacent and distal cells of the body.

My group has studied exosomes since 2005, and has broad expertise in their isolation and characterisation from different biological sources and pathologies. We are pioneers in the study of exosomes secreted by hepatocytes (the principal cells of the liver). We've shown these hepatic exosomes to be useful in identifying minimally invasive markers of liver disease, and have provided a repertoire of molecules that could aid in the development of novel diagnostic and prognostic tools.

In addition to exosomes, your team is an authority on metabolomics. Could you explain this term and what is unique about your methodology for this particular research area?

Metabolomics is a recently established technology for measuring small compounds. It covers more than 50,000 different molecules, including sugars, fatty acids, lipids, nucleotides, vitamins and drugs. Our methodology permits the measurement of more than 1,000 different molecules simultaneously in a small volume of sample. Metabolomics has the potential to identify specific, sensitive disease biomarkers, and



A signature of success

Cellular biologists at the **Centre for Cooperative Research in Biosciences, CIC bioGUNE**, Spain, are spearheading advancements in diagnostic technology. Though their approaches are familiar to few, their results may soon be enjoyed by many

INNOVATION OFTEN TAKES the form of a novel integration, the marriage of seemingly disparate concepts. The work of Dr Juan M Falcon-Perez, leader of the Exosomes Group at the Metabolomics Unit of the Centre for Cooperative Research in Biosciences (CIC bioGUNE), Spain, exemplifies this form of innovation. His team couples the recently developed metabolomics technology with the nascent domain of exosomes. In so doing, Falcon's team finds itself at the leading edge of an uncharted territory, and one which promises to revolutionise medicine.

METABOLOMICS AND EXOSOMES

Metabolites, the products of metabolism, are analogous to fingerprints at a crime scene, their identification evidencing the crime: disease. Being indicative of specific cellular processes, metabolites provide

insights into the mechanistic basis of toxicity and other phenomena.

Metabolomics is an inherently broad field of study, and its principles are applied to a diverse selection of biological research topics. Falcon applies metabolomics in a proprietary manner to determine the 'metabolome', or metabolic fingerprint, of exosomes.

Otherwise known as extracellular vesicles, exosomes are microscopic membranous sacks secreted into the bodily fluids by a variety of different cell types. The cargo, and thus function, of these vesicles varies greatly, hence their implication in a vast selection of physiological and pathological processes, from coagulation to cancer.

DIAGNOSTICS

More specific, more sensitive, less invasive: these are the diagnostic ideals to which Falcon aspires. While Falcon's work is of relevance to a number of pathologies, liver disease is his present focus.

Liver disease is heterogeneous and multifactorial in nature, and, according to the UK's National Health Service, among the top five causes of premature death. This is a fact attributable to our increasingly sedentary lifestyle and over-indulgence in fatty foods and alcohol. In acknowledgement of the age-old aphorism 'prevention is better than cure', Falcon's work provides the medical practitioner with prescience, enabling the identification of metabolomic biochemical signatures that precede the most deleterious phases of the disease.

elucidate the mechanisms underpinning the generation of disease, in turn facilitating the identification of novel therapeutic targets.

How has your involvement in the European systems genetic network for the study of complex genetic human disease using genetic reference populations (SYSGENET) and the European Network on Microvesicles and Exosomes in Health and Disease (ME-HAD) supported your research?

SYSGENET is a collaborative European initiative coordinated by the Helmholtz Centre, Germany, to generate model organisms for the study of complex phenomena such as neurological, infectious and metabolic diseases. ME-HAD, another European initiative, encourages collaboration in the study of the potential functions and applications of exosomes. Thanks to these networks, the group has established several collaborations with laboratories distributed around Europe, helping us to develop our specialties. These initiatives have also fostered international recognition of our group as leaders of exosome and metabolomic research.

As its co-Founder and Vice President, could you outline the aims of GEIVEX (Grupo Español para la Innovación e Investigación en Exosomas)?

Along with five other Spanish groups, GEIVEX was founded as one of the first national associations for the investigation of exosomes. The main aim of GEIVEX is to promote innovation in the field of exosome research, and to further their application in clinical medicine. To this end, we organise symposiums and training courses, provide fellowship funds to mobilise researchers, and organise meetings with clinical and funding agencies to promote the potential applications of exosomes.

What are the next major goals for your research group?

Answering some key questions: how is the generation of exosomes regulated? What are they generated for? What are their intermediate and final destinations? To answer these questions, it will be necessary to accrue researchers and funding from national and international agencies. Close collaboration with biotech and pharmaceutical companies will also be essential in realising these goals.

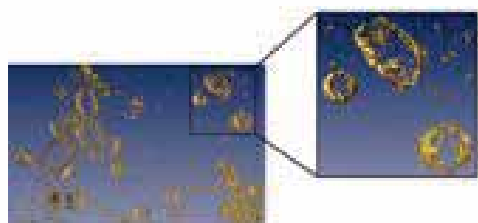
INVESTMENT IN EXOSOMES

Interest in exosomes is not just limited to the biotechnological and pharmaceutical companies. The food industry is attracted to because many popular goods including beer, wine, fruits, probiotics and milk contain exosomes. These vesicles carry many of their features what could have important implications in health.

The discovery of urinary exosomes served as a catalyst for Falcon's research; urine is the preferred bodily fluid for non-invasive diagnosis, easy to obtain and permissive of continuous follow-up. Studying model organisms, the Metabolomics Unit observed the contents

of urinary exosomes changing with the progression of liver disease, presenting the possibility of using these exosomes as biomarkers. Falcon expands: "This is an easy way for physicians to monitor therapy efficacy and, should the treatment be ineffective, modify the intervention to improve the final outcome".

Falcon concedes that much work remains before exosome-based biomarkers are employed in the clinic: "Inter-individual variability and a lack of standardised protocol constitute some of the impediments we face, and to overcome these obstacles, academia, funding agencies and industry must join forces".



Cryo-Electron Tomography of EXOSOMES, in collaboration with Nicola Abrescia and David Gil (CIC bioGUNE).

EXOSOMES AND METABOLOMICS

OBJECTIVES

- To improve knowledge on the functional role and applications of extracellular vesicles (eg. exosomes) in normal metabolism and disease
- To promote metabolomics technology for discovering new low-invasive disease markers and unravelling the molecular mechanisms behind metabolic diseases

KEY COLLABORATORS

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DR JUAN M FALCON-PEREZ is a molecular and cellular biologist at CIC bioGUNE, Spain, with more than 18 years of research experience and over 50 publications in indexed

scientific journals. He studied at the University of Seville and received his PhD from the Autonomous University of Madrid, Spain, before completing two postdoctoral positions, including his recently completed five-year appointment at the University of California, Los Angeles, USA. Falcon-Perez is an expert in applying -omics technologies and exosomes as platforms for biomarker discovery. He has led and pushed several national and international initiatives on metabolomics and exosomes in collaboration with academia and industry.





Revitalising business

Professors Raymond Levitt and Kim Wikström and Dr Ashby Monk seek to demonstrate how effective cooperation in the supply chain can diffuse innovation in mature industries. They explain how the value of infrastructure modernisation is being realised through mutually beneficial investor partnerships

Why might it be worthwhile for a mature industry to give thought to modular versus integral innovation?

RL: In mature industries, the 'system architecture' of the product or service – the specification of each key component's function and its interfaces with other components – is becoming ever more standardised and rigid. Its supply chain therefore tends to fragment, as specialised external firms can more efficiently produce and enhance components than the original developer.

Innovations to individual modules that align with the system architecture, and as such do not affect the specification or assembly process of any other modules, are called 'modular innovations'. These can be easily adopted and diffused through the supply chain – like a faster microprocessor. In contrast, innovations to individual modules that require matching changes in the specifications or installation process for other modules, such as touch-screen tablet computers, are known as 'integral innovations'. These are generally much more difficult to adopt and diffuse.

Managers in mature industries should be cautious about approving the integral innovations of their supply chain partners, unless they can commit substantial coordination resources to ensuring that the innovative module can be installed and operated with existing or co-modified interfacing modules. Successfully adopting and diffusing an integral innovation often requires the original developer or groups of component manufacturers to reintegrate the supply chain legally by merger and acquisition, or virtually through alliance contracting.

Recently, buildings were reported to consume 40 per cent of all energy in the US,

30 per cent of which was wasteful. Has this picture improved?

RL: In developed economies, most of the existing building stock is old and was never built with energy efficiency as an important objective. The challenge of retrofitting to enhance energy efficiency is that the building owner seldom reaps the savings, since utility bills are often paid by tenants according to the fraction of the total building area they occupy, rather than their actual use. This 'broken agency' problem impacts many areas of energy efficiency, but is especially acute in commercial buildings. As energy prices increase and efficiency awareness goes up, third parties are stepping in as financial arbitrageurs of the potential profits that can be incurred. Solar City in the US is one such example.

You identify the shipping industry as requiring an infrastructure makeover. Where might interventions be required?

KW: Current regulatory frameworks hamper sustainable business development and innovation. The industry needs restructuring to become an integral part of the logistical ecosystems of which it is part. Higher utilisation of capacity (eg. replacing land transport), new technology and fuel types would reduce emissions and, in turn, environmental pollution. The number of actors must be reduced, and novel technologies in cargo handling – which extensively impact the overall logistical chain – and innovations across the entire supply chain – especially in information management – need to be developed.

Why do you believe the shipping industry has potential for an ecosystem makeover?

KW: Mainly because it is lagging behind other transport industries in efficiency and innovation,

and has enormous potential to impact sustainability in supply chains. Both short-sea and global container shipping are of growing importance to society. Connecting with inland water transportation would open up significant innovations and renewables in supply chains.

How is financing of civil and social infrastructure assets changing?

AM: Suboptimal access points and governance structures tend to intermediate institutional investors from such long-term alternative assets. Over the past few decades, the external fund managers investing in infrastructure have enjoyed a disproportionate share of the economic returns created in these illiquid markets. Therefore many long-term investors, such as insurance companies, pension funds, sovereign wealth funds, endowments, foundations and family offices, have begun reconsidering the way in which they access these assets. Some funds have launched in-house teams that invest in infrastructure directly. Others, however, face serious challenges in building that kind of internal expertise. So most investors are seeking to re-intermediate their investments in the domain of infrastructure, and work with more aligned, external agents rather than pursue pure disintermediation.

RL: We are seeing an increasing trend towards delivering many kinds of civil infrastructure as a long-term service. Public-private partnership, or P3, consortia of private firms self-finance and deliver infrastructure services to governments and their users as a 25-50 year service, rather than delivering infrastructure products to the government to operate and maintain. Thus, P3s eliminate a great deal of the inefficiency and broken agency that exists with traditional, design-bid-build infrastructure procurement.



Governing business ecosystems

Research on governance of investments in real assets, such as infrastructure or cargo ships, is currently underway at the Global Projects Center at **Stanford University** and **Åbo Akademi University**. The research points to a need for re-architecting the Finnish cargo shipping industry at the business ecosystem scale

THE BALTIC SEA coastline of Finland is dotted with about 40 ports – the legacy of one thousand years of Finnish seafaring and trade. Together, they process nearly 90 per cent of all foreign trade and represent infrastructure assets amounting to hundreds of millions of euros. Previously, these ports were largely owned by and funded through the municipality they served. However, regulations changed this year and formerly municipal ports became limited companies. Apart from making each one financially self-sufficient, the change is designed to foster competition.

This year also saw the EU Sulphur Directive come into force for the Baltic and North Seas, in order to protect fragile marine environments and limit sulphur oxide emissions into the air from marine fuels. Shipping companies operating in these areas have had to switch to new fuels, like marine gas oil, or take technical measures, such as installing scrubbers on their ships, which has led to a 'sulphur surcharge' on freight costs to recoup some of the costs of 'green investment'. "The same directive will come into force globally within five years, meaning pilot activities within this area have huge potential for business opportunities,"

explains Dr Kim Wikström, Professor of Industrial Management at Åbo Akademi University, Finland.

Finland's shipping infrastructure is significantly underused, on average only reaching 70 per cent utilisation. In addition, ships can be left in ports up to 40 per cent of the time. Apart from representing poor investment management, this adds to the local environmental burden. It is against this backdrop that Wikström has recently analysed the logistics business ecosystem of Finnish ports, in collaboration with colleagues from Stanford University, USA.

GROWING INVESTMENTS THROUGH COOPERATION

Wikström, Professor Raymond Levitt, Dr Ashby Monk and Michael Bennon of the Stanford Global Projects Center, are collaborating in the five-year REBUS research programme. REBUS aims to create a collection of proven business practices that deliver advantage in terms of innovation, growth and efficiency. For this project, academic and public researchers from across the world are working with private companies to help them develop and explore the benefits of 'relational business practices,'

where companies work together to maximise value for the business ecosystem in which they participate, as well as for each participant individually. This is complicated, because a business ecosystem can comprise different types of companies with divergent goals and differing managerial mindsets. Yet open communication, negotiation, cooperation and trust are essential.

A key influence in REBUS is Professor W Richard Scott's Institutional Theory framework that posits how institutions are perpetuated and how they change over time. "It allows us to analyse supply chains from the traditional economist's perspective of contracts and incentives, but also from the points of view of sociologists who study group norms, and psychologists who study beliefs, culture and identity," Levitt explains. "It has greatly enriched our ability to understand and influence the delivery of complex goods and services through fragmented supply chains."

In terms of institutional behaviour, legal and regulatory processes are fundamental for inculcating trust. Thus a key aspect under development in REBUS is an enabling legal

RECONFIGURING THE SUPPLY CHAIN TO DIFFUSE INNOVATIONS IN MATURE INDUSTRIES

OBJECTIVE

To design organisation structures and governance regimes for project and matrix organisation structures in construction and other project-based industries.

KEY COLLABORATORS

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Professor Michael Garvin, Virginia Polytechnic Institute and State University, USA

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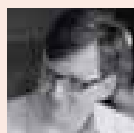
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DR RAYMOND LEVITT has been working at Stanford University since 1980. There, he founded and directs the GPC, where he conducts his research on organisation and governance of projects and project-based companies as the Kumagai Professor in the School of Engineering.



DR ASHBY MONK is Senior Research Associate and Executive Director of GPC at Stanford University, USA, and Visiting Research Associate at the School of Geography and the Environment at the University of Oxford, UK. Monk conducts research aimed at enhancing the governance of institutional investors to enable them to invest directly in real assets.



DR KIM WIKSTRÖM is Professor of Industrial Management, with a specific focus on project business and industrial marketing, at the Faculty of Science and Engineering at Åbo Akademi University, Finland. He conducts research in business models of project-based companies and governance of industrial investments.

model with modular contract structures that promulgate the healthy function of the business network by warding off conflict in joint projects, which protects the interests of all.

A FRAGMENTED INDUSTRY

As the supply chain in a mature industry fragments over time, ownership of the product and/or service delivery process disperses. This is especially apparent in the construction, automotive, computer and mobile phone industries. Apart from integration or quality issues that commonly arise, institutionalised system architectures that lock in component functions and interfaces in mature industries can severely inhibit system-level innovation.

A radical change in governance mechanisms, with an emphasis on creating shared interests and more transparent information sharing, would improve investment performance

The shipping industry has evolved over time into an ecosystem where the actors' goals are misaligned or conflict, while their activities are interdependent. One root of inefficiency in the Finnish shipping industry is the current regulatory environment. Regulation inhibits open information exchange, therefore stifling innovation. The supply chain is so fragmented that a complete overhaul of the business ecosystem is deemed necessary, including its institutions, governance and the ways in which value is created and shared among participants.

ECOSYSTEM SUPPLY CHAIN ANALYSIS

Levitt and Wikström have co-authored a new framework for obtaining better understanding of the success of large investments by analysing them as parts of the business ecosystem. Given that the governance of ecosystem workflows largely determines the value created, the framework guides analysis of workflow interconnections and interdependencies between supply chain participants, according to the degree of conflict resolution. They have trialled the model in a case study of the short-sea – Baltic coastline – cargo shipping ecosystem to pinpoint barriers to efficiency and sustainability.

The short-sea logistics ecosystem must transport goods via marine and port logistics for export industry users in a sustainable way. Its business ecosystem includes ship owners, shipyards and technical companies that supply ship components, port companies and operators, export brokers, logistics tenants,

cargo owners and the ships themselves. As an industry's competitiveness depends on the health of its whole ecosystem, the case study looked at the business activities and the interactions between them, the resources involved, and the role of each actor across a ship's lifecycle. It paid particular attention to the nature of the actors' governance and whether their goals were aligned. Levitt, Wikström and their colleagues characterised each interdependency as pooled, sequential compatible or contentious (or a mix of any of these), and estimated their importance. This led them to identify several dysfunctional areas where enhanced governance could improve ecosystem functionality.

HEALING FRACTURED SUPPLY CHAINS

This case study highlighted that management inattention to the contentious-reciprocal nature of some links restricts value creation – eg. shipyards build ships to minimise initial cost to ship owners; this increases the ship's operating cost for shipping companies; higher operating costs are then passed on to export users who depend on marine cargo services. A radical change in governance mechanisms, with an emphasis on creating shared interests and more transparent information sharing, would improve investment lifecycle performance by leveraging efficiency and innovation.

One of the challenges that remains is identifying the new governance mechanisms required: possibilities include virtual integration of the ecosystem actors through alliance contracting arrangements, enabling better communication flows and tightening links between activities, and recasting the role of cargo brokers by setting up an electronic cargo logistics marketplace. Practical options include maximising ship flexibility to allow mixed cargoes, and ensuring adequate separation of cargoes through automated cargo handling.

Reinvention of the industry must realign the business ecosystem through re-intermediating its supply chain and enhancing its governance. The first obstacle, however, is confronting and overcoming entrenched habits and traditions in a mature, heavily institutionalised environment. There are multiple ways to address behavioural barriers to the relational business practices needed for improved supply chain efficiency. First, aligning the actors' incentives at the whole ecosystem level fixes the 'broken agency' problem. "Long-term alliance contracting with reimbursable contracts and system-level profit sharing can create system-level incentives similar to those in legally merged firms," Levitt observes. Second, collocation of teams helps to build mutual trust and enables easier reallocation of costs and revenues, as well as sharing of information. Where this is not feasible, digital imaging and simulation can be used to share information and expedite discovery of design, manufacturing or operations problems and clashes. Last but not least, creation of a strong shared ecosystem identity helps to refocus the behaviour of individuals toward ecosystem optimisation.





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FOLLOWING

Social media is becoming an increasingly popular channel for information sharing and has changed the way in which individuals interact, personally and professionally. This important technological trend has big implications for how researchers communicate and collaborate. Seeking to discover first-hand how researchers engage with social media, *International Innovation* asked a selection of contributors:

Q To what extent has social media altered the way you communicate, both on a personal and professional level?



DR JUAN FALCON-PEREZ
(CIC bioGUNE, Spain):

Thanks to the internet and social media, in the past few years knowledge about, and interest in, different scientific topics has substantially increased within the non-scientific community. This has generated the need for specialised journals and magazines in which specialists tell a story and/or share results in terms that the layman can understand. Social media provides many possibilities to disseminate what is happening in laboratories, but it is important to be rigorous about what information is shared.

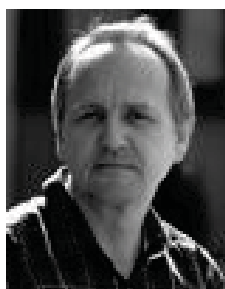
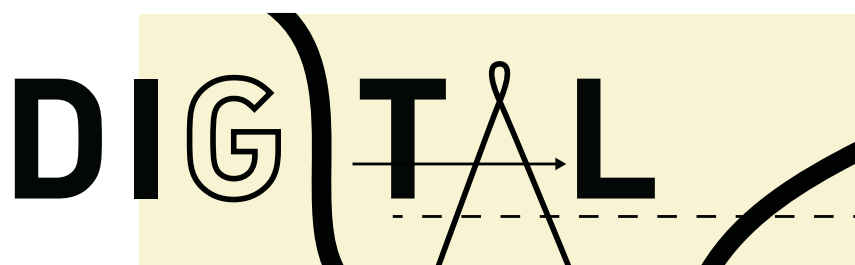


PROFESSOR RAYMOND LEVITT
(Stanford University, USA):

I use social media sparingly and selectively to interact with others in both my professional and personal lives. I am a firm believer that the active and thoughtful use of 'publish and subscribe' protocols in everything from email to social communities is a way to stay informed and also to inform others about interesting and meaningful content. Importantly, this enables one to do so without becoming overwhelmed or overwhelming others with unrestricted 'many to many' communications that may be of little or no interest to the receiver.

I use wikis and blogs in my classes as ways for students to communicate with the instructional team and each other, and to access and build on each other's knowledge and ideas. In addition, I participate in communities like LinkedIn to track down and follow people of interest and ResearchGate and Google Scholar to access and track my own research publications and related publications of interest by others.

In my personal relations, I use Google+ to share photos and comments only with restricted lists of family and friends. I do not post to Facebook or Twitter.



PROFESSOR DAMIJAN MIKLAČIČ
(University of Ljubljana, Slovenia):

It seems to me that social media channels such as Facebook, Twitter and Google+ are not yet fully accepted by researchers. Maybe this is because the leading scientists grew up before the appearance of the internet and social media, or because certain social media channels that may be more appropriate to be used by scientists are yet to evolve – channels such as Research Gate and LinkedIn are the right answers. In our group, we have been experimenting with using Twitter to announce to interested parties that a new research paper has been published, but the community is accepting it very slowly. After almost two years we only have 27 followers, although www.electroporation.net has had almost 6,000 unique visitors since being created in September 2012.

FOOTPRINTS



DIANA GARNHAM
(Science Council, UK):

Social media provides me with a platform for personal expression within a professional context, enabling me to connect directly with others in real time. It's a great way for sharing some of the positive and uplifting events I attend, such as award ceremonies at member organisations, as well as letting followers know what I find interesting from keynotes and speeches as they happen. Hashtags and trending let me know whether I am in or out of step with others! Because of my professional role, I am careful not to use Twitter for personal photos or comments as I feel this would blur the lines between my personal identity and professional role and responsibilities, but I am happy that my personality and values come through in my tweets.

The possibilities for social media to connect directly with professionals on Science Council registers means our current 'big question' debate on how to describe a professional scientist is a more engaging and free-flowing discussion, and we hear from individuals we might otherwise never have reached. In terms of the future, I believe social media has huge untapped potential for facilitating public engagement with science and scientists. We can explore together some of the key issues of transparency about researchers and their values, ethics and professional conduct, and whether (or how) science is contributing to public good.



DAVID PHIPPS, KRISTA JENSEN AND MICHAEL JOHNNY
(York University, Canada):

Knowledge mobilisation is a suite of activities that connect research and researchers to partners who can use that research to inform innovative and improved products, policies, services and professional practices. These connections help to maximise the economic, social and environmental impacts of research beyond the academy.

We use certain social media tools to help mediate connections between research and its use. We published a book chapter on the role of social media in knowledge mobilisation (http://bit.ly/yorkspace_knowledge_mobilisation). Beyond the theory presented in that chapter, the key to successful social media use is a well-considered social media strategy that considers goals, audience, channels, the active conversation, resources and evaluation. There are a number of social media planning guides to assist with this. We collaborated with NeuroDevNet to make a social media Guide of Guides (http://bit.ly/socialmedia_guides), an annotated bibliography presenting a selection of social media guides we feel offer the best advice.

At York University and in ResearchImpact-RéseauImpactRecherche (RIR), Canada's knowledge mobilisation network, we use the following social media channels:

Mobilize This! Blog (160,000+ views from 149 countries) for thinking out loud, editorials, commentary and announcements

Twitter @researchimpact (6,300+ followers) for engaging, broadcasting, dissemination and community building

LinkedIn ResearchImpact Group (401 members) for discussions, announcements and commentary in related LinkedIn Groups

Slide Share (25,995 views) and **You Tube** (7,747 views): a repository of content including presentations and videos we have produced or are sharing

You will note we do not use Facebook in our own work. However, we help researchers consider their use of Facebook where that tool makes sense for them. Our knowledge mobilisation stakeholders are not using Facebook for their work, so neither do we. However, if your customers, clients, stakeholders and partners are active on Facebook then you should consider either being active on your own Facebook page or becoming active on theirs. But carefully consider whether you should be using a personal or professional Facebook persona when being active in the professional Facebook pages of others.

The number one question we get asked is 'How do I drive traffic to my social media?'. That is the wrong question. When starting to implement your social media strategy your first action should be to see where there is existing traffic and become an active contributor to those conversations. Comment on blogs and videos. Retweet. Share content (yours and others') in those conversations. That will raise awareness of your social media channels and others will, over time, become active contributors to your social media.



Perspectives on electroporation

Electroporation is connecting science, industry and medicine. Three experts from different fields, **Professors Damijan Miklavčič** and **Javier Raso** and **Dr Georgeta-Mihaela Moiescu** share their experiences using the method

How did you become interested in the field?

DM: I first heard about electroporation during my undergraduate studies as a means to transform bacteria. At that time it was considered a crude, yet efficient, means of gene transfer that could only be used in bacteria. At the 1989 World Cancer Congress in Hamburg, Germany, however, I spotted a poster by Drs Jean Belehradek Jr, Stephan Orlowski and Lluís M Mir. They demonstrated the 1,000-fold cytotoxicity of bleomycin (an antibiotic) when

combined with electroporation. I decided we needed to bring it to our patients in Ljubljana, Slovenia. In a way, that was the start of my more than 25-year long, fruitful and rewarding scientific journey!

Despite the wide-ranging potential of the technique, why is electroporation proving slow to bring to market?

MM: A medical treatment's safety and efficacy are more important than its 'speed to

The potential of pulsed electric fields

Short high-voltage electric pulses can be used to alter cell membrane properties. This technique, called electroporation, is beginning to reach its potential and is coming into common use, partly thanks to a recent drive from a COST initiative to streamline research and facilitate inter lab communication

THE CELL MEMBRANE is a selectively permeable phospholipid bilayer that surrounds and separates a cell's contents from its extracellular surroundings. Everything that enters or exits a cell must do so via its membrane. Proteins embedded in the membrane allow the transfer of specific ions and molecules into and out of the cell. It has been shown that by exposing cells to an electrical field to such membranes their permeability can be increased. This change in permeability can be reversible or irreversible

depending on the parameters of electric pulses applied. This technique, termed electroporation, is a powerful method for introducing molecules that would not otherwise cross the membrane into cells.

Electroporation can also be used to do the reverse; increased permeability can allow the extraction of molecules from cells. Additionally, it is sometimes used to introduce foreign proteins into cell membranes, or even to induce neighbouring cells to fuse. Irreversible electroporation is an effective way to kill cells and can be particularly useful for non-thermal pasteurisation, food

treatment and eliminating harmful bacteria in a clinical setting, especially those that have become immune to many antibiotics.

This powerful and diverse tool has been implemented in a wide variety of settings. For example the labelling of neurons with fluorescent dyes for imaging, transfection of cells with novel genes, targeted cancer treatments, food and biomass processing, and microbial inactivation in water treatment, to name but a few. Although its applications

market'. Drug approval by the Food and Drug Administration (FDA) takes between eight to 12 years for the most successful drugs. This doesn't include the years needed to go from concept to compound, nor those taken for the medical community to accept and implement a drug or device. In 1991, the first clinical trial of electrochemotherapy of melanoma metastasis started at the Institut Gustave Roussy in Villejuif, France. In 2005, the Cliniporator device for electrochemotherapy was introduced to the clinic and, in 2006, standard operating procedures for cutaneous and subcutaneous tumours became available. Patients have benefited ever since, including over 10,000 patients in Europe bearing skin primary tumours or metastasis for which conventional treating procedures were ineffective.

JR: For many years, the lack of reliable and viable industrial-scale equipment limited the commercial exploitation of pulsed electric field (PEF) processing in the food industry. However, recent developments in pulse generators have enabled the design of PEF equipment specifically for the food industry, with a capacity of up to 50 tonnes per hour. Next, we must design low-cost pulse generators tailored for each specific task. Applications of PEF in

some food industries such as wineries are circumscribed to a short period of the year due to the seasonal availability of the grapes. Reduction in pulse generator cost is essential for PEF technology introduction in industries that have extended depreciation periods for the equipment.

Which skills has your team contributed to EP4BIO²MED? Beyond the health and environment applications, have you been surprised to learn these technologies can have significant impact elsewhere?

DM: From the very beginning (the early nineties) our group was active in exploring electroporation in the field of biomedicine – focusing on electrochemotherapy and gene electrotransfer for gene therapy and DNA vaccination. A few years ago I realised that there is another 'universe' in which electroporation is called PEF treatment and is used in food processing. Although these two worlds coexisted for decades, they rarely interacted. This was actually the trigger for me to propose this COST Action – to be able to pull together resources and knowledge from both universes and facilitate faster progress, creating a kind of wormhole.

Gene therapy holds marked potential for the next generation of cancer therapies. What are the unique qualities of electroporation treatments?

DM: Electroporation is a nonviral means of delivering DNA and RNA fragments into cells *in situ*. This is being tested in clinical studies – primarily for cancer treatment, but we can soon expect efficient DNA vaccination against other diseases. This will be feasible with the use of electroporation.

What are the short-term scientific missions (STSMs)?

MM: STSMs support the mobility of researchers who want to learn new techniques, perform experimental work using instruments and/or methods not available in their own laboratory and foster or strengthen collaborations with complementary teams. In total, 64 missions have been funded by COST TD1104 Action over three years, while 68 research and academic institutions from 18 European and two North African countries, as well as Israel, New Zealand and the US, have been connected by human and scientific bridges.

are plentiful, electroporation has yet to fulfil its scientific, clinical and commercial potential. There is a strong need for a better understanding of the mechanisms by which electroporation works, and for the development of new techniques optimised for their applications. There is also a need to implement the technique at an industrial scale and bring it from the scientific periphery into common use.

COMMUNICATION IS KEY

It has been suggested that one of the reasons why electroporation has not yet taken centre stage in many fields is simply poor knowledge transfer. There has been a lack of interaction between researchers from different fields using similar techniques, and this has created redundancy in the field, forming a barrier to progress.

A COST TD1104 Action has established an international network of researchers,

institutions and industries that will aid the development of electroporation-based technologies and treatments. "The main objective of this Action is to streamline European (and wider) research on electroporation, ranging from basic research to industrial and medical applications, by collecting, pooling and transferring knowledge to partners," explains Professor Damijan Miklavčič of the University of Ljubljana, Slovenia. The project, also known as EP4Bio²Med, seeks to advance basic mechanistic understanding of electroporation, overcome the limitations of existing applications and facilitate the development of new technologies.

EP4BIO²MED

To date, the project comprises 575 individual participants from 240 institutions in 43 different countries. These are divided into five working groups, each focusing on a different arm of the

COST TD1104 Action's objectives. Over half of the participants are focused on basic research under the guidance of Marie-Pierre Rols at the Institute of Pharmacology and Structural Biology at the French National Centre for Scientific Research. The goal is to understand and model the biological, physical and chemical mechanisms of electroporation. By better understanding how electroporation works at this level, the researchers hope to design improved technology and methods for use in other areas. Thanks to COST's interconnectivity, this work can readily inform the remaining four working groups, which focus on different applications of electroporation.

Led by Giovanna Ferrari of ProDAL Scarl and the University of Salerno, Italy, the second working group considers the use of electroporation in food processing and pharmaceutical applications. The primary goal here is to develop better equipment and improve process

COST TD1104 ACTION

OBJECTIVES

- To provide effective steps to increase European expertise in electroporation
- To improve communication between international groups through interdisciplinary knowledge exchange on electroporation-based applications

KEY COLLABORATORS

For a full list of participating countries and working groups, visit: www.electroporation.net

FUNDING

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PROFESSOR DAMIJAN MIKLAČIČ

has remained at the University of Ljubljana since completing his PhD in Electrical Engineering in 1993.

He held the position of Vice-Dean of Research from 2003-05 before his appointment to Head of the Department in 2007; a responsibility he still holds. He has authored or co-authored over 900 papers, including over 230 original articles in peer-reviewed scientific journals, and his work has been cited over 4,300 times.



GEORGETA-MIHAELA MOISESCU

received her PhD in Pharmacy and Biophysics from both Paris-Sud University, France, and Carol Davila University of Medicine and Pharmacy, Romania, in 2007. She coordinates the short-term scientific missions (STSMs) within COST TD1104 Action.



JAVIER RASO

received his PhD in 1995 from the University of Zaragoza, Spain. Today, he is Professor of Food Technology at the same institution.

He is the author of more than 80 peer-reviewed papers and is currently appointed as Vice-Chair of COST TD1104 Action.

design for these industries, drawing from cutting-edge research in a wide range of fields. Working group three, led by Julie Gehl of Herlev Hospital, Denmark, considers medical applications, not only aiding the dissemination of current cutting-edge clinical knowledge, but also identifying novel applications and providing a standardised clinical protocol for electroporation's use in a clinical setting.

A recent COST action has established an international network of researchers, institutions and industries that will aid the development of electroporation-based technologies and treatments

Group four is led by Wolfgang Frey of the Karlsruhe Institute of Technology, Germany, and aims to make electroporation technologies that are economically competitive and efficient for environmental applications, particularly the processing of biomass. Finally, group five led by Stefan Toepfl of the German Institute of Food Technologies is dedicated to developing new technologies, disseminating technical knowledge and ensuring that safe and reliable electroporation systems are developed for both industrial and clinical use.

EDUCATION, TRAINING, SUPPORT AND INVESTMENT

At the heart of the project is solid knowledge sharing, as Miklavčič explains: "Achieving the objectives of the action did not only depend on the number of participants, but mainly on the effective interdisciplinary exchange of knowledge between researchers working in electroporation in different disciplines". One way this has been achieved is through the construction of a database for information sharing between COST member groups. This pools together contact details and project related information, including ongoing projects, electroporation related research topics, and also information pertaining to the techniques and equipment being used by each institution.

This makes it much easier to share with other researchers and to remain informed about what their collaborators are working on.

COST TD1104 Action continually invests in education and support for its members through the organisation and provision of funding for meetings, training schools, knowledge dissemination and 'short-term scientific missions'. This educational drive includes several annually held training schools, including 'Electroporation-based Technologies and Treatments' in Ljubljana (www.ebtt.org). "Based on our experience we have organised a similar school in the field of food processing, 'pulsed electric field (PEF) school'," Miklavčič explains. "This took place for the first time in Zaragoza, Spain, in 2014 and then in Salerno, Italy, this year. Next year it will be held in Dublin, Ireland." COST TD1104 is also organising the first world congress on electroporation in Portorož, Slovenia, in September. The idea is that this will be the first of many, and will include over 350 participants and provide an additional platform for the exchange of ideas.

Another key success measure for the researchers has been the introduction of a unifying terminology for describing electroporation. "In the biomedical field the technique is termed 'electroporation' and in food processing it is known as PEF," Miklavčič explains. "The participation of experts from various disciplines in this COST Action has contributed to standardising the terminology." What is particularly exciting is that this already fruitful technique is still in its early stages. With improved knowledge infrastructure, electroporation, via COST, is now poised to reach its promised potential.



Pilot Plant PEF microbial inactivation at ProDAI scarl, Salerno, Italy.

electroporation

COST
European Cooperation in
Scientific and Technological Research





Speaking the same language

Dr Elsbeth Kalenderian heads a team of dental faculty members, intent on communicating their development of a standardised terminology for oral diagnoses. They believe the system will become widely adopted and benefit dentists and their patients around the world

What motivated you to establish the Dental Diagnostic System (DDS)?

Dr Joel White: I believe there are two areas of motivation from a dental care perspective. First, we require a diagnosis that is clear and can be used to educate and inform the patient and the provider. We are diagnostic driven but there is no way to capture the diagnosis in the electronic health records (EHRs) unless we have free-form text buried in the chart notes. So, by having a standardised terminology, we can capture a granular diagnosis in the EHRs by the provider. This helps us inform providers of the specific treatment procedures for diagnoses.

Second, it helps us to inform the patient about why a particular procedure is being done by providing detailed reasoning behind each diagnosis. From an educational perspective, it enables us to foster a diagnostic-centred academic approach that will enable our students to learn.

Dr Muhammad Walji: The main motivation was that although we had a data repository with procedure codes, there was no means of explaining the reasoning behind the procedure. We were unable to perform secondary data analysis or research because there was no diagnosis.

Did the lack of a unified system impact your work at a local and national scale?

JW: Locally, there was no way to capture the diagnosis in any structured format. Even if you could capture a diagnosis and extract it from the treatment notes, a lab form or somewhere in the EHR, there was still no way to compare it with anybody else's, rendering the data meaningless. Dental diagnosis couldn't be used, summarised or compared at a regional, national or international level. For those who don't use a diagnostic terminology, those barriers still exist.

Dr Maxim Lagerweij: Previously, each university had to develop its own system, which could therefore only be used locally. Now, many people can invest in the same system and work together effectively.

The DDS consists of over 1,500 terms. Were there any that did not make the cut?

EK: We have tried not to include nondescriptive 'generic' terms like, NOS (not otherwise specified) or NEC (not else classified).

Dr Oluwabunmi Tokede: We retired some terms following expert recommendations. For example, we significantly revised the temporomandibular joint (TMJ) category – masticatory muscle contracture was retired and replaced by two terms: myostatic contracture and myofibrotic contracture. Myogenous TMJ disorder (TMD) pain was also retired.

JW: The DDS has been viewed by content experts and is updated every year. A great example of a term that did not make the cut is class I cavity, which is part of Black's Classification of Cavities and doesn't give the tooth, site, activity or extent of disease, whereas modern caries diagnosis refers to all of them.

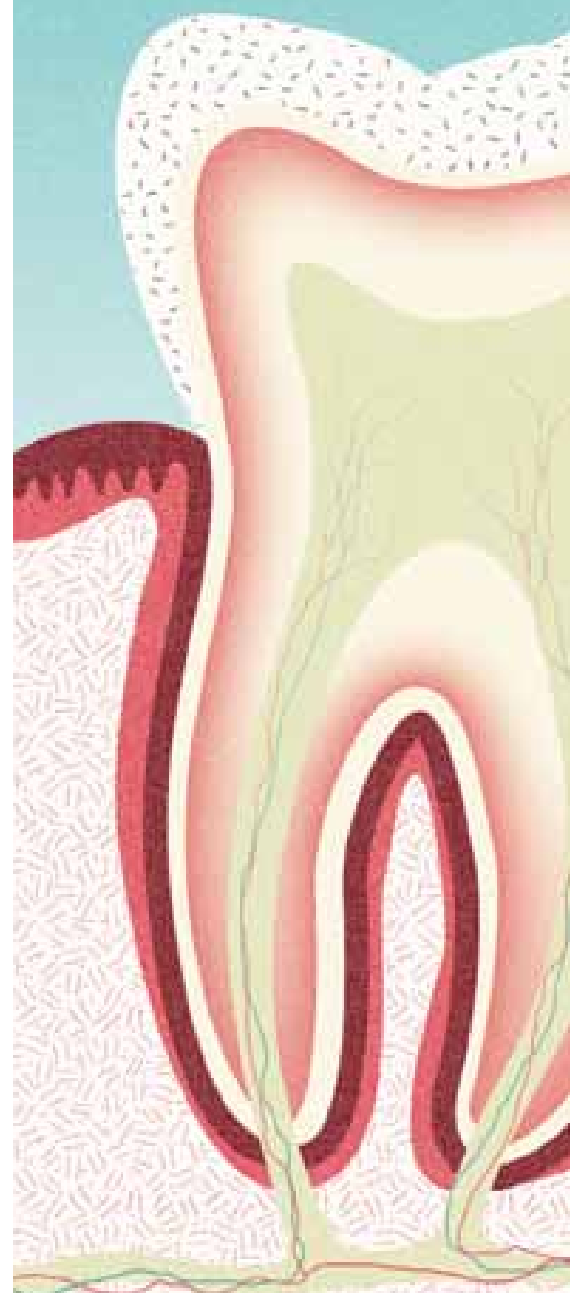
The DDS' standardised terms will bring to light instances of patients with comparable diseases who receive similar treatments but with varying results. Why do you believe it is important to highlight these discrepancies?

MW: By collecting the data in this way we are ensuring that in the future we'll be able to tailor treatments more effectively. Research on disparities shows that people with different ethnicities or race receive different treatments, or respond differently to the same treatment.

How do you envisage the next generation of dentists will use and adapt the DDS?

EK/OT: The next step for the DDS is becoming an international standard as a dental interface technology, with the Systematized Nomenclature of Medicine (SNOMED) providing the reference terminology and the International Classification of Diseases acting as its classification for billing purposes.

MW: I expect it will become second nature as this is an effective, standardised method for dental care providers to document their work.





Standardising representation

A multidisciplinary group of dental researchers based at the **Harvard School of Dental Medicine** has developed the Dental Diagnostic System. This is a consistent language within the electronic health record that facilitates effective communication between clinicians, patients, students and epidemiologists

The Dental Diagnostic System – formerly known as the EZCodes – comprises around 1,500 terms that define concepts at the appropriate granularity required by oral health providers

For over a century, medical practitioners have been capturing the cause of death in patients, a practice wholly beneficial to the development of effective treatment procedures and advances in quality of care. The level of consistency that exists between doctors from around the globe is facilitated by the use of standard reference terminologies. The International Classification of Diseases (ICD) and the Systematized Nomenclature for Medicine (SNOMED) are two reference terminologies widely used as dictionaries of medical and dental terms.

Surprisingly, dentistry has never had a similarly effective system of its own. This is, in part, because of a lack of a readily available classification system dentists can refer to. Attempts to address this problem have been made throughout the years, one of which culminated in the creation of the reference terminology called Systematized Nomenclature of Dentistry (SNODENT). However, this system has proved largely ineffective, not least because it is composed of more than 6,000 terms, is not widely available and is yet to be finalised. Furthermore, due to its size, many doubt its potential to be easily incorporated into the electronic health records (EHRs) in an organised, user-friendly way.

DOCUMENTING DIAGNOSES

In the available reference terminologies of ICD, SNOMED and SNODENT, there were not sufficiently granular terms for dental use that accurately and completely defined dental diagnosis to the level used in current oral diseases diagnoses. Now, in an attempt to fill

this gap, a team of researchers has developed a standardised tool for documenting diagnoses of oral health-related conditions. Led by the Harvard School of Dental Medicine's Dr Elsbeth Kalenderian, the group has created a common and consistent language specifically applicable to the field of dentistry. The Dental Diagnostic System (DDS) – formerly known as EZCodes – comprises around 1,500 terms that define concepts at the granularity required by oral healthcare providers.

The project is funded by the National Institute of Dental and Craniofacial Research (NIDCR), and seeks to enable the capture, storage, sharing, retrieval and aggregation of oral health data. In achieving this, the DDS ensures that the descriptions of both diagnoses and treatments are presented in a consistent and effective manner.

AN ONGOING PROCESS

The team of faculty members includes Drs Rachel Ramoni, Joel White, Muhammad Walji, Oluwabunmi Tokede and Maxim Lagerweij, united by a common goal to improve dental research, education and patient care by creating a go-to source of data for clinical and public health research. There were several considerations for the researchers to take into account during the process of compiling a terminology with such a variety of applications. First and foremost, ensuring the standardised terminology is used consistently and accurately. "That is the reason the DDS research team completes ongoing validation and measuring. We wish to ensure the diagnostic treatment pairs are being used correctly," explains Walji. "It is important to keep the terminology updated frequently because the way clinicians think might change."

The DDS aligns dentistry with medicine, in terms of establishing a standard clinical practice. Enabling diagnoses to be clearly recorded after examination and investigation



is important to facilitate communication between clinicians, patients, epidemiologists, researchers and students. The DDS provides a repository from which they can, for instance, chart good clinical judgement, draw upon information for research and analyse the varying efficacies of prescribed treatments.

IMPLEMENTATION TOOLKIT

While the standardisation of dental diagnostic terminologies is of obvious benefit to dentistry, it is important that additional consideration is given to how the terminology will be shared. Facilitating and encouraging its use is key to the system realising its potential. With that in mind, NIDRC is supporting the development of the DDS implementation toolkit, which will enable the terminology to be rolled out to general practitioners. "Each patient has a documented diagnosis that will inform the general practitioner," Kalenderian adds. "This will impact care because we can develop the outcome metrics, running the database to figure out which patients are overtreated, undertreated or appropriately treated, and then continuously fine-tune."

Over 15 dental institutions from the US, Canada and Europe use the DDS for patient care, teaching and research. Incorporated within axiUm, Exan Corporation's dental EHR, the DDS is used by almost every dental school in the US. The DDS has been shown to be useful and accurate, and its terms are routinely paired with dental procedures providing a treasure trove of usable data on dental diagnosis and treatment for appropriateness of care and outcomes research.

The DDS is a crucial component of the BigMouth Dental Data Repository (which houses data from six institutions with nearly 2 million patients), ensuring its standing as the single most important source of dentistry research. Structured data entry is essential for developing effective electronic health systems

and helping clinicians use them in a meaningful way. With the creation of the DDS, the team

A MATTER OF PRINCIPLE(S)

The DDS's guiding principles are to:

- Include appropriate oral health concepts from existing reference terminologies, for example those of the International Classification of Diseases, SNOMED and SNODENT
- Adhere to best practices in terminology development. As such, each term is assigned a preferred term and non-semantic identifier
- Facilitate retrieval by hierarchically structuring concepts into categories and subcategories
- Evaluate and refine the terminology on a regular basis
- Link diagnostic terms to procedure codes
- Include assertional knowledge such as definitions, incidence, prevalence, guidance to clinicians and mapping to reference terminologies

DENTAL DIAGNOSTIC SYSTEM

OBJECTIVE

To compile and establish an accepted, standardised terminology for oral diagnoses.

KEY COLLABORATORS

Dr Rachel Ramoni; Dr Oluwabunmi Tokede, Harvard School of Dental Medicine, USA

Dr Muhammad Walji, University of Texas Health Science Center at Houston, USA

Dr Joel White, University of California at San Francisco, USA

Dr Maxim Lagerweij, Academic Centre for Dentistry, Netherlands

PARTNERS

For a full list of the Dental Diagnostic System development and implementation team, visit: www.dentaldiagnosticsystem.org/about/

FUNDING

National Institutes of Health

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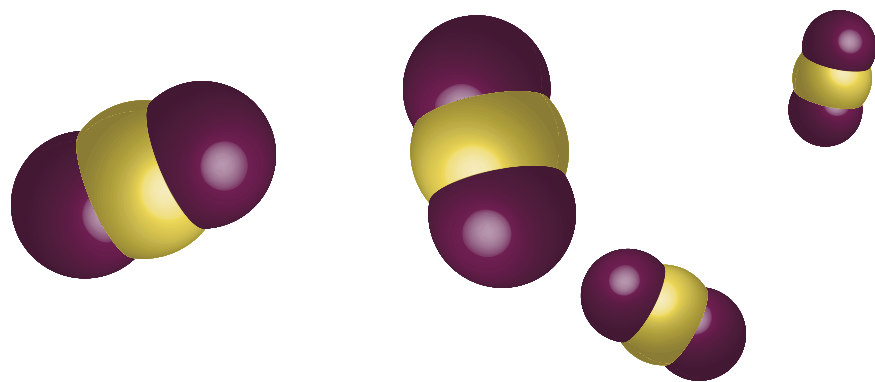
www.dentaldiagnosticsystem.org

<http://linkd.in/tesMUGD>



ELSBETH KALENDERIAN received her Doctor of Dental Surgery (DDS) degree from University of Groningen, Netherlands, before embarking on her residency in Oral and Maxillofacial Surgery at Boston University, USA. In 2007, she made the transition to an academic career at the Harvard School of Dental Medicine, starting as Assistant Dean for Clinical Affairs. She currently serves as Associate Professor and Chair of the Department of Oral Health Policy and Epidemiology.





Capturing carbon

Dr Deanna D'Alessandro leads a team of researchers working with metal-organic frameworks, materials with the potential to deliver more energy efficient gas separation processes. Below, she outlines her inspirations, discoveries and research aims

What is your inspiration for studying inorganic materials exhibiting novel physical properties?

In contrast to existing classes of solid materials, such as bulk metals, polymers and amorphous carbons, my work focuses on a class of materials known as metal-organic frameworks (MOFs). These materials have an enormous range of tunability, and provide a 'playground' for scientists to explore deeply fundamental phenomena, whilst being of tremendous interest to industry.

Could you explain what MOFs are and how they might be of use?

MOFs (also known as coordination polymers) have been known for decades, but have recently enjoyed a resurgence in interest owing to their extraordinarily high porosities, which make them ideal for applications in gas capture and storage. These materials consist of metal ions linked by organic bridging ligands to form crystalline 3D structures. An enormous range of properties can be realised in these materials owing to the plethora of metal ions and ligands that can be combined. Furthermore, these materials have the unique capability of integrating multiple functionalities alongside their highly porous structures.

Your team has developed CO₂ adsorbents on the principle of redox-swing. Can you elaborate on this phenomenon?

The current industrial method for CO₂ capture involves the use of aqueous amine solutions, which are heated to boiling point in order to remove the captured gas. This process is extremely energy intensive and explains, in part, why CO₂ capture is implemented

at so few industrial sites worldwide.

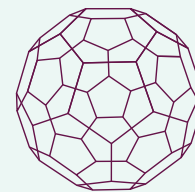
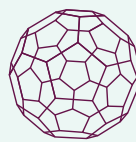
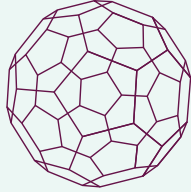
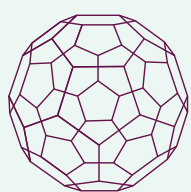
One potential application of our work on electronically active MOFs is their use in redox-swing capture processes. Here, the material possesses a different affinity for CO₂ in its different electronic states. We can switch between these states using either an electrical stimulus or light, which triggers a change in the redox state of the material.

The structure, chemistry and physical properties of a material are inextricable. Have you made any new discoveries regarding this relationship?

MOFs provide an ideal platform to interrogate the relationship between structure and function in materials – their crystalline nature is such that the location of the constituent atoms can be characterised at the atomic scale. Coupled with this, our team has developed new 'spectroelectrochemical' techniques that allow us to probe optical properties as a function of the electronic state of a material. In this way, we can pinpoint the origins of changes in the properties. With collaborators at the Australian Institute of Nuclear Science and Engineering, we can also gain insights into the exact location of adsorbed gas molecules in MOFs using neutron diffraction techniques.

Finally, what are the ultimate aims of your research?

My group's research is particularly targeted at problems of environmental significance and aims to contribute both fundamental and applied knowledge. In shaping solutions to these issues, I have sought to train and mentor young scientists who will contribute their skills in a variety of ways.



Functional inorganic materials

Researchers at **The University of Sydney** have been involved in developing highly porous 3D solids known as metal-organic frameworks to capture carbon. As well as being key to reducing greenhouse gas emissions, they have capabilities for a range of other applications

FACILITATING THE WORLD'S transition to a low carbon economy is crucial in the quest to reduce greenhouse gas emissions. One effective means of doing this is through carbon capture and storage (CCS), where up to 90 per cent of the carbon dioxide (CO₂) emitted from the use of fossil fuels in industrial processes is captured, transported and stored – usually in the form of a liquid – several kilometres underground.

The properties of MOFs are key to their suitability in capturing carbon, with just 1 gram of an MOF capable of having a surface area equivalent to that of a football field.

Methods for achieving CCS have existed for decades, but the practice of piping carbon emissions below the Earth's surface, as opposed to releasing it into the sky above, is not widespread for energy companies and other industries. As is so often the case, employing current technologies is considered unprofitable and therefore not a viable option.

CARBON SEQUESTRATION

Dr Deanna D'Alessandro is investigating newly created, incredibly adsorbent materials to capture carbon and much more. Comprising D'Alessandro and a large team of experts, the five-year project has been granted AUS \$6 million by the Australian Science and Industry Endowment Fund, and seeks to deliver more energy-efficient gas separation processes. The team's collaborative work has focused on integrating amines and other groups into metal organic frameworks (MOFs), materials which have a highly selective interaction with CO₂ and a crystalline structure. "X-ray crystallography provides us with an unambiguous determination of the structure of a MOF, allowing us to gain

intimate knowledge of how the structure affects the function," explains D'Alessandro.

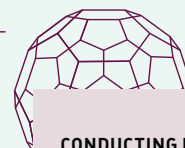
The properties of MOFs are key to their suitability in capturing carbon, with just 1 gram of a MOF capable of having a surface area equivalent to that of a football field. However, while storing the captured carbon underground could dramatically reduce the negative impacts of burning fossil fuels to meet our energy needs, it is often necessary to create a financial incentive for doing so to increase uptake of the technology.

With this in mind, D'Alessandro's team has also looked at ways to utilise the captured CO₂. "Converting CO₂ into commodity chemicals is one possibility; however, this process is extremely energy intensive because CO₂ lies at a thermodynamic minimum. Given the versatility of MOFs, we are investigating ways to integrate catalytic centres that reduce the energy penalty for CO₂ conversion," explains D'Alessandro. "Towards this goal, we are developing electro- and photo-catalytic MOFs that catalyse the transformation of CO₂ into other products such as methanol, methane and carbon monoxide, amongst others."

POWERFUL POTENTIAL

The applications of this team's research could have a significant global impact; for example, there is a real possibility that in the future MOFs will be capable of carrying enough hydrogen to power hydrogen cars. The researchers have also developed novel *in situ* techniques for performing solid-state spectroelectrochemistry and applied them to MOFs and porous organic polymers. This could lead to the rapid assessment of optical and electronic properties of materials as a function of their redox state.

The far-reaching potential of this large Australian team's discoveries has led to international collaborations with colleagues in China and the UK to employ these new techniques to systems including electrocatalysts, conducting polymers, supramolecular complexes and battery materials. Overall, it seems clear that while these novel adsorbents are able to effectively capture CO₂, their huge potential is also capturing the research team's imagination.



CONDUCTING NANOPOROUS MATERIALS: TOWARD MOLECULAR DEVICES

OBJECTIVES

- To explore the electronic properties of metal-organic frameworks
- To capture carbon dioxide in these materials

KEY COLLABORATORS

For a full list of group members, visit:

<http://bit.ly/1SBe8Z4>

PARTNERS

The University of Melbourne

The University of New South Wales

Commonwealth Science and Industrial Research Organisation (CSIRO)

Australian Institute of Nuclear Science and Engineering (ANSTO)

FUNDING

Australian Research Council (ARC)

The Science & Industry Endowment Fund, Australia

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DR DEANNA D'ALESSANDRO has been an ARC Queen Elizabeth (III) Fellow since 2011. She completed her PhD at James Cook University, Australia, before embarking on

postdoctoral appointments at the University of Sydney, Australia, and the University of California at Berkeley, USA. Today, her research spans the areas of inorganic chemistry, physical chemistry and materials science.



THE UNIVERSITY OF
SYDNEY



The way of tau

Neuroscientist and biochemist **Dr Naruhiko Sahara** gives an introduction to tau proteins, and explains why these unassuming molecules have been the focus of his long-term research interest over the last few years

What initially spurred your interest in neuroscience and neurodegenerative diseases?

Perhaps because I am the youngest child in my family, the life and death of older people have become an important topic for me. My chosen academic discipline was protein biochemistry, and my original goal was to study disease mechanisms of the human cataract. I have always worked in the field of biochemical research and, over the course of my career, I have focused particularly on human diseases related to ageing.

Could you outline the main objectives of your research?

My research is largely focused on studying the mechanisms of Alzheimer's disease. As an expert biochemist and molecular biologist, I have worked on discovering the mechanisms of disease pathology as well as the development of better diagnostics and therapeutics using *in vitro* and *in vivo* model systems.

As Senior Researcher and Assistant Director of the Neuromolecular Dynamics Team at the Molecular Imaging Centre, Japan, can you summarise the main research projects you are currently focusing on?

Our previous studies have successfully demonstrated that our novel radioligand is suitable for use in positron emission tomography (PET). Following on from this achievement, our current project aims to confirm the merits of our PET tracer for the diagnosis of Alzheimer's disease and related neurodegenerative diseases. Furthermore, we hope to develop imaging agents for earlier tau-condition diagnosis.

In parallel, our other research aim is to develop imaging-based diagnostic procedures such as imaging biomarkers for brain protein ageing – a term to explain the dysfunction of proteins associated with neurodegenerative disease.

You are examining the mechanisms of Alzheimer's disease, among other neurodegenerative diseases, by concentrating on different aspects of protein biochemistry

and neurochemistry. What work is being conducted here at present?

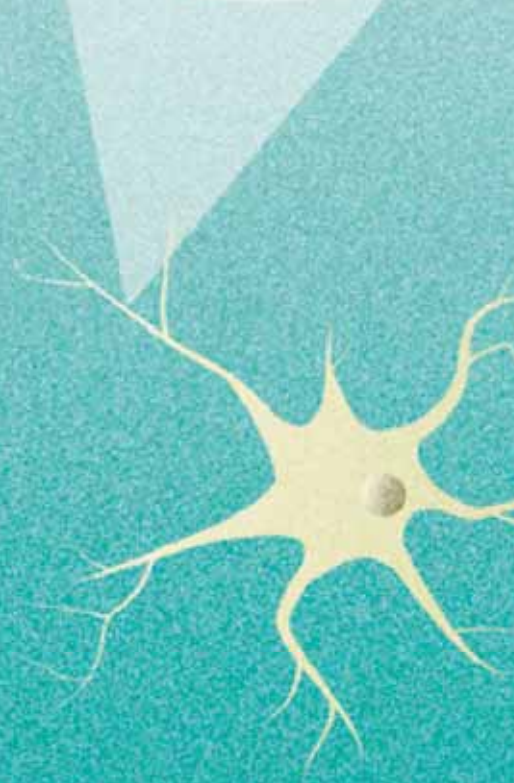
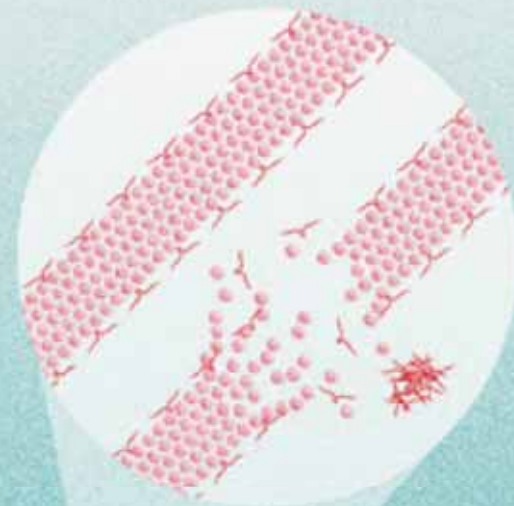
At the National Institute of Radiological Sciences, Japan, we have multiple imaging systems for imaging the brains of small animals including mice, rats, marmosets and macaques. Using certain animal models resembling human diseases, we have conducted neuroimaging studies on methods such as magnetic resonance imaging (MRI), PET and multiphoton microscopy. MRI and PET are non-invasive approaches to detect any abnormality of brain functions.

How do you aim to better facilitate collaboration between the basic neurochemistry and brain ageing research fields?

Currently, I am an investigator on a national research project called Brain Protein Aging and Dementia Control, which is supported by the Japanese Government. We aim to make novel insights and develop therapeutic tools for brain protein ageing. Within this project, researchers from basic and clinical fields of medicine get together and grow their networks. Experts in molecular biology, protein biochemistry, neuropathology, neurology and imaging are cooperating together and driving this new academic field.

For 10 years, your research has focused on tau protein dysfunction; what fundamental questions have you set out to answer here? Have you been able to provide answers to these questions to date?

In Alzheimer's disease, neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein and neuronal cell loss coincide within the same brain regions. The progressively expanding anatomical distribution of NFTs is concomitant with growing brain dysfunction. Therefore, tau protein must have toxic effects in the neurodegenerative process. However, there is currently no clear way to identify toxic species of tau protein. To find these species, I have examined tau aggregation processes using several experimental systems including recombinant tau protein aggregation assays, cell culture systems, transgenic mouse models and extracted proteins from human autopsy brains.



New knowledge in neurodegeneration

A team of neurological and imaging scientists at the **National Institute of Radiological Sciences** in Japan has been responsible for the development of novel models and imaging methods to study the brain under disease conditions associated with neurodegeneration

AT A MOLECULAR level, microtubules are extremely important to life. Not only do they make up, along with microfilaments, a large proportion of the cytoskeleton, which gives cells their structure, but they are also integral to the movement of components within the cell and even to cell division. In a sense, microtubules are like roads; once they have been established, vesicles containing many kinds of proteins and molecules can travel along them, moving from one part of the cell to another.

Microtubules cannot accomplish these important goals alone. Although they can be comparatively large, sometimes achieving lengths of around 50 μm , microtubules are in fact made up of only two protein subunits – tubulin alpha and beta. In order to become stable over such great intracellular distances, these dimers rely on a range of microtubule-associated proteins, including tau proteins, which join to them and hold them steady. There are many forms of microtubule-associated proteins that prevail in different cell types – and tau proteins are associated exclusively with nerve cells.

DISEASE CONDITIONS

Tau proteins have been the subject of much study in recent years, partly because their operation has been linked with the onset of Alzheimer's disease. Under normal conditions, tau is present predominantly in the axon of the nerve cell, and binds to the subunits of microtubules as they form. By binding to them, tau proteins make the growing tubule more stable, and help it to build up faster. In the nervous tissues of a patient with Alzheimer's, however, the distribution of tau protein is rather different. Here, the protein accumulates abnormally – but it is hyperphosphorylated, meaning that intracellular signalling prevents it from functioning.

In such cases, the protein can no longer bind with microtubules, or perform its function in stabilising them. The structures therefore become fragile and are often subject to detachment and disintegration – a phenomenon that may be causative of the observable symptoms presented by Alzheimer's patients.

TAUOPATHY

One group at the National Institute of Radiological Sciences (NIRS) in Japan is eager to get to the bottom of the role of tau proteins in neurodegenerative diseases. Led by Dr Naruhiko Sahara, the researchers have made much progress in recent years towards understanding this so-called 'tauopathy'.

"My goal is to investigate therapeutic interventions and understand the mechanisms of tau-induced neurodegenerative diseases; toxic tau species, tau oligomers, hyperphosphorylated tau proteins and the ageing process for tau proteins are all undefined terms," Sahara explains. The work he carries out along with colleagues began some years ago with their development of a novel mouse model of tauopathy, and the decision to investigate – by subjecting the model to neuroimaging studies – whether this pathology led to white matter dysfunction. For Sahara, the results of these first-of-their-kind studies were intriguing enough to prompt further examination; it seemed that tauopathy could be detected early using magnetic resonance and diffusion tensor imaging, because its accumulation had an impact on the ultrastructure of the white matter.

These mouse models, which are unusual in that they overexpress human tau, provide a unique opportunity to get to grips with the protein and understand its role in disease. The protocol that Sahara has developed, which brings these murine models together with efficient imaging methods, is already being used as a standard both in academia and industry to elucidate tauopathy and propose new therapeutic tools and drug delivery systems.

Now, Sahara and his collaborators will push this work even further, seeking methods that can open up *in vivo* imaging and help researchers visualise neuropathology in living brains. "After 20 years' experience in molecular neurochemical research, I now find myself working in neuroimaging," he reflects. "It's lucky that I could bring my neurodegenerative disease models with me!"

ESTABLISHING A NOVEL *IN VIVO* BRAIN IMAGING SYSTEM FOR DETECTING TAU-INDUCED NEURODEGENERATION

OBJECTIVES

- To use *in vitro* and *in vivo* model systems in order to discover the mechanisms of disease pathology and develop better diagnostics and therapeutics for Alzheimer's disease and related neurodegenerative disorders
- To establish a novel research field to connect basic neurochemistry with brain ageing

TEAM MEMBERS

Dr Makoto Higuchi, Team leader • **Dr Takashi Horiguchi**; **Dr Jun Maeda**; **Dr Bin Ji**; **Dr Masahiro Maruyama**, Senior researchers • **Maiko Ono**; **Dr Anna Barron**; **Dr Shimajo Masafumi**, Researchers • **Takeharu Minamihisamatsu**; **Sayuri Sasaki**, Technical Staff • **Kana Osawa**, Assistant

Dr Ichio Aoki, Team leader of Multimodal Molecular Imaging Team, NIRS, Japan • **Dr Takafumi**

Minamimoto, Team leader of Neuroinformation Team, NIRS, Japan • **Dr Yoshiaki Yamaguchi**, Team leader of Structural Glycobiology Team, RIKEN-Max Plank Joint Research Center for Systems Chemical Biology, RIKEN, Japan

FUNDING

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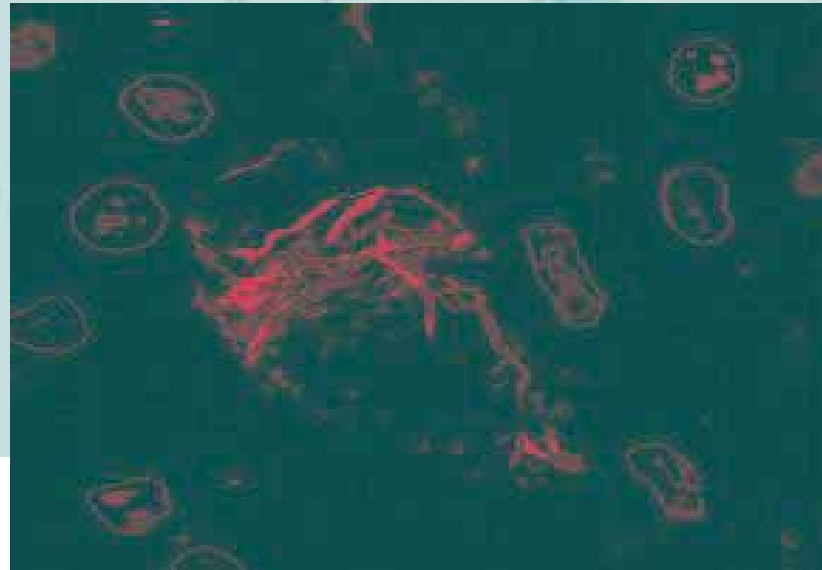


DR NARUHIKO SAHARA is Senior Researcher and Assistant Director of the Neuromolecular Dynamics Team in the Molecular Neuroimaging Program, National Institute of

Radiological Sciences, Japan. He is also one of the group leaders of the Governmental Scientific Research Area named Brain Protein Aging and Dementia Control, and coordinates the research of therapeutic development for brain protein ageing in this area. Sahara is Courtesy Research Assistant Professor in the Department of Neuroscience and in the Center for Translational Research in Neurodegenerative Disease. He was selected as the 2012 Thomas H. Maren Junior Investigator Awardee, which supports promising young investigators in the University of Florida College of Medicine. Over the past 10 years, Sahara has studied tau protein biochemistry, and has established a protocol for examining tau biochemical abnormalities in tau transgenic mice, which is now a standard method in the field.



RNA metabolism's role in amyotrophic lateral sclerosis



Distinguished University **Professor Michael Strong** describes how he first became involved in amyotrophic lateral sclerosis research and the evolving concepts that are changing our understanding of the disease

What first inspired you to research the pathobiology of amyotrophic lateral sclerosis (ALS)?

As a final year medical student studying at Queen's University in Kingston, Ontario, I had the opportunity to spend three months in Denmark where I found myself on a neuromuscular service that was also the national referral centre for ALS. I was intrigued by the number of cases of a disease that I was taught was sufficiently rare that I might see only one or two in my lifetime. When I found out that Denmark has about the same incidence rates as are seen worldwide, I began reading more about the disease.

When I began my training as a neurologist at Western University, Canada, I studied with Dr Arthur Hudson who had written a great deal about the disease and established the second ALS clinic in North America. He really influenced my decision to do postdoctoral work on the topic.

In recent years, our understanding of ALS has changed to reflect the fact that it is a multisystem degenerative disorder, not a single-system one as once believed. Can you explain why developing our knowledge is important?

This needs to be viewed in two frameworks: at the level of cell biology and clinically. From the vantage of the cell, understanding that ALS can be at the intersection of a number of seemingly divergent biological processes going awry opens opportunities to develop individualised therapies. The analogy here is cancer biology in that multiple pathways can give rise to

malignant transformation, so there are multiple therapies. As it currently stands, even if we only have alterations in RNA metabolism and impaired proteasome function as the two major pathways, we already have two seemingly unique pathways. Now, we need to understand how these can be identified.

Clinically, understanding that there is a significant percentage of the patient population who will have frontotemporal dysfunction immediately changes the game: is this an intersection of two disease processes or a single disease with the potential of multiple systems involvement?

How has your research contributed to improving the potential for novel ALS therapies?

If the basis of ALS is a disorder of RNA metabolism, and if this is due to alterations in the expression of specific RNA binding proteins, these proteins never exist in their native state. They are always going to be modified in a post-translational manner and this modification alters their function. So the question is: can we identify which state is the key interacting state and then identify drugs that will alter this state?

Could you discuss some of the evolving concepts in RNA metabolism with relevance to your work?

The concept that ALS may be a disorder of RNA metabolism for the majority of patients continues to evolve. We know that in response to injury or stress, the cell will divert its genesis of proteins towards those that are important to respond. It makes sense that the

cell would 'bundle' together a number of these proteins and their related regulatory proteins into a single upregulation of gene expression at the level of the DNA. How this is regulated is less certain.

In what direction is research into RNA metabolism and ALS currently heading?

New questions are arising about how RNA granules are formed. DNA transcription leads to the production of the respective RNA species that are bundled together into granules within the nucleus and then transported into the cytosol. Depending on their composition, these granules may be loaded onto the transport mechanisms of the cell and sent where they are required (transport granules), stored until they are needed (stress granules) or targeted for degradation (processing bodies). In being degraded, RNA transcripts are acted upon by microRNAs whose function is to regulate RNA degradation in a process known as RNA-mediated gene silencing.

The exciting concept is that these are formed as hydrogels – matrices of proteins that come together and dissociate 'freely' (nothing is free in the cell), so that by interchanging components, the function of the granule changes readily. There is recent work to suggest that the formation of the pathological RNA granules of ALS may in fact take their origin from these hydrogels. If so, this fundamentally changes how we think about the alterations in RNA metabolism that underlie this process.

Interaction of fibrils in a single cell –
RGNEF (green)/ubiquitin (red).

Interaction of fibrils in a single cell –
RGNEF (green)/FUS (red).

In search of a cause

Thanks to groundbreaking research carried out in the Department of Clinical Neurological Sciences and the Robarts Research Institute at **Western University in Canada** the amyotrophic lateral sclerosis community has a clearer understanding of the disease's pathogenesis than ever before

IN 1923, A young man named Lou Gehrig spiced up the American baseball scene with his stamina and hitting prowess. A seven-time All-Star player and named the most valuable player on several teams that won the World Champion series, Gehrig was considered one of the best players of his day. It seemed like nothing would stop him.

In 1939, that all changed. Gehrig announced to his adoring public that he was leaving the game as he had been diagnosed with amyotrophic lateral sclerosis (ALS) – a disorder also known as Lou Gehrig's disease.

WHAT IS ALS?

The ALS Association defines the disorder as a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. With time, these cells degrade and die, giving way to muscle weakness and atrophy throughout the body as the brain loses control. Eventually, ALS can lead to paralysis, respiratory failure and even death.

While an aggressive loss of motor neurons does indeed occur with ALS, more recent research has uncovered the fact that more than half of those affected with the disease also develop one or more syndromes of frontotemporal dysfunction. The involvement of non-neuronal cells has altered the classical single-system view, and ALS is now recognised as a multisystem degenerative disorder.

A STRONG INVESTIGATION

At the vanguard of efforts to unravel ALS's pathogenesis in the hope of developing future therapies is Professor Michael Strong. His clinical and lab work at Western University's Robarts Research Institute has garnered him numerous awards in recognition of the insights into ALS that he has provided.

Over the last decade, research carried out by Strong's lab has led to profound shifts in the way humanity understands the biology of ALS. Among this is convincing evidence – which is supported by other research labs – that is making it look more and more likely that the culprit behind the disease's aetiology is rooted in the life cycle of RNA molecules. "There is an increasing consensus that a significant component of the underlying pathobiology of ALS can be directly attributed to fundamental alterations in RNA metabolism," Strong points out.

HALLMARKS OF DEGENERATION

The question for Strong, and the ALS community as a whole, is to find out what is happening in RNA metabolism that leads to the degeneration of motor neurons. Strong started this investigation by looking at hallmarks of motor neuron degeneration in ALS: neuronal

cytoplasmic inclusions (NCIs). These inclusions contain neurofilament (NF), a major structural component of the neuronal cytoskeleton that can be divided into three grades (light, medium and heavy) and fit together to form a final structural filament.

Looking at ALS cases, Strong and his team found that the expression ratio for the smallest NF (NFL) came up short. This scenario has been shown to cause motor neuron degeneration in transgenic mice. According to the researchers, there are two main possibilities for this deficiency in NFL: either it is a problem at the DNA level concerning reductions in gene expression, or it is down to the loss of RNA. "I really don't like working with DNA so we did a 'Hail Mary pass' and designed an experiment that would test the RNA question," recalls Strong.

Strong's lab has led to profound shifts in the way humanity understands the biology of ALS

The risk of bypassing the DNA angle paid off – it proved that the issue of RNA stability is indeed a major factor in explaining ALS pathogenesis. His team discovered that the NFL deficiency is caused by an instability in its RNA (NEFL RNA) that leads to the loss of the NFL transcript. Furthermore, it turns out that the fate of the messenger RNA that makes the NFL protein (NEFL mRNA) is targeted for degradation through RNA-mediated gene

Interaction of fibrils
in a single cell –
RGNEF (green)/p62 (red).

CLINICAL NEUROLOGICAL SCIENCES

OBJECTIVE

To understand the role of alterations in RNA metabolism as a fundamental disease process underlying the motor neuron degeneration of amyotrophic lateral sclerosis (ALS).

KEY COLLABORATORS

Dr Heather Durham, Montreal Neurological Institute, Canada

Dr Christine Vande Velde, University of Montreal, Canada

Dr Eran Hornstein, Weizmann Institute of Science, Israel

Dr Robert Bowser, Barrow Neurological Institute, Arizona

FUNDING

ALS Society of Canada

Canadian Institutes of Health Research (CIHR)

European Research Projects on Rare Diseases (E-RARE-2)

Ontario Brain Institute

Ontario Neurodegenerative Diseases Research Initiative

Michael Halls Endowment

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MICHAEL STRONG is Dean of the Schulich School of Medicine and Dentistry at Western University, a Distinguished University Professor and the Arthur J Hudson Chair in

ALS Research. His basic research focuses on the study of alterations in neurofilament metabolism in degenerating motor neurons in ALS and how perturbations in RNA metabolism contribute to this process. His clinical research has been central to identifying the frontotemporal syndromes of ALS.

silencing. "Such alterations placed the motor neuron at an increased risk for both oxidative and glutamatergic injury," Strong notes.

BIOMARKERS TO SPOT THE DIFFERENCE

In cases of familial ALS, where there are mutations in superoxide dismutase 1 enzyme (SOD1) giving rise to the disease in some families, a protein is present that causes the loss of NEFL mRNA stability. Taken on its own it is difficult to draw a solid conclusion. However, upon learning at a conference that TAR DNA-binding protein 43 (TDP-43) aggregates could be found in ALS and that it is a dual DNA- and RNA-binding protein, Strong's interest was piqued. "Within three months my lab showed that TDP-43 was an RNA-binding protein, that it interacted with NEFL mRNA and that it was a stability determinant," he states.

Strong and his team have shown that among the mRNA-binding proteins that contribute toward the stability of NEFL mRNAs is a collection of proteins – including mutated SOD1 and TDP-43 – which are now known to associate within the NCIs in ALS spinal motor neurons. Not only that, but these mRNA-binding proteins have been identified in association with specific variants of familial ALS. Based on their known roles in motor neuron degeneration, Strong employed these proteins as disease biomarkers in order to develop a novel means for discriminating between the individual variants of ALS (with or without genetic mutations). Using a colorimetric immunohistochemistry (IHC) approach, this was the first study to try and exploit the distinctive immunoreactivity patterns of spinal motor neuron NCIs for such a purpose.

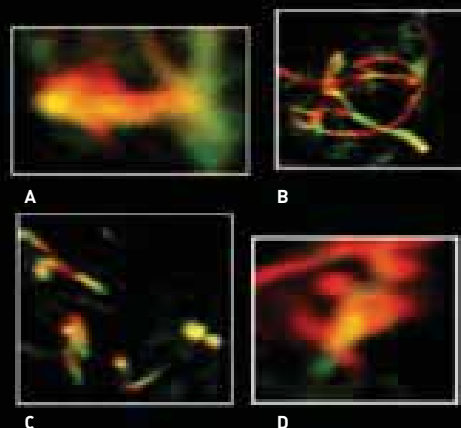
He found that the unique IHC signature of mutated SOD1 makes it possible to differentiate these cases from other ALS variants. "Potentially, a routine IHC-based analysis of spinal motor neurons could be a huge help in identifying familial cases not previously thought

A. RGNEF (green)/ubiquitin (red).

B. RGNEF (green)/p62 (red).

C. RGNEF (green)/FUS (red).

D. RGNEF (green)/TDP-43 (red).



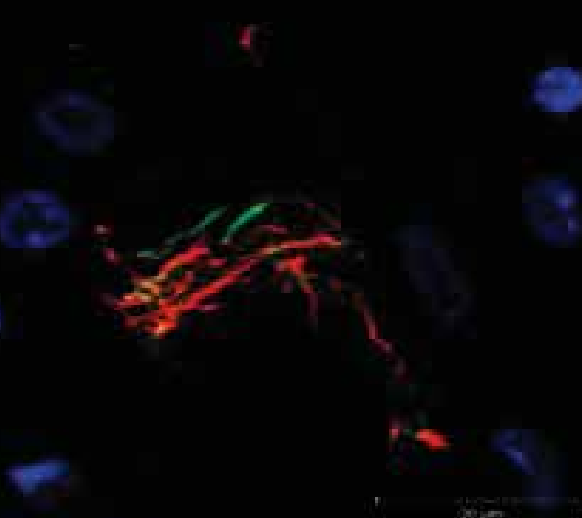
to possess mutations of SOD1," he enthuses.

A PUZZLE OF A PROCESS

Strong's groundbreaking studies have significantly impacted the way motor neuron degeneration in ALS is understood, bolstering his hypothesis that changes to RNA metabolism, while not the sole pathway, are major players in the aetiology of the disease. Indeed, it is the presence of NCIs that are considered to be ALS's key neuropathological hallmark.

What is not certain, however, is the process leading to the formation of such pathological inclusions. Strong is looking at the cellular response to environmental stress – the formation of stress granules. "It's the million dollar question. How do environmental conditions lead to these pathological inclusions?" he asks. By potentially altering post-translational modifications in RNA-binding proteins, environmental stress, along with RNA-binding proteins already prone to aggregation, could change the formation and function of stress granules. Strong thinks that these stress induced changes may in turn be responsible for producing protein aggregates that significantly impact RNA metabolism.

There are many questions that need to be answered before the pathogenesis of ALS can be fully revealed. If Strong's hypotheses are correct, what then determines which RNA species are chosen and bundled into a granule? How is it decided which microRNA interact with which RNA species and in which order? Furthermore, how are these dysregulated in ALS? Answers to these questions may be slow to reveal themselves, but it is only through landmark research like Strong and his lab's that these questions can be asked at all.



Interaction of fibrils in a single cell – RGNEF (green)/FUS (red).

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RESEARCH



The living (from the) dead

Professor Dr Carlijn V C Bouten heads a laboratory performing important research on engineering heart valves, vessels and myocardium. Alongside her collaborator **Dr Dr Patricia Y W Dankers**, she tells *International Innovation* about their biomaterial-based *in situ* tissue engineering experiments that ultimately seek to regenerate numerous organs

What inspired you both to pursue a career in regenerative medicine? Why is it an interesting area of study?

From a scientific point of view, it provides an opportunity to perform research at the interface of materials science, chemistry, biology, and medicine.

One aspect we particularly enjoy is working in multidisciplinary research teams. Regeneration of the body with external stimuli and materials is challenging but, when successful, can be applied to many different tissues and organs. For this, we need an in-depth insight into the regenerative capacity of the body and discover ways to 'seduce' the body into repairing itself. Contributing to the amelioration of quality of life in an ageing population and providing sustainable healthcare are key motivations too.

Could you outline the overarching aims of your research and why they are of socioeconomic importance?

Our work concentrates on achieving simple, low-cost and lifelong solutions to the complex problem of regenerating cardiovascular tissues. Instead of growing living tissues in the lab, which is the classical tissue engineering approach, we are growing tissues inside the body. By starting with a 'dead' synthetic material we aim to circumvent complex, expensive and logistically intricate tissue culture in the lab, as well as complex regulatory issues.

How does your approach to constructing heart tissue differ from traditional regenerative medicine techniques? What are the benefits of this novel method?

In situ tissue engineering is the key difference. Instructing cells and tissue inside the body

enables us to use the body's own capacity to regenerate. The materials we use are made of supramolecular polymers that are held together by highly directed, specific and non-covalent interactions. The interaction we employ in said materials is hydrogen bonding, in combination with additional hydrophobic and pi-pi interactions.

These supramolecular interactions give dynamics to the materials, resulting in materials that are able to adjust to either the tissue or organs they are brought into. Because of the nature of these interactions, bioactive moieties, such as peptides and drugs, can be easily incorporated (via the same supramolecular motif), through a modular approach. This results in bioactive biomaterials that are able to instruct cells and tissues.

With regard to your work on valve tissue regeneration, what are the challenges impeding its development as a clinical application? How are you addressing these issues?

The translation from bench to bedside requires intensive and prolonged collaboration between engineers, clinicians and patients. We have longstanding, fruitful collaborations in which we always aim for a result that will ultimately benefit the patient.

We have incorporated SMEs directly into our multidisciplinary research teams for acceleration and alignment of translation. Partners in our team have also developed a health technology assessment strategy to evaluate economic and clinical impact, as well as for stratification of the relevant patient groups for early-stage application.

One of the major problems is that translation is very expensive – fortunately, we are relatively

successful in gaining funding for our research. Our direct collaboration with SMEs means that they can apply (and progress) the knowledge we obtain towards society in a fruitful way. In addition, we avoid the regulatory hurdles and logistical complexities associated with, for example, classical tissue engineering or stem-cell approaches for regenerative medicine. This, in turn, means that our research is attractive to investors and end-users, as it drastically reduces the clinical translation pipeline.

Finally, how do you envisage your multidisciplinary collaborations will impact society?

We are in the process of pursuing several applications; examples include blood vessel grafts (such as vascular access grafts), heart valves, and smart drug delivery to regenerate the infarcted myocardium. Ultimately, our dream is that there will one day be no need for re-implantation or any other intervention. This is of particular relevance in the case of young patients requiring an implant that needs to grow within their body.

If we can achieve these goals, the impact on society will be considerable. The realisation of these aims will be a result of our collaborations with medical doctors, engineers, materials scientists, chemists, biologists, companies and patient associations.





Synthetic scaffolds

Researchers from the **Eindhoven University of Technology**, Netherlands, are developing *in situ* engineered biomaterial-based tissues. This pioneering project involves multidisciplinary public-private-patient international collaborations and aims to provide lifelong solutions to cardiovascular problems

EACH YEAR, THOUSANDS of people receive life-saving or life-transforming transplants. Similarly, artificial prostheses help individuals perform daily activities – such as walking or eating – that often results in restoration of function and improved quality of life. The wonders of medicine and engineering have evidently contributed to society; however, the transplantation of donor organs and prosthetics is not without its problems. For instance, the reliance on donor tissues is limited by availability, and so, useful as they can be, they have intrinsic shortcomings. Likewise, artificial limbs can never truly replicate their original counterparts, and there are huge healthcare costs to consider as well.

A burgeoning global population that is living for longer necessitates the development of solutions for an increasing number of chronically ill people. Importantly, the costs of associated social welfare are also on the increase, reinforcing the need for sustainable and affordable solutions that can ease the burden placed upon society.

Considerations such as these have led to the emergence of a new discipline; namely, regenerative medicine. The body's ability to regenerate is perhaps one of its more fascinating properties. Living cells can

enable healing, for example, leading to the establishment (or re-establishment) of normal body function. Now, researchers from around the world are exploiting this regenerative property to improve lives, reduce future healthcare costs and usher in the next generation of living prostheses.

SUMMONING THE LIVING

To address the pressing need for regenerative medicine solutions for priority diseases, a team of researchers at the Eindhoven University of Technology has sought to develop breakthrough technologies that 'seduce' the body to regenerate itself. This has culminated



A tissue-engineered heart valve. Courtesy: Eindhoven University of Technology (Photo: Bart van Overbeeke).

in the development of materials-based tissue engineering approaches for cardiovascular, orthopaedic and nephrology applications.

With expertise in biomaterials and bioengineering Professor Dr Carlijn V C Bouten and Dr Patricia Y W Dankers are heading collaborations that pool knowledge, skills and resources from a broad range of disciplines to develop *in situ* engineered tissues of the cardiovascular system. Rather than growing living tissues in a laboratory, they have opted to grow tissues inside the body. Beginning with a bioinspired, synthetic scaffold, implanted at the site of destination, the group has been creating living substitutes for damaged or diseased tissues. What is put into the body can be thought of as 'dead' but, after being implanted, this scaffold gradually develops into a living, functional part of the body. To advance this technology, a multidisciplinary public-private-patient collaboration has been established in the international consortia 'iValve', 'iValve' and the EU Seventh Framework Programme (FP7) project 'ImaValve'.

The team has produced a synthetic scaffold that becomes a living, functional heart valve by recruiting endogenous cells to form new tissue

CRE@TE

Both Bouten and Dankers helped to establish the Center for Regenerative Engineering at Eindhoven (CRE@TE), which is part of the bioinspired engineering track of the Institute for Complex Molecular Systems. The aim of the Center is to merge a variety of engineering sciences relevant to advancing the field of regenerative medicine, such as biomedical engineering, materials science, chemistry and physics. With Dankers' main expertise being in supramolecular biomaterials, and Bouten's in cardiovascular tissue engineering, their collaboration has centred on addressing problems with the cardiovascular system.

Focusing on heart valves, vessels and myocardium, the team has, for instance, produced a synthetic scaffold that becomes a living, functioning heart valve by recruiting endogenous cells to form new tissue. The implanted scaffold slowly degrades, leaving a new valve that is recognised by the body as its own. Thus far, the proof of concept of the new approach was shown in preclinical studies; the next step is to develop the technology for application in the (diseased) patient.

The potential for revolutionising treatments for heart defects is there: "The benefits of synthetic scaffolds – as opposed to biological scaffolds – is that they can be manufactured on demand. We can also tailor the material's mechanical, structural and chemical properties to yield scaffolds that mimic biological signals (bioactive), or respond to biological cues (bioresponsive)," explains Bouten. In doing this, they circumvent an expensive and logistically complex tissue culture in the lab.

AFFECTING DEFECTS

A young patient with a defective heart valve often needs to be operated on around two to three times throughout their lifetime, having replacements implanted that cannot adapt to body growth and are subject to wear and tear. As well as the trauma associated with repetitive surgical procedures, there is a significant cost attached to each of them. However, with the development of an *in situ* engineered valve originating from a synthetic scaffold, the team has made significant strides in reducing the burden placed on patients and healthcare systems.

The researchers hope that this device will ultimately be available for implantation in humans, encouraging the growth of a natural heart valve and enabling the individual to lead a normal, healthy life. The expected additional benefit will be that implanting the synthetic scaffold will only require a single operation and the valve can be implanted through the groin, meaning the surgery is minimally invasive.

BEYOND SYNTHETIC VALVES

Perhaps most significant is that the potential applications of this research are far-reaching and could one day provide solutions for a wide range of medical conditions. Indeed, the team is currently conducting research in nephrology, where they are hoping to ameliorate dialysis by using smart living kidney membranes based on supramolecular materials. The possibilities are vast: "Our approach can be used for almost all tissues in the body," explains Dankers. "The challenge is to adjust the material in such a way that it has similar properties to the respective tissue."

That their synthetic valve can be manufactured cheaply and posted to local surgeons anywhere in the world means that, once the findings have been translated for human usage, it has the potential to serve a worldwide market in a cost-effective and renewable way – something we can all take heart from.

CENTER FOR REGENERATIVE ENGINEERING AT EINDHOVEN

OBJECTIVE

To develop simple, sustainable and cost-effective solutions to regenerating cardiovascular tissues through material-based *in situ* tissue engineering.

KEY COLLABORATORS

Professor Dr E W Meijer; Professor Dr Frank P T Baaijens; Dr Sandra Loerakker; Dr Cecilia Sahlgren, Eindhoven University of Technology, Netherlands • **Professor Dr Marianne C Verhaar; Dr Steven A J Chamuleau; Dr Eva van Rooij,** University Medical Center Utrecht, Netherlands • **Dr Jolanda Kluin,** Academic Medical Center Amsterdam, Netherlands • **Professor Dr A Pieter Kappetein; Professor Dr Hanneke J M Takkenberg,** Erasmus Medical Center Rotterdam, Netherlands • **Professor Dr Simon P Hoerstrup,** University Hospital Zürich and Swiss Center for Regenerative Medicine, Switzerland

PARTNERS

Dutch Heart Foundation, Netherlands • **SupraPolix,** Netherlands • **SyMO-Chem,** Netherlands • **Xeltis,** Switzerland • **Appletree CI Group,** Switzerland • **Medicut,** Germany

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CARLIJN V C BOUTEN is Professor of Cell-Matrix Interaction in Cardiovascular Regeneration in the Department of Biomedical Engineering of the Eindhoven

University of Technology, Netherlands. Her research concentrates on new engineering approaches to regenerate the tissues of the human heart. She leads the 'Regenerative Medicine' theme within the University's strategic 'Health' arena.



PATRICIA Y W DANKERS

is Associate Professor of Supramolecular Biomaterials for Translational Biomedical Science in the Institute for Complex

Molecular Systems and the Department of Biomedical Engineering at the Eindhoven University of Technology. Her particular research interests are on the design and synthesis of bioinspired functional biomaterials.



Chlamydia trachomatis complications

Professor Servaas A Morré is an experienced researcher in the field of *Chlamydia trachomatis*. Here, he discusses his extensive research interests in genetics, his hopes for reducing incorrect triage for subfertile women and the translation of his findings into a novel diagnostic application

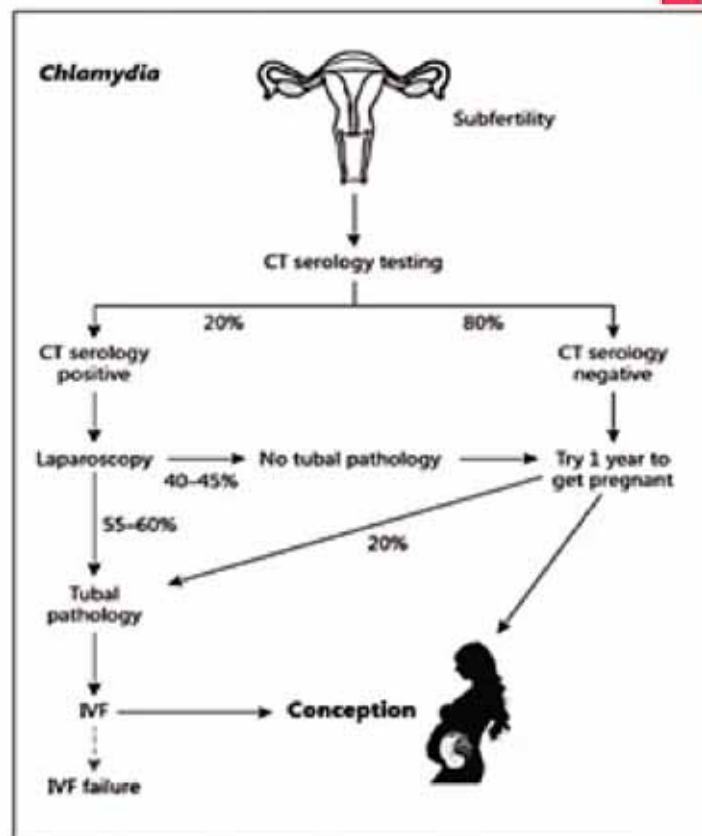
You are Head of the Laboratory of Immunogenetics at VU University Medical Center, Coordinator of the Dutch *Chlamydia trachomatis* Reference Laboratory, Director of the Institute of Public Health Genomics at Maastricht University and Founder of, amongst others, the spin-off company TubaScan Ltd. What are your main research activities within each of these roles?

In all of these positions, the main research line is *Chlamydia trachomatis* (CT) infections and the late complications in women, its causes and, most importantly, female infertility. In the first setting, we began by identifying the role of host genetic factors in the susceptibility to – and severity of – infection. The second setting is where we monitor the potential emergence of new variants of CT strains in the Netherlands, which could be missed by diagnostic assays. In the third setting, we focus on the translation of genetic- and genomic-derived data into healthcare settings. In the final setting, we are in the process of developing a new diagnostic host marker assay on the basis of CT recognition and inflammation to improve tubal pathology diagnoses.

How are your research lines funded, considering grants have become more difficult to obtain due to the recession?

In 2007, Dr Sander Ouburg and I obtained a grant from the EU Sixth Framework Programme (FP6), entitled 'Contribution of molecular epidemiology and host-pathogen genomics to understand CT disease'. The grant was for €500,000 and funded the EpiGenChlamydia Consortium – the true beginning of our line in host-pathogen genomics for CT infection. The aim of the Consortium was to structure transnational research so that comparative genomics and genetic epidemiology could be performed in large numbers of unrelated individuals.

After that grant ended in 2010, we received an SME-based EuroTransBio grant for €3.3 million,



The relation between serology testing for *Chlamydia trachomatis* (CT) and laparoscopy and the percentages of incorrect triage of women. Host genetic markers in this decision tree will be added to reduce 40-45% and 19 per cent to significant lower numbers. [IVF= *in vitro* fertilisation].

from the end of 2011 until mid-2015. We then received another SME-based Eurostars grant for €1.6 million to translate our findings from bench to bedside, which started in July 2015.

In my field, there has been a shift in funding to SME-based grant schemes for the development of new diagnostic applications out of basic research lines. This exciting change will result in genuine contributions for patients and healthcare systems!

One major cause of subfertility is tubal pathology. Can you explain why this is a significant issue and the efficacy of existing diagnostics procedures?

The sexually transmitted bacterium CT, alongside other sexually transmitted infections

(STIs) like *Neisseria*, can cause scarring inside the tubes. This can lead to ectopic pregnancies and, eventually, infertility, due to completely occluded tubes. Current diagnostic approaches often include CT serology as a diagnostic triage for deciding if, in most cases, laparoscopy should be used to assess tubal pathology, or if the woman should try to get pregnant for another year. It is our hope that by adding host genetic marker profiles to serology we can reduce the number of incorrect triages.



Translational potential

Researchers from **TubaScan Ltd** in the Netherlands are intent on developing a diagnostic tool to improve the predictive value for the diagnosis of tubal pathology – a leading cause of subfertility. By adding host genetic markers to *Chlamydia trachomatis* serology, they hope to reduce the incorrect triage of women and the incidences of potentially needless invasive procedures

Are there any upcoming conferences or events taking place that you are particularly looking forward to?

I present most of my work at chlamydia, genetic, STI and gynaecology meetings, and organise the Annual Amsterdam Chlamydia Meeting (AACM) each year. February 2016 will be AACM's 11th year and will be linked to a special supplement in the journal *Pathogens in Disease*. In addition to this, I organised the European Chlamydia Meeting in 2012 in Amsterdam, Netherlands, a meeting that is organised every four years, with the next one scheduled to take place in Oxford, UK, in September 2016. I am really looking forward to this meeting, in which between 250 and 300 chlamydia experts from around the world will present their latest work.

Last but not least is the International Chlamydia Meeting, which is also held every four years (two years after the European meeting), and alternates between taking place inside and outside the USA. We are currently involved in making a bid-book to be presented in September 2015 to the International Board, to see if we can host the meeting in the Netherlands in 2018. That would be a huge honour!

CHLAMYDIA TRACHOMATIS (CT) is the most common sexually transmitted bacterium in the world. Indeed, in 2013, more than 200,000 people in the UK alone tested positive for this infection, and worldwide, over a 100 million. It is almost always easily and effectively treated, with some 95 per cent of people cured if they take the prescribed antibiotics correctly. However, a significant problem with CT is that it is usually asymptomatic in women. Because of this, many affected individuals are unaware they have CT and can be infected for months, or even years, and transmit to other people.

This is particularly problematic for women as, if chlamydia is not treated, it can spread to the womb, ovaries or fallopian tubes, potentially causing serious problems such as pelvic inflammatory disease, ectopic pregnancies and tubal pathology – the latter being one of the main causes of subfertility, with CT being the most common cause for infertility.

The burden of subfertility is considerable on those trying to conceive, both from a financial and psychosocial perspective. Fifteen per cent of couples in the developed world trying to conceive are affected by subfertility; the substantial emotional distress this can cause necessitates early and correct diagnosis of tubal pathology, and there are a range of methods to improve detection.

Some of your work has touched on plant genetics and *Drosophila* – a genus of small flies. Has this work contributed in any way to your study on CT infections today?

My work on *Drosophila* was part of an additional internship at the end of my biochemistry and molecular biology studies to improve my chances of getting a good PhD position – this was my second encounter with genetics. The internships that focused on plant and yeast genetics all added to my general interest in host-pathogen interaction from a genetic perspective and are, indeed, contributing to the work I am currently performing.

OBJECTIVES

- To improve early diagnosis of tubal pathology through *Chlamydia trachomatis* (CT) serology
- To identify the host genetic, pathogen and environmental markers responsible for the differences in CT outcomes in order to advance subfertility diagnostics
- To develop a genetic test that is incorporated into routine diagnosis of subfertility

KEY COLLABORATOR

Dr Sander Ouburg, VU University Medical Center, VU University and TubaScan Ltd, Netherlands

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Elucigene Diagnostics, UK

ClinicaGeno Ltd, UK

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Netherlands Genomics Initiative

EuroTransBio: CHAT

Eurostars: TubaTEST

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PROFESSOR SERVAAS MORRÉ

has been working on *Chlamydia trachomatis* infections for over 20 years, with a central focus on female infertility and women's reproductive

health. He is a serial entrepreneur in the field of infectious disease diagnostics and human biomarkers. The coordination of large, international, EU-funded consortia is the basis for his translational output.

NEEDLESS PROCEDURES

One standard method for diagnosing tubal pathology is laparoscopy – a form of surgical procedure that allows a surgeon to access the inside of the abdomen and pelvis without making a large incision. This is an invasive, labour intensive and expensive procedure which can lead to additional complications in around 1.5 per cent of cases. What is more, a significant percentage of the women undergoing laparoscopy do not have tubal pathology. It is for these reasons that a preferred method for the identification of women with tubal pathology would have a higher predictive value.

However, it has repeatedly been shown that the results from CT serology alone, can lead to incorrect triage of women. Currently, women who are found to have a negative CT serology test result are advised to try to conceive for one year, but 20 per cent of those actually have tubal pathology, rendering the advice to continue attempts at conception obsolete. Those women with a positive CT serology test are given a laparoscopic examination, with some 40-45 per cent subsequently found to not have severe tubal pathology. It is with these alarming statistics in mind that a team of researchers has set out to improve both the negative and positive predictive values for the diagnosis of tubal pathology.

DETERMINING INDIVIDUAL RESPONSES

Led by Professor Servaas Morré, the team is investigating ways to significantly improve the incorrect triage percentages based on CT serology alone. In CT, along with other infectious diseases such as malaria or hepatitis, there are a range of reasons why one individual might experience a different outcome than another individual; where one woman might not suffer from any complications brought about by CT, another might be found to have tubal pathology. If the researchers can identify the host genetic, pathogen and environmental markers responsible for the differences in outcomes from CT, then subfertility diagnostics can be improved, enabling doctors to predict and identify those at the greatest risk of severe complications from CT.

Morré and his colleagues have identified that differences in CT outcomes are often a result of genetic variations, such as single nucleotide polymorphisms (SNPs), in the genes responsible for bacterial sensing receptors on local vaginal and tubal epithelial cells. Indeed, the more genes found to be affected by SNPs, the more abnormal the immune response, which signifies an increased chance of developing severe complications. The team is therefore intent on improving the predictive values for

tubal pathology diagnosis by combining CT serology with the addition of a host genetic marker assay: "We are going to include markers involved in pathogen recognition, inflammation modulation and tissue scarring," explains Morré. "These so-called SNP markers cause changes in gene function and results in both good and bad gene expression."

GENE SEQUENCES

Previous research on twins has demonstrated that there is almost a 40 per cent heritability factor in an individual's response to CT infection, meaning that the nucleotide sequence of a person's genes is largely responsible for their reaction to CT, where one person might be cleared from the infection, another could develop late complications. Thus far, Morré and his team have identified several relationships between an individual's SNP profile and their chances of developing tubal pathology: "Our first proof of principle showed that having limited SNPs in a series of five genes involved in pathogen recognition indicated a low chance of tubal pathology after CT infections, whereas having two or more SNPs results in a much higher chance – almost 80 per cent higher in fact," Morré discloses. "We are currently extending the set of genes to the best 50 SNPs in order to better predict who is at risk of developing late complications after CT infection."

Having made several key findings in host genetics for CT infections to be translated via public health genomic approaches, it is Morré's intention to develop a new diagnostic assay based on host markers – a development that is set to take place in his team's spin-off company TubaScan Ltd. Through SME grants and collaboration with several key clinical opinion leaders in the field, the development of a genetic test as part of a routine diagnosis of subfertility is a genuine possibility in the future. If this can be achieved, it will enable the saving of time and significant amounts of money by decreasing the amount of unnecessary laparoscopies and other invasive procedures. In addition, it will reduce the amount of time affected individuals spend unsuccessfully attempting to conceive, meaning the option of *in vitro* fertilisation (IVF) can be more readily taken.

Ultimately, in showing that host genetic variants play a role in an individual's immune response to CT, Morré and his team have paved the way for additional research into other infectious diseases. While more work needs to be done to translate these findings into real-world practice, the potential for successful translation is there.



Maastricht UMC+



Maastricht University

VU university medical center





The game of life

Dr Hamidou Tembine, an electrical and computer engineering specialist by training, shares the story behind his innovative laboratory, which focuses on understanding complex strategic interactions using game theory

When did you first become aware of game theory? Can you introduce the key concepts associated with this approach to complex problems?

As an undergraduate student, I was lucky to have a wonderful mentor at École Polytechnique, France, who allowed me to study algebraic topology and its connections with optimisation under uncertainty and game theory, and who encouraged me to continue these initial works throughout my career.

Game theory is particularly useful from an intellectual thinking point of view. As I see it, in any given interaction – whether that is an exchange between firms, people or agents in social science; animals, species, genes or molecules in biology; particles, atoms, stars or planets in physics; users, nodes or access points in engineering; or machines, servers or protocols in computer science – game theory identifies aspects that each entity should consider before making a decision. The basic model of game theory tells us that we should identify the strategic interaction between players in any given situation; we should ask ourselves who the players are, what options are open to them and what the preferences, goals, beliefs and conjectures that will influence them are likely to be.

What are the primary aims and objectives of the Learning and Game Theory Lab, which operates within the Division of Engineering at New York University Abu Dhabi, United Arab Emirates?

The Learning and Game Theory Lab focuses on understanding how entities learn and interact

with each other at the atomic, non-atomic and mixed scales. To this end, we investigate the network formation and structure of one or more entities – such as agents, mobile users, servers and virtual machines. This research aids our understanding of the fundamental principles that drive mean-field interactions and how this leads to the development of learning and design at the micro- and macroscopic level.

Who currently makes up the Learning and Game Theory Lab and what expertise do they offer to your studies?

The Lab currently contains two postdoctoral researchers, one PhD student, two undergraduate students and me. My two postdocs have PhDs in Small Cell Networks and Machine Learning and Smart Grids respectively, while the PhD student has a background in computer vision and deep learning. As our research team relies on a mixture of experimental techniques, computation and fundamental learning theory, I find that it is more stimulating and scientifically productive to have a range of group members with a variety of different experiences and backgrounds.

Was game theory's versatility immediately obvious to you? In your opinion, are there any limits to its reach?

Most of game theory's applications are unrealistic because they take only a few elements from the complex real world, and place these in an environment that is usually very stylised. We are populating these stylised environments with anticipations, beliefs, outputs, numerics, learning procedures and so on – and then, at the end of the story, the model

(whether it be partial, complete or learned) is only good if the underlying procedure is interesting. At the end of the procedure, we feel that we have gotten some sort of an insight into the real-life interaction, and observed how the participants reason and the way the real interaction is likely to go.

What is wrong with this model is that the real-life interaction contains other aspects that are not limited to the traditional economic, monetary, execution time and transmission delay, and computational complexity viewpoints. In short, as I see it, people who do 'real-life' game theory develop and generate data that provide insights concerning how to better understand various types of interactive real-world situations, and this allows us to push the theory towards more realistic considerations.

Many people become aware of game theory in their higher education careers. Despite its complexity, do you think awareness of game theory should be encouraged at an earlier age?

One of the educational objectives of the Learning and Game Theory Lab – and a particularly important one at that – is to develop educational games as a tool for building the foundation of game theory strategies for pre-school and elementary school kids. These learning games and songs for kids are fun, teach important skills and are free.



Strategies for success

Situations that call for strategic decisions can be difficult regardless of their context, but one interdisciplinary lab at **New York University Abu Dhabi** is demystifying how such decisions are made, and using its conclusions to solve persistent problems

IN ITS MOST basic sense, a game is a situation that calls for strategic behaviour on the part of the player(s), and many interactions between different entities can therefore be formalised as ‘games’. Game theory is the branch of mathematics and logic devoted to such modelling; it can be applied to a huge diversity of situations in human and animal behaviour, and has proven particularly effective in economics, evolutionary biology and politics. The field was first explored by mathematician John von Neumann in the early 20th Century.

When people think of game theory, they tend to remember another John: John Nash, the economist who, in 1951, conceived of the eponymous Nash equilibrium. Nash equilibria exist in all competitive games with multiple players, and constitute situations in which neither player can improve their payoff by changing their strategy while the other player’s strategy remains the same. For example, consider two drivers approaching a simple crossroad from different directions. They can each choose from two strategies: drive on, or wait. If both drivers drive on,

there will be a crash; if both wait, there will be a mutual delay. Therefore, if one driver chooses to drive on, and the other chooses to wait, they are in Nash equilibrium; neither would change their strategy while the other’s remains the same.

IN SEARCH OF EQUILIBRIUM

This might sound like an arbitrary situation, but its utility is actually very high. The value of Nash equilibria is that they are self-governing; even if all traffic lights at junctions, and laws surrounding them, were to be removed, people would gravitate towards a situation whereby one driver waits while the other drives because neither can change without disadvantage. Nash equilibria are strategic situations that help make the processes modelled predictable – whether they are evolutionary, sociological or economic. Of course, one pitfall of game theory is that it runs the risk of being reductive. If two drivers drive on simultaneously, they will not always crash; people do not always choose the strategy that is best for them, and there are random factors that can influence the actual outcome of strategic decisions.

Game theory is therefore an approach with great potential – if it is employed in the right way. One group dedicated to unlocking this potential is the Learning and Game Theory Lab at New York University Abu Dhabi in the United Arab Emirates. Led by Dr Hamidou Tembine, who is also Assistant Professor of the University’s Electrical and Computer Engineering Department, the Lab takes a robust approach to game theory, producing theoretical models that are resistant to the noise and random disturbances that invalidate other theoretical constructs. During the course of their work, the team has applied their models to a huge diversity of strategic problems – including how to keep a marriage together, how to encourage energy users to favour off-peak times and how best to make use of 4G networks.

ELECTRIC FEEL

In the field of energy, Tembine and his colleagues have been looking at ways of using Nash equilibria to shift the public’s electricity consumption habits. Currently, the volatility of the domestic electricity

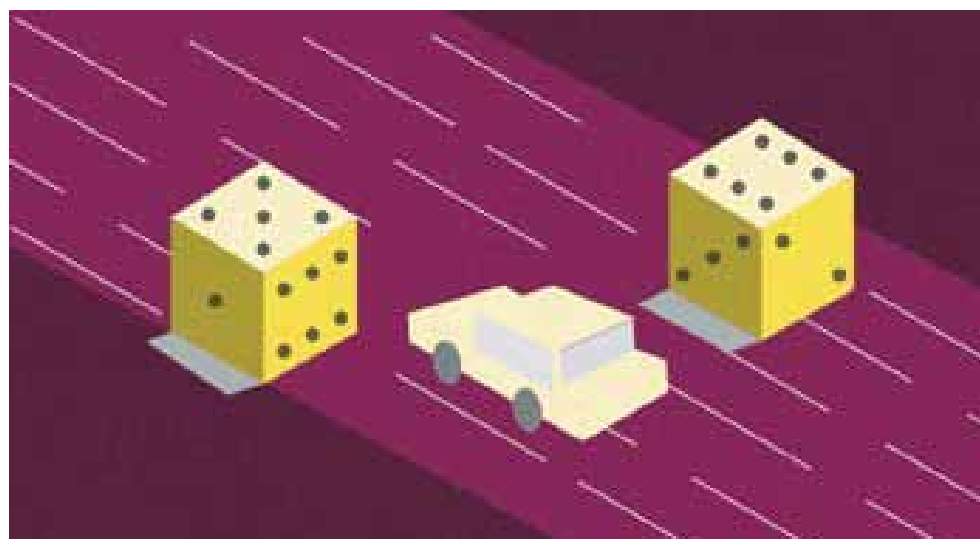
The participants considered in the study were able to move around one-quarter of their consumption from peak to off-peak hours – a change motivated by the perceived benefit of the lottery system

market is a problem for energy providers – and an over-reliance on electricity at peak times, incurring higher fees, is a problem for users. To overcome this challenge, the scientists invited 1,000 people to join a special programme. Under the rules of the programme, participants agreed to have a smart meter fitted to measure their consumption, and users who were able to move a certain proportion of their usage out of the peak times were automatically entered into a lottery. The prize of the lottery was a function of the total shifted consumption.

“What is surprising and interesting from this sample population is that most of the people decide to join the programme not because of electricity cost in peak hours but because of the possibility to win the big reward,” Tembine explains. Surprisingly, the participants considered in the study were able to move around one-quarter of their consumption from peak to off-peak hours – a change motivated by the perceived benefit of the lottery system. Extending the programme to cover an entire city or region is not without its challenges, of course, but the true potential of the group’s experiment lies in the fact that participants actively chose to engage with this model. What is more, particular information on the participants was not required prior to its initiation.

GOING WIRELESS

In the same year, the group published a second study that used game theory to draw human behaviour and electrical systems together. ‘Game Dynamics and Cost of Learning in Heterogeneous 4G Networks’ was published in the *Institute of Electrical and Electronics Engineering Journal on Selected Areas in Communications*, and examined in detail the strategies employed by users to make the most of 4G networks. The paper illustrates the importance of hybrid and heterogeneous learning schemes as employed in wireless systems, where individual users make choices that have concomitant results influenced by the actions of other users of whom they are unaware.



Tembine’s approach was novel in that it tolerated variability of the demands, uncertainty of system parameters, random activity of users, time delays and errors and noise in measurements in the long term. The game theorists experimented on a number of participants through OPNET simulations (a tool to simulate the behaviour and performance of any type of network), gathering a wealth of data on the way 4G users tend to behave and the learning strategies employed. Based on this, they then introduced a novel learning scheme called ‘cost-to-learn’, a framework that excels beyond others in that it incorporates the cost of switching in both effort and time. It therefore captures more realistic data on the behaviour of users.

WEDDING BELLS

More recently, Tembine and his collaborators have turned their attention to purely social issues. “Marriage has been, and is still, a fascinating societal phenomenon,” Tembine states – and, in 2014, he published a paper examining how married couples can strategise to best achieve marital stability. It was a timely study; empirical divorce rates are at an all-time high, and by putting social issues such as marriage on a mathematical footing, the researchers were able to lay the groundwork for future endeavours in this area. In particular, their approach relied on mean-field game theory – a model that explains phenomena where strategic decisions are made by individuals within a large population.

The models generated by the team took into account the feeling states not only of the couple, but also of the people in their social networks, and examined the optimal amount of effort that should be invested in keeping the relationship together. The results suggested that investing effort in sustaining a marriage is worthwhile as long as the current state of the couple has not fallen too low, and the cost of that effort is acceptable. Using the model, investigators will be able to gain a theoretical grasp of the key processes associated with marital dissolution and stability – an insight which could potentially be used to design interventions.

LEARNING AND GAME THEORY

OBJECTIVE

To use game theory to improve understanding of human learning and strategic decision making.

PARTNERS

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FUNDING

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HAMIDOU TEMBINE received his PhD in Computer Science from the French Institute for Research in Computer Science and the University of Avignon, France, in 2009. As an avid researcher in the field of game theory, Tembine has received numerous early career awards, including the Institute of Electrical and Electronics Engineering ComSoc Outstanding Young Researcher Award in 2014. He is co-author of 150 scientific publications and two books.



Bridging over water troubles

Dr Jon F Bartholic is Director of the Institute of Water Research, an organisation that provides timely information to address contemporary land and water resource issues. He discusses some of their ongoing programmes and reveals his hopes for future achievements

Can you introduce the core aims of the Institute of Water Research (IWR) and explain what makes its approach unique?

The uniqueness of our approach lies in the fact that we address real-world contemporary challenges through a process that includes co-creation of solutions (that generally involves real-time decision support tools). This co-creation involves end users, government, industry, environmentalists and policy makers, as well as both basic and applied researchers, educators and technical support.

IWR facilitates, informs, enriches and operationalises the process. The indigenous knowledge of end users is frequently a critical part of the ultimate operational system. Information technology systems that are usually web accessible for all participants are often maintained by IWR and continually updated to allow analysis of progress, identification of potential new problems and acknowledgment of successes.

The IWR website is rich in content, including online tools and courses. Why are these activities important for the Institute?

We look at the website as a component of a larger outreach activity for the dissemination of new information and ideas. As such, it provides access to our array of web-accessible tools. IWR is continually evolving, with new research findings and tools to equip leaders and organisations with resources, education and motivation. The utilisation of these findings and technologies helps assure a more sustainable planet that incorporates sustainable practices for an ever-growing population.

Tool innovation and development is key for IWR. Can you give an insight into some of the tools the Institute is involved with?

We have ongoing projects in collaboration with Michigan's Department of Environmental

Quality and numerous other government agencies, state-wide water guidance committees and basin-wide organisations. We are continuing development on a number of tools to aid with more informed decision making, in order to both enhance food production and assure sustainable water resource ecological systems.

Many discussions have involved the evolution of the Water Withdrawal Assessment Tool (WWAT) process that we initially programmed and brought online. The WWAT system has guided decision making relative to new high-capacity wells over the past five years. Now, however, the system is revealing numerous watersheds in the state that may be approaching their limit, as new wells may be having an adverse resource impact on nearby streams. Thus, even more advanced approaches need to evolve in order to better manage today's problems. IWR is working to co-create these progressive web-based decision-support systems for guiding actions related to water quantity and quality, using systems such as the Great Lakes Watershed Management System, High Impact Targeting, and Environmental Learning Using Computer Interactive Decisions.

As part of IWR's commitment to education, students learn from a breadth of topics including science, law and economics. How does Michigan State University support these interdisciplinary approaches?

Many of the faculty and staff at IWR have joint appointments and/or assignments in academic departments in a variety of colleges throughout the University. Through these individuals our activities find their way into widely dispersed classes. Additionally, we have developed a Watershed Management Certificate Programme which has four three-credit courses that are available on the web. These classes can be taken for credit by Michigan State University students

or attended by others for a Certificate of Completion.

Overall, offering this series of courses has benefited students and those working in a variety of professions; they have been able to attend the programme and greatly enhance their understanding of environmental and watershed management and planning.

Finally, what do you hope to achieve before 2020, in terms of improving wider engagement in, and commitment to, sustainable practices?

We are confident that we have provided many individuals and organisations with new concepts, processes and tools to serve as a starting point for further growth and dissemination of 21st Century information technologies. Furthermore, we hope that the development of new and improved tools will help our users find solutions to guide the sustainability of natural and agricultural systems and their interactions. Some of our successes will inform and motivate individuals around the globe to co-create with colleagues to evolve even better management methods solutions, and new policies that specifically incorporate the decision-support technologies.

As more systems are put in place, databases can compile information from the deployed web tools with the aid of satellites and expanding ground measurements and other data inputs. This is so that, in real-time over space, we can keep assessing the degree of our progress, learn from the outcomes and continue to improve decision-support tools. In analysing the interconnectivity between them and users, we can ensure a brighter future.

Water wonderful world

Researchers at **Michigan State University** are creating integrated information technology systems to inform decisions that improve water quality and sustain food production and ecology. They hope their work will help provide solutions for future generations

WATER IS ESSENTIAL for life and yet, according to the latest figures on Water.org, 769 million people in the world currently do not have access to it. More than 840,000 people die each year from a water-related disease, so even those with access to water are not necessarily safe from harm. Indeed, according to an announcement made by the World Economic Forum in January 2015, the water crisis facing humankind is the single biggest global threat (based on its impact on society as a measure of devastation).

As the Earth is effectively a closed system, the total amount of water it contains is more or less constant. The volume – made up of liquid, solid, gas or biological – totals approximately 1.4 billion cubic metres. However, while the net volume of water will never change, the population of the Earth will. The UN has projected that there will be approximately 2-3 billion more people on the planet by 2050. This increase will naturally lead to greater demand for water for a range of uses, such as drinking, washing, power, transportation, ecological needs and food production. It is therefore extremely important for the human race to consider ways in which the world's natural resources of water can be protected both now and for future generations.

QUALITY COORDINATIONS

The Michigan State University (MSU) Institute of Water Research (IWR) was established to address some of the challenges facing contemporary land and water resources. Led by Director Dr Jon F Bartholic, the team coordinates multidisciplinary efforts surrounding water quality and quantity problems, and investigates land use from a watershed perspective. One key method of satisfying the need to conduct and facilitate research and outreach has been the development of methods to understand the processes affecting resources, monitor trends and model the potential impacts of behaviours.

Ultimately, IWR provides vision, supports activities and supplies information on constituents within critical water issues. Educating people on the problem is necessary for solutions to be widely adopted and to emphasise the universal responsibility required to protect resources. "At IWR we have encompassed techniques and approaches that utilise satellites, databases, modelling and the internet to provide various scenarios and options at different scales," Bartholic adds.

INFORMATION FLOW

The team's endeavours have culminated in the establishment of a series of web-based tools to aid and empower local organisations and units

SIDMA

The Social Indicators Data Management and Analysis (SIDMA) tool, part of the Social Indicator Planning & Evaluation System developed by the Great Lakes Regional Social Indicators team, provides the general public with consistent measures of change within a specific watershed. It can be used by decision makers at local, state and federal levels to estimate and assess the impact of any efforts and resources put in place.

Tracking progress is an effective tool for measuring the success of a system, or for confirming whether or not attitudes, awareness and behaviours are changing within a particular community. Encouraging individuals to take responsibility for their actions is key to achieving water quality goals in the future.

www.iwr.msu.edu/sidma

INSTITUTE OF WATER RESEARCH

OBJECTIVE

To establish an institute that effectively links science and technology for the sustainable management of water resources.

KEY COLLABORATORS

US: **The Nature Conservancy • US Army Corp Engineers • Great Lakes Protection Fund • US Environmental Protection Agency • Great Lakes Restoration Initiative • US Department of Agriculture • National Institutes of Food and Agriculture • US Geological Survey • US Department of Agriculture • Natural Resources Conservation Services • US Environmental Protection Agency • The Stewardship Network • Great Lakes Commission • Michigan Department of Agriculture & Rural Development • University of Michigan • AgBio Research; Michigan State University Extension**, Michigan State University

INTERNATIONAL: **American University of Central Asia**, Kyrgyzstan • **Lanzhou University**, China • **MS Swaminathan Research Foundation**, India

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DR JON F BARTHOLIC is Director of the Michigan Institute of Water Research (IWR). He focuses on water quality-quantity issues, using information technologies to develop

web-based decision support systems to address a wide range of critical water-land use issues from a watershed perspective. As Director, he collaborates with universities and international colleagues, as well as local, state, regional, governmental and international organisations. IWR is one of 54 water institutes located at each land grant university in the US and its territories.



of government in protecting the world's natural resources. For example, the Great Lakes Watershed Management System (GLWMS), is one of the first online systems to allow web-based field level estimates of sediment and nutrient load reductions. It enables users to conduct field-scale scenario evaluations of land cover changes and develop best management practices (BMPs) online.

Additionally, the System enables users to discover the benefits of particular actions: "The BMPs are automatically geo-referenced so cumulative benefits can be determined and shown spatially," Bartholic points out. "GLWMS can enhance local cooperation, understanding and problem/solution implementation." Such a web-accessible science-based system ensures that those responsible for implementing practices can do so from a well-informed perspective.

ENCOURAGING EVOLUTION

Other systems co-created by the multidisciplinary team, including NECO, SIDMA

and GLCCN (see boxouts), intend to ensure informed decisions are made for improving water quality and availability. Alongside this, MSU supports IWR's commitment to educating students in alternative ways: "Students are provided with access to the newest web-based information technology tools being developed. This growing group of better informed individuals from throughout the state and region has established an impressive network for dissemination and utilisation of new findings from IWR and other research facilities," Bartholic explains.

Ultimately, the programmes and tools IWR has established, and continues to develop, facilitate an education, leading to better qualified critical feedback, which is crucial to applying newfound knowledge. By encouraging collaborations and pooling of knowledge, the potential reach for the employment of sustainable practices is global.

NECO

Networked Neighborhoods for Eco-Conservation Online (NECO) is a web-based system developed by IWR. It helps individuals in the Great Lakes region map to share information, photos and experiences about their rain barrels, rain gardens and other water conservation practices.

The site has three main goals:

- Increase the effectiveness of existing environmental groups and organisations
- Motivate individuals to adopt environmentally beneficial behaviours and practices
- Improve the health of the Great Lakes through the adoption of environmental stewardship practices

By focusing on connecting people through their site and social media channels, NECO encourages and inspires people from the region to come together to make a tangible difference to their environment.

www.networkedneighbors.org

GLCCN

The Great Lakes Clean Communities Network (GLCCN) was established to facilitate change by encouraging people to forge partnerships, collaborate and generate new ideas. Supported by the Great Lakes Protection Fund, the Network, which is set to launch later this year, features a central online hub and will include four main components:

- **Connect:** Creating a network of environmental practitioners in communities and organisations throughout the Great Lakes
- **Share:** Providing a platform for people to discuss their ideas and strategies to address environmental concerns in a community
- **Tools:** A catalogue of helpful online tools, tips and technology to help improve the local environment
- **EcoScore:** Enabling individuals to chart and evaluate progress towards achieving their own environmental goals

www.iwr.msu.edu/glccn

RESEARCHER PROFILE

PROFESSOR NICHOLAS J PINTO



ELECTROSPUN POLYMER FIBRES

OBJECTIVES

- To understand fundamental charge transport/charge storage processes in conducting, semiconducting and electro-active polymers
- To create nanofibres using electrospinning for the fabrication of better electronic devices and sensors
- To train and inspire the next generation of scientists toward higher education and professional careers in science

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NICHOLAS J PINTO has a PhD in Physics from Montana State University, USA, and is now a professor at the University of Puerto Rico at Humacao. His research includes electrospun polymer fibres for use in organic electronics at the nanoscale. A co-inventor on two US patents, and the author or co-author of several publications, his focus is to motivate undergraduate students to seek advanced degrees in science and engineering.



RESEARCH GOALS

Compared with their inorganic counterparts, organic polymer semiconductors have marked potential for the way in which electronic devices are manufactured and used. Not only can these high-potential materials improve efficiency and reduce costs in the production of devices such as solar panels and OLED televisions, scientists are also investigating how they can help advance the development of flexible displays. Continuing to prove their value in studies across the world, the materials boast higher thermal stability, improved compatibility with chemical and biological functionalities, and, above all, enhanced electrical conductivity. It is no

wonder, therefore, that capturing this potential is big business.

Despite their wide-ranging potential, organic polymer semiconductors are proving difficult and costly to produce on a large scale. Aiming to make their use in devices and sensors commonplace, Professor Nicholas J Pinto and his team at the University of Puerto Rico (UPR) at Humacao are exploring the fundamental charge transport and storage processes of these polymers. What is more, Pinto is involving a group of undergraduate students in his work, fulfilling another ambition: to engage and motivate the next generation of researchers to pursue a career in STEM.

METHOD

Pinto's team judged that in order to fabricate better devices and sensors using electro-active polymers and their composites, their fundamental mechanisms of charge transport and charge storage must be properly understood. A process known for its simplicity, efficiency and low cost, the key to realising their manufacturing aim has been electrospinning, which the UPR team is using in an intriguing and unique way to create polymer nanofibres.

Prior to electrospinning, the first port of call for Pinto's team was taking temperature-dependent conductivity and dielectric permittivity measurements (DPMs). Nanofibres naturally possess a confined environment for charge flow. As a consequence, any defects are likely to lead to changes in charge transport. "These defects give us a handle on how best to prepare a defect-free nanofibre," Pinto explains. "Notably, DPMs on nanofibres will also shed light on charge relaxation processes in a confined environment." The team found that due to the nanofibres' small diameter and, therefore, large surface-to-volume ratio, the materials have the potential to be used in the fabrication of low-power consumption devices and supersensitive and rapid-response sensors. In creating these nanofibres, Pinto is endeavouring to combine materials that possess different electronic, mechanical and optical properties.

IMPACT

The team has already enjoyed great success in preparing nanofibres from electrospinning, particularly in the recent preparation of polylactic acid (PLA) blended with the conducting polymer polyaniline doped with camphor-sulfonic acid (PANi-CSA). The former being a thermoplastic, biocompatible and biodegradable polyester, and the latter being a common conducting polymer known for its natural ability to synthesise. While their pairing is not new, Pinto's team is the first to prepare the nanofibre at the lowest PLA concentration recorded in the literature.

The group has identified that the PLA/PANi-CSA nanofibre has the potential for reducing the toxicity of electronic devices. Remarkably, the findings can even have applications in 3D printing of mechanical parts for bone repair. Establishing these new methods of combining polymer materials will undoubtedly lay the foundations for incorporating nanofibres into electronic devices.

Ultimately, the impact of this research stretches beyond the creation of improved devices. Pinto hopes that exposure to a broad range of subjects – in this case, physics, nanoscience, polymer science and electronics – will increase the number of students participating in scientific research. Students currently involved in Pinto's research are being trained in the scientific methodology and gaining sound and relevant research experience. "These opportunities will not only help them in their graduate studies, but also improve their future employment opportunities," Pinto enthuses.



Fragile freight

Initiated by HaCon, a European project seeking to identify and correct the many challenges facing the single wagonload transport system, **Lars Deiterding** and **Niklas Galonske** are designing and building rail transport systems of the future

To begin, could you introduce the work of the HaCon consulting team?

LD: The HaCon consulting team specialises in rail freight transport and intermodal transport chains. Using our broad competencies and experience we're able to provide a wide spectrum of consulting services, including the development and coordination of research projects; advising on policy matters; preparation of funding applications; market analyses; and the development of transport concepts. We are often involved as a project coordinator, so our job starts at the very beginning of the process, ie. forming a general project idea and project consortium. Essentially, we're responsible for providing our partners with an optimal framework for their research activities. This involves taking care of the main administrative duties while our partners concentrate on the research. Wherever appropriate, we provide advice and technical expertise.

What was the main motivation for creating the Viable Wagonload Production Schemes (ViWaS)?

LD: Although intermodal transport has developed into a dynamic rail freight product that competes with road transport, we still see a demand for high-quality and efficient conventional rail freight services below the block train level. In particular, the classical single wagonload (SWL) transport system has shown considerable loss of transport volumes and market shares due to unfavourable cost structures and low-quality standards. We are confident that our expertise and ideas will generate important improvements for this rail product.

Could you describe your role within the initiative?

NG: ViWaS is the first EU-level research project exclusively dedicated to SWL. As Project Manager, I have been responsible for setting it up, coordinating the work and all of the administrative duties, and promoting the project's results. We are happy that the EC has acknowledged the importance of this type of transport and has provided the necessary funding. This enables our project partners to conduct necessary analyses and improvements they would not otherwise be able to do under current economic pressures.

Why is ViWaS so important to the European economy?

LD: The European economy is largely dependent on high-functioning logistics and transport systems, with all available modes being used. In this context, it is worth mentioning that some important industries such as steel, chemicals, automotive and timber rely on SWL transport. SWL still makes up roughly 30 per cent of rail transport volumes in Europe. When stabilising these volumes, other modes will increase their capacity to better cope with rising transport demands. We therefore urgently need improvements to SWL.

What have been the biggest innovations to come out of this initiative?

NG: It would not best serve the ViWaS project to highlight one or two innovations; most developments show their full effectiveness in combination with other improvement measures. However, it's possible to highlight some concrete results that are connected with technological developments. For instance, various prototypes have made it possible to make freight wagons modular. The Flex Freight Car is a light container wagon equipped with a drive-on floor. This wagon serves as the base for different types of superstructures and can be flattened. Another example is the Container Loading Adapter, a superstructure that can be added to a conventional container wagon to facilitate the loading and unloading of containers in sidings.

Major improvements have also been achieved in the field of wagon telematics. The new telematics devices generate larger amounts of better data, and for less money, compared to previous devices. A high-accuracy load sensor, which is part of the telematics system, is currently in the final development stage.

Having reached the final phase of the ViWaS project, we're pleased to see it has succeeded in producing important tools for improving the flexibility, visibility and thereby efficiency and quality of SWL transport.





Haulage systems overhaul

The single wagonload transport market may be on the precipice, but that does not mean it has outlived its potential. **HaCon** is leading an international development project to bring some much needed improvements to Europe's transportation networks

IN EUROPE TODAY, the landscape of rail freight transportation is undergoing significant changes. In 2005, single wagonload (SWL) transport accounted for 39 per cent of Europe's rail freight transportation market share, but only five years later this number dropped to just 30 per cent. With a near to nonexistent level of competition within the SWL market itself, low-quality standards and unfavourable cost structures have become widespread. While it may be lacking in internal competitiveness, it faces strong competition from conventional block trains, intermodal transport and road transport services.

Despite the current state of SWL transport, it still provides a vital service to industries wanting to shift freight below the block train level. In a bid to halt its deterioration, the Viable Wagonload Production Schemes (ViWaS) project has been undertaken to breathe new life into the SWL market through improvements in cost efficiency, transport quality and sustainability.

Co-financed by the EU Seventh Framework Programme (FP7), ViWaS is a 39-month R&D project aimed at identifying weaknesses in the European SWL transport network and searching for solutions. Heading the project is HaCon, a company with a track record that puts it among the top European players in the field of traffic, transport and logistics. At its helm are Lars Deiterding, Executive Director and head of the consulting team for freight transport and logistics, and Niklas Galonske, the company's Project Manager and consulting team leader for ViWaS. Together, they bring over 30 years combined experience in research and analysis of the international railway industry, as well as in coordinating, consulting, managing and providing technical guidance for numerous international projects.

UP TO SPEED

Together with the project partners, the HaCon team has pinpointed a vicious cycle eating away at the SWL market. As demand has dropped, the response among many European countries has been to save money by cutting the least cost-effective tracks, yards and sidings, and generally scaling back their networks. Reduced connectivity has made it harder to send or receive goods, so it is little wonder that customers are looking to take their money elsewhere. In order to combat this, Deiterding



and Galonske have identified several key areas where improvements could radically bring down costs and boost SWL efficiency.

To ensure the viability of SWL systems, the team first identified the importance of trunk lines being used to their full potential by operating trains. In partnership with the Swiss Institute for Transport Planning and Systems (IVT), a simulation tool has been developed for the optimisation of SWL production schemes. The group hopes the tool, wagonSim, will help overcome challenges in network usage and cost efficiency. Based on an existing public transport model, wagonSim is able to infer the current status of the network by modelling the physical infrastructure (a network's capacities and available train routes) and the production network. Successfully simulating the basic model of a current SWL network, the wagonSim tests have already provided one of the project's partners with a baseline from which they can develop new ideas for network improvements.

Further aiding the implementation of these improvements is the introduction of onboard communication technology – telematics – for load tracking and tracing. This helps operators to optimise the wagon dispatch and rescheduling processes and inform their customers instantly about any changes to the transport schedule. They can also play an invaluable role in determining a wagon's lifecycle by giving accurate data on their actual

mileage. By addressing these problem areas, new telematics devices of ViWaS partner Eureka can help vastly improve the dispatching processes, resulting in shorter stand-still times and increased efficiency.

REINVENTING THE WAGON

A major factor hampering the efficiency of SWL transport is the organisation of costly and complex 'last-mile' services. Here, a multiplicity of necessary and time-consuming tasks conspire to put the brakes on SWL networks. The project partners have identified a range of solutions to simplify last-mile procedures, reducing overall workloads and saving time and money.

The most notable among these is the development of modular freight wagon technologies. The Swiss Split operating system SBB Cargo has been able to bring maritime containers on shuttle trains or barges to Switzerland, using the domestic SWL network for further distribution. In the Swiss gateway terminals, containers are currently placed onto conventional wooden-floored wagons and secured in place. To do this, terminal employees have to nail wooden blocks around the container into the wooden floor of the wagon. In addition to being slow, wooden-floored wagons have high maintenance costs compared to their steel counterparts. ViWaS has developed two technical solutions for container transport on

the SWL part. Both solutions make existing container wagons accessible, allowing unloading and loading by fork lifts. The 'Container Loading Adapter' of SBB Cargo is a mobile platform that is set on a container wagon. Wascosa's 'Flex Freight Car' already integrates an accessible floor and, moreover, is extremely light weight. This means that it can carry one of the highest payload of its class in Europe.

The project's partners have pinpointed a vicious cycle eating away at the single wagonload transport market

The Wascosa wagon also addresses challenges posed by non-containerised freight. Often, different commodities call for specific types of wagon, such as timber. In these instances, many wagons end up running a lot of mileage when empty in SWL production schemes. However, the Wascosa wagon comes with rearrangeable stacking bodies that accommodate an array of cargo types. Such flexibility allows for instant response to changes in demand with real benefits in productivity and overall operating efficiency.

IN SMART COMPANY: LEADERS IN EUROPEAN TRANSPORT LOGISTICS

In 2015, HaCon was named among the '50 Smartest Companies' in the world as ranked by Massachusetts Institute of Technology. With 30 years of transport consulting and software development expertise behind them, the group is now responsible for designing the European transport system of the future

Based in Hannover, Germany, HaCon was founded in 1984 on the expertise of three engineers specialising in public transport, freight traffic and railway operation research. Now, with over 30 years' experience and a dedicated team of more than 250 specialists in transport planning and IT, HaCon has firmly established itself as one of Europe's lead players in developing high-quality traffic software planning, scheduling and information solutions.

HaCon is also home to a dedicated team of consultants specialising in rail freight and combined transport projects. Using a highly integrated and results-orientated approach, the group aims to assist customers through the combined skills of transport engineers, geographers, lawyers and IT specialists. Working with project sponsors, including the EC, HaCon has amassed a considerable amount of project management experience. Among its service portfolio are successes in requisition and subsidies, the completion of financial and administrative formalities and the overall coordination of all parties involved such as railway companies, shipping agents, institutions and associations.

www.hacon.de

VIABLE WAGONLOAD PRODUCTION SCHEMES (ViWaS)

OBJECTIVE

To strengthen the competitiveness of single wagonload and wagongroup transport in Europe.

PARTNERS

Bentheimer Eisenbahn AG; HaCon Ing. GmbH; Eureka Navigation Solutions AG; Technische Universität Berlin, Germany

Federal Institute of Technology in Zurich, Institute for Transport Planning and Systems (ETH Zurich IVT); SBB Cargo AG; Wascosa AG, Switzerland

Société Nationale des Chemins de Fer, Fret (Fret SNCF), France

Consorzio IB Innovation, Italy

NEWOPERA Aisbl, Belgium

FUNDING

EU Seventh Framework Programme (FP7)

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LARS DEITERDING is Executive

Director of HaCon and head of HaCon's consulting team for freight transport and logistics. He has more than 15 years of experience

in research and expert analysis in all areas of the international railway industry, including the planning and design of railway systems, infrastructure capacity analyses and rail operational studies.



NIKLAS GALONSKE holds a diploma degree in Civil Engineering from the University of Hannover, Germany.

After acting as a consultant, with a focus on infrastructure assessment

and railway operations, he joined HaCon in 2005. He supports the consulting team as a project manager and team leader.

RALLYING FOR THE RAILWAY

Considering the rail transport system as a whole, Deiterding and Galonske know that there are a great many aspects that need addressing, but not all can be tackled at once. Equally important to the implementation of new technologies is the development of market-driven business models, ICT in an administrative context and advanced management procedures. One area they are particularly concerned with is the improvement of the rail transport sector's carbon footprint.

While rail freight is regarded as an ecological mode of transport, current calculation tools are not designed to take into account the emissions from intermodal transshipment processes. The HaCon consultants, therefore, have sought to fill this technology gap with a calculation tool to cover the entire transport chain. Based on the detailed infrastructure, equipment and processes of intermodal terminals, the Intermodal Terminal Eco-Efficiency Calculator (ITEC) computes their energy use (including greenhouse gases contributions), identifies the main energy consumers and helpfully shows the impacts of implemented and planned greening measures.

Deiterding and Galonske have overseen the development of a range of products up to prototype status and given their proven application within the scope of ViWaS; many are only a hair's breadth from being marketable products. The project leaders, however, are not under any illusion that the SWL market can be saved overnight, as remarkable though its achievements may be, it cannot rejuvenate the system on its own. Where it does succeed is in showing exactly where and how improvements can be made. Gearing up along with its partners to present the project's findings, the word might begin to spread and bring about what SWL really needs: an environmentally friendly, Europe-wide approach to strong logistics solutions.



Wascosa's 'Flex Freight Car' and Timber Cassette, and SBB Cargo's 'Container Loading Adapter'. Source: HaCon





The phloem: a nutrient delivery superhighway

Professors Christina (Tina) Offler and **John Patrick** have collaborated for over three decades. Their scientific curiosity has led to several important discoveries of how nutrient flows in plants are regulated. Below, they provide an insight into some of their history, inspiration and progress

How did your collaboration begin, and how has it endured?

JP: Tina joined the Department of Biological Sciences as a part-time tutor and taught several undergraduate plant biology courses for which I was responsible. I was impressed by Tina's independent spirit, her pragmatic desire to refocus her research from palaeobotany to plant physiology and her tenacious commitment to pursuing a full-time academic career. This ultimately led to initiating what has proven to be an enduring and highly productive collaboration based on complementary skills and an egalitarian approach.

TO: In 1979, encouraged by John, I attended the Annual Meeting of the Australian Society of Plant Physiologists (now Scientists) to discover 'what plant physiology was about'. I subsequently developed microscopy skills that enabled me to visualise plant cell structure and became fascinated by the interdependency of cell structure and function, and its implications for whole plant function. In 1982, excited by the prospect of making new discoveries, I joined John in his quest to understand phloem unloading. He mentored me through the early years of our collaboration and the rest is history peppered with doses of tolerance and mutual respect.

Could you explain how the experimental models you have developed have significantly contributed to understanding phloem unloading?

TO&JP: Cells forming the pathway delivering nutrients from the phloem (a vascular pipeline extending throughout the plant body) to nourish developing cells of a plant organ are embedded in a tissue matrix. This renders their accessibility for experimental studies technically difficult. However, in developing seeds of grain legumes, the maternal and filial generations do not share common cell walls. Thus, severing the maternal compartment (seed coat) around its equatorial region allows the two coat halves to be removed from the underlying cotyledons (embryo). This simple surgical procedure

allowed – for the first time – independent study of nutrient release from seed coats and nutrient uptake into cotyledons. Once nutrient release and uptake cells were identified, we developed techniques to obtain large numbers of their protoplasts for more refined membrane transport studies.

To study differentiation of cells specialised for membrane transport of nutrients (transfer cells), we established an experimental system in which epidermal cells of excised bean cotyledons – when placed into culture – rapidly and synchronously differentiate into a transfer cell morphology and function comparable to their *in planta* counterparts. This system provides ready access to thousands of differentiating transfer cells for cell and molecular studies at the single cell level.

The key objective of your work is to understand the mechanistic basis of nutrient flows and their regulation. Can you highlight your main discoveries thus far?

TO&JP: These have included:

- Identifying cellular pathways of phloem unloading and cellular sites that form key bottlenecks impeding nutrient flows through these pathways
- Hormonal regulation of plasmodesmal hydraulic conductances at sites of phloem unloading
- Identifying and functionally characterising membrane transporters involved in seed filling
- Assembling our findings into a model of phloem unloading that unifies phloem transport to, with nutrient demand by, developing seeds
- Finding transfer cells located at sites of nutrient release and uptake within developing seeds and demonstrating their pronounced capability for sucrose, amino acid and ion transport



- Elucidating the signalling cascades regulating formation of the specialised ingrowth walls of transfer cells

What have been some of the most exciting aspects of your work to date?

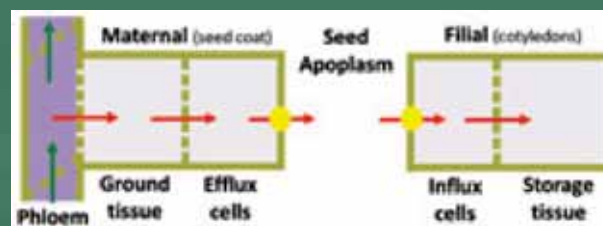
TO: Our work has elicited a sense of excitement and satisfaction on a number of occasions. Notably, we discovered that, by placing the flat surface of bean cotyledons on a culture medium, their epidermal cells differentiate into transfer cells. Another high point arose when Honours student, Mark Talbot, dropped his scanning electron microscope stub on the lab floor. This error serendipitously led to developing a powerful technique to visualise the intricate invaginations of transfer cell ingrowth walls – a central plank in advancing our understanding of their differentiation.

JP: For me, it was an Honours student, Bob McDonald, insisting on using developing seeds to study phloem unloading. This led us to spend an entire day convincing ourselves that there was no structural linkage between seed coats and cotyledons. In the end, we developed the seed coat cup system that has transformed understanding of transport mechanisms and their regulation mediating nutrient release. Constructing a mechanistic model demonstrating how nutrient demand is integrated with phloem unloading in, and phloem transport to, a developing seed was also very satisfying.

Going with the flow

Researchers from the **University of Newcastle**, Australia, are on a quest to discover mechanisms regulating nutrient flows to and within developing plant organs that markedly impact crop yields

THE FOOD AND Agriculture Organization of the United Nations (FAO) predicts that by the year 2050, the world's population will reach 9.1 billion. In order to feed this significantly larger population, it is estimated that current food production levels will have to increase by 70 per cent. Unfortunately, for most staple crops, there is an ever-narrowing gap between improvements in crop yield and increments in global consumption. If the world is to provide global food security by 2050, this trend needs to be reversed.



The phloem unloading pathway during seed fill.

For over three decades, Conjoint Professor Christina (Tina) Offler and Emeritus Professor John Patrick from the University of Newcastle, Australia, have conducted collaborative investigations to understand the mechanistic basis of nutrient flows and their regulation. The findings, emerging from their curiosity-driven studies, have the potential to provide translatable solutions that address the world's imperative to improve crop yield.

CROP YIELD DETERMINANTS

Increases in crop yields are achieved through refining agronomic practices in combination with breeding programmes to enhance resistance to pests and diseases, confer greater adaptation to abiotic stresses and increase yield potential through alleviating physiological and biochemical constraints. Two key developmental phases contribute to yield potential – setting harvested organ numbers, followed by filling these with biomass.

All nutrients (carbon compounds and minerals) required to support harvested organ development are transported from leaves through a vascular pipeline, the phloem. Thus, yield potential is a function of nutrient acquisition by the crop and the proportion of acquired nutrients delivered to the harvested organs by phloem transport. Both processes are active areas of international enquiry.

Proportioning of phloem nutrient flows between developing plant organs largely depends on

their relative capacities to facilitate exit of nutrients from the phloem and transport these to cells undergoing growth or storage. This cell-to-cell transport is referred to as phloem unloading.

PHLOEM UNLOADING AND NUTRIENT PARTITIONING

Offler and Patrick's research has focused on elucidating cellular pathways of phloem unloading, identifying the transport mechanisms and discovering how these are regulated. Their progress in understanding phloem unloading is attributed to developing simple, but extremely powerful, experimental models that have provided technical access to study the process. These models have included decapitated stems as mimics for the setting phase and developing seeds of grain legumes and cereals for the filling phase.

By experimentally manipulating these models, the two researchers have identified phloem unloading pathways and key bottlenecks impeding nutrient flows. "Universally, a bottleneck is imposed by hydraulic conductance of the cytoplasmic threads (plasmodesmata) interconnecting phloem conduits with the surrounding cells," they explain. "As seeds enter their filling phase, an additional limitation is imposed by membrane transport of nutrients from and into cells comprising the phloem unloading pathway."

These findings identified a method for exploring opportunities to increase yield potential through discovering mechanisms regulating plasmodesmal hydraulic conductances and membrane transporter activity. For the setting phase, Offler and Patrick have shown that phytohormones up-regulate conductances of plasmodesmata located at the phloem interface with the surrounding cells. Moreover, this response is accompanied by increased phloem transport to the phytohormone-enriched site in decapitated stems. The current challenge is to verify that these processes are reproduced in organs undergoing setting.



Polarised calcium signal (green) in a developing transfer cell.

PHLOEM UNLOADING AND TRANSFER CELL BIOLOGY

OBJECTIVES

- To discover mechanisms regulating phloem unloading of nutrients
- To understand regulation of transfer cell development

KEY COLLABORATORS

Ongoing: **Professor Antony Bacic**, Australian Research Council Centre of Excellence for Plant Cell Walls, The University of Melbourne, Australia • **Professor Chris Grof**, **Associate Professor Yong-Ling Ruan**, University of Newcastle, Australia • **Dr Hans Weber**, **Dr Ruslana Radchuk**, Leibniz Institute of Plant Genetics and Crop Plant Research, Germany

PARTNER

Australia-China Research Centre for Crop Improvement
<http://bit.ly/ACResearch>

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Australian Research Council (ARC)

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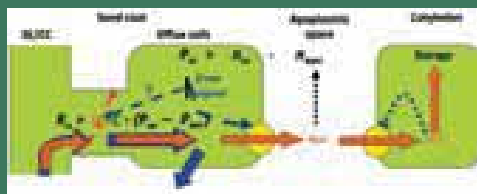
www.newcastle.edu.au/profile/john-patrick



CHRISTINA OFFLER completed her PhD in Palaeobotany at The University of Adelaide, Australia, where she developed her eye for plant structure. She works at the University of Newcastle, Australia, where, alongside colleague Patrick, she expanded this skill to establish pathways of nutrient flow from cell-to-cell in developing plant organs and to study differentiation of transfer cells – specialised cells displaying intricate wall invaginations and an enhanced capacity for membrane transport of nutrients.



JOHN PATRICK received his PhD from Macquarie University, Australia, where he began a 'career odyssey' of understanding nutrient partitioning by evaluating influences of vascular geometry, and subsequently phytohormones. In collaboration with Offler, his long-term research programme is discovering cellular pathways, mechanisms and regulation of phloem unloading at the University of Newcastle, Australia.



Model of phloem unloading in developing seeds.

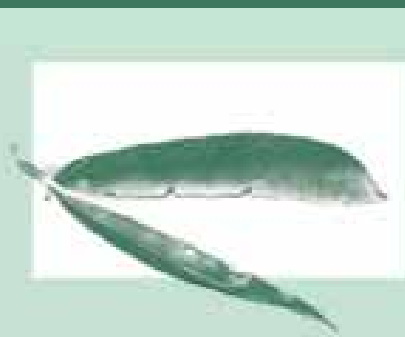
More progress has been achieved in understanding regulation of nutrient flows during seed filling. A starch biosynthesis mutant of pea led to the discovery that sucrose demand for starch biosynthesis in the embryo is met by adjusting sucrose supply through negative feedback regulation of plasma membrane-located sucrose transporters. Alterations in sucrose uptake by the embryo are sensed by a complex turgor homeostat mechanism located in the seed coat that proportionately adjusts their sucrose release and plasmodesmal conductances.

Similar mechanisms regulate flows of mineral elements through the phloem-unloading pathway. Collectively, this suite of regulatory mechanisms assembles into a control network linking phloem supply of nutrients with their downstream demand by storage cells. Proof of concept for the proposed control network was demonstrated by selectively overexpressing a potato sucrose transporter in pea seeds causing a 10 per cent increase in their biomass. This inspired Offler and Patrick to include transfer cell biology in their research portfolio, as these cells are ideal vehicles to further enhance transport capability through embedding more transporters in their amplified plasma membrane surface areas.

TRANSFER CELLS: ENHANCING TRANSPORT CAPACITY

The highly invaginated ingrowth walls of transfer cells form scaffolds to support amplified surface areas (up to 20 fold) of plasma membrane. Significantly, transfer cells are located at sites for nutrient release and uptake in developing seeds of certain species of grain legumes. Upon developing cell-specific isolation procedures, the team demonstrated – for the first time – that these transfer cells contained all the membrane transport properties of nutrient release and uptake (see above). Moreover, the substantial amplification of their plasma membrane areas, enriched in transporters, was shown to confer these cells with an extraordinary capacity for membrane transport.

These findings laid the foundation for Offler and Patrick to embark on an exciting research programme, using their cotyledon culture system, to discover the mechanisms underpinning differentiation of cells to a transfer-cell morphology. Their research programme is being progressed in two phases. Currently the team's focus is to



A SHARED JOURNEY

In addition to many graduate students and postdoctoral fellows, there are a number of colleagues whose collaborations opened new horizons Offler and Patrick might not have otherwise explored, as they explain:

Our conceptual understanding of phloem unloading has been sharpened by robust interactions with Emeritus Professor Aart van Bel (University of Giessen, Germany), while the late Professor Vince Franceschi (Washington State University, USA) introduced us to a suite of valuable plant cell biology techniques that substantially refined our understanding of cellular pathways of phloem unloading and transfer cell biology.

A chance meeting with Professor Wolf Frommer (Carnegie Hall, University of California, Berkeley, USA) culminated in a valuable collaboration to identify and functionally characterise transporters facilitating seed and fruit loading. Professor Steve Tyerman (The University of Adelaide, Australia) and the late Professor Alan Walker (The University of Sydney, Australia) widened our research endeavours to include characterisation of ion channels participating in phloem unloading and fine tuning of our analyses of sugar release and turgor homeostasis.

Our current research programme on transfer cell biology benefits from the bioinformatic skills and seed biology knowledge of Drs Ruslana Radchuk and Hans Weber (IPK, Germany). In addition, interactions with Professor Tony Bacic (The University of Melbourne, Australia) have instigated new areas of enquiry into cell wall synthesis, organisation and composition.

identify the inductive signalling cascades and the downstream machinery responsible for constructing the transfer cell ingrowth wall to generate the amplified area of plasma membrane. Once completed, this will be followed by a study to elucidate induction, targeting and embedding key transporter proteins in the amplified plasma membrane.



Making a connection

Telecommunications expert and former technology researcher **Dr Louis Fox** explains how his organisation is connecting Californian research and education institutions

Can you introduce the main aims of the Corporation for Education Network Initiatives in California (CENIC), and the context in which it was established?

CENIC connects California to the world – advancing education and research state-wide by providing the world-class network essential for innovation, collaboration and economic growth. Our non-profit organisation operates the California Research and Education Network (CalREN), a high-capacity network designed to meet the unique requirements of over 20 million users, including the vast majority of K-20 students together with educators, researchers and other vital public-serving institutions. CENIC's Charter Associates are part of the world's largest education system; they include the California K-12 system, California Community Colleges, the California State University (CSU) system, California's Public Libraries, the University of California system, Stanford, Caltech and the University of Southern California. CENIC also provides connectivity to leading-edge institutions and industry research organisations around the world, serving the public as a catalyst for a vibrant California.

How have CalREN and the California OpenFlow Testbed Network (COTN) changed the CENIC members' network capabilities?

Our members are the most highly connected community in the world – all research universities are connected directly at 100 gigabits per second (Gbs⁻¹); CSU campuses at 10 Gbs⁻¹; most California Community Colleges at 1-10 Gbs⁻¹, with a goal of 10 Gbs⁻¹ for all; County Offices of Education (58 of them!) at 1-10

Gbs⁻¹, with a goal of 10 Gbs⁻¹ for all; and library jurisdictions at 1-10 Gbs⁻¹, with several 10 Gbs⁻¹ library jurisdictions (many of which are national or global firsts), and the world's first 100 Gbs⁻¹ library system in the offing.

Is collaboration particularly important to achieving CENIC's aims? Could you highlight some of the outcomes of these partnerships, such as those with the California Telehealth Network and the Energy Science Network?

We are a platform for collaboration between and among the educational segments, and we therefore undertake and facilitate a number of collaborative endeavours. That might mean, for example, enabling libraries to be a part of CENIC, since they have some partnerships with local K-12 schools or community colleges. This kind of thing extends across the education spectrum. We also connect a lot of cultural institutions, such as the Exploratorium in San Francisco – a fabulous science museum – and SFJAZZ, the first freestanding facility built for jazz in the US. Jazz is an indigenous American art form, and therefore has a great cultural importance. SFJAZZ can derive many benefits from their connectivity: they might audition a student using the network, or they might do a concert at a school with high definition video and sound.

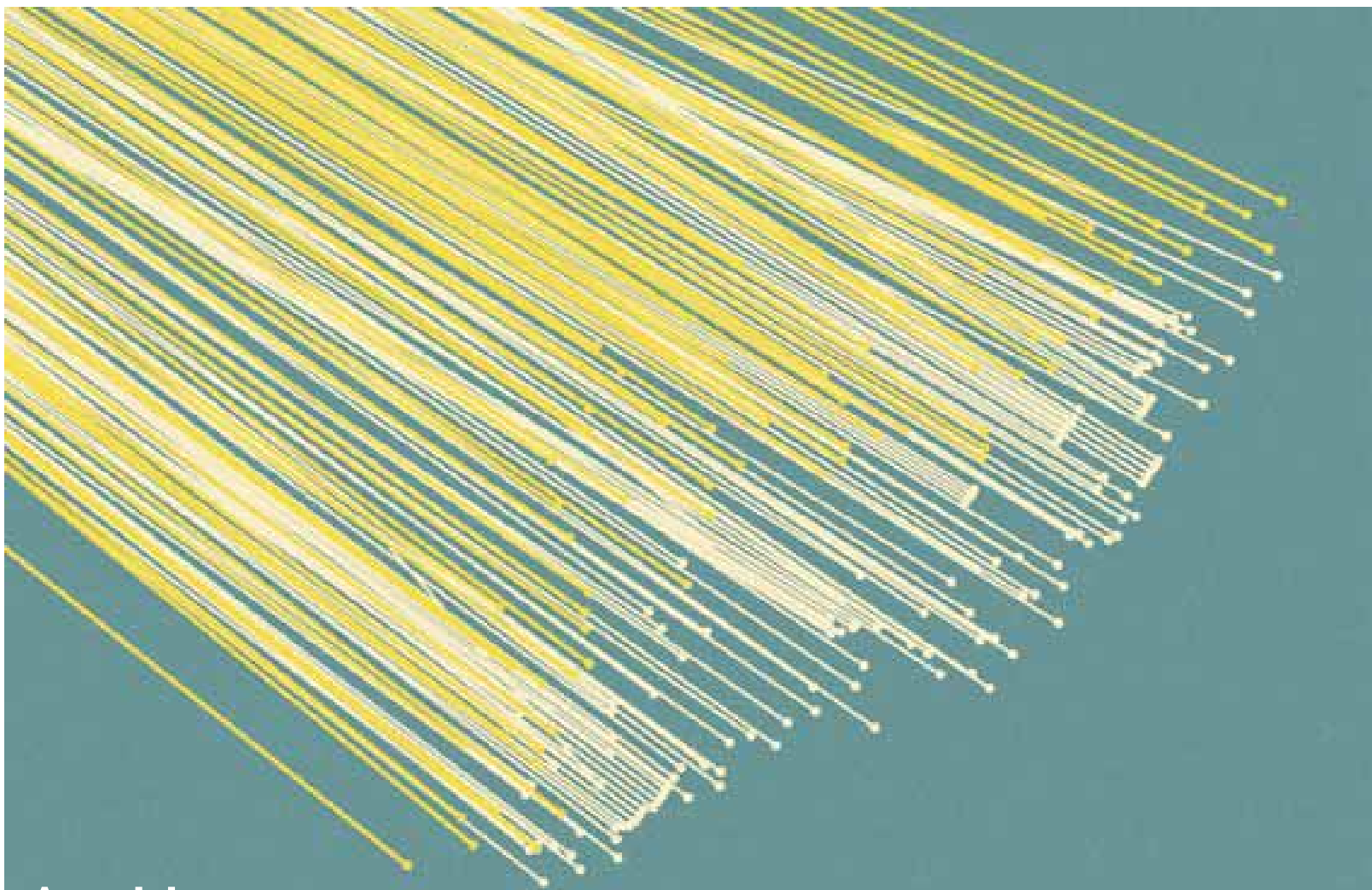
What have been the greatest challenges in connecting universities with high-speed networks at low cost?

For networks, the biggest challenge in California is the geography. Most people, even in the US, think of California as being this handful of big cities, but it's also a mountainous

and rural state, which is a complicating factor. So, there's a diversity of geography and serving these communities often requires complex and costly construction projects.

Do you aim to replicate the CENIC model elsewhere to give research and education institutions a competitive advantage by providing high performance networks at low cost?

Yes – in fact, we are already doing this! There are research and education networks like CENIC throughout the US; some of them are state-based and some are regional. We are very involved with our region, so we work with network partners; for example, the Western Regional Network – a Western regional collaboration; the Pacific Northwest Gigapop – they serve Washington, Idaho, Montana and parts of Oregon; the Front Range Gigapop, which serves Colorado and Wyoming; and the New Mexico Gigapop. Collectively, we have put together fibre assets throughout the west that enable really important scientific collaborations to go on between and among the research institutions in our state. We also partner with national networks like Internet2 and the Energy Sciences Network. One that I haven't mentioned yet is Pacific Wave, an international peering fabric that allows research and education networks from around the world to interconnect with our network and operate as if it were a single network fabric. CENIC's model exists in other places, it's just that the scale that we do things in California has more in common with other national networks than state networks, given the size, complexity and number of institutions in California.



A golden opportunity

The **Corporation for Education Network Initiatives in California**, USA, is seizing opportunities to improve network infrastructure between education organisations in the Golden State

IN MANY WAYS, communication is the hallmark that distinguishes humans from other animals. Although some species have been observed to develop relatively complex verbal communication, none can approach the loquacity of humankind – and supported by increasingly powerful technology through history, this compulsion to talk with one another has led to an incessant stream of information passing between people all over the world. In fact, human discourse has become so ubiquitous that much of it seems redundant. The internet, for example, facilitates the passage of important messages between communicators worldwide – but much of its traffic is concerned with subjects as banal as sharing amusing videos and idle chatter.

The growing private demand for data – including, increasingly, mobile data – puts heavy pressure on existing commercial infrastructure. This presents a problem

– while consumers are amicable to the prospect of spending an increasing amount of money on securing internet access, public institutions such as libraries, universities and medical centres do not necessarily have that capacity. Research and education are the foundation of a strong economy, as well as being powerful forces for quality of life and societal development. It is therefore essential that institutions dedicated to these pursuits be allocated the resources they need to succeed. This includes networking resources, particularly since collaborative ties are a real asset in both research and education.

ALL-TERRAIN FIBRE FOR HIGH-SPEED RESEARCH COLLABORATION

Establishing network infrastructure at the capacity required by these critically important public entities is not easy – and in certain areas, it is especially difficult. California, for example, is the largest of all the US states in terms of population; 1 in 8 US citizens

call the state home. It is also geographically diverse, with terrain ranging from fir forests and mountains to deserts and valleys. It is in California that both the highest and lowest points in the contiguous US can be found. The Golden State is also the second-most likely to experience earthquakes, preceded only by Alaska, and is also at high risk of wildfires. These factors make it very challenging to establish reliable networks of the type required for collaboration between partner institutions. Yet California is also home to a number of world-leading education and research organisations, such as the University of California campuses, Stanford and Caltech, as well as Department of Energy laboratories and NASA research centres, all of which rely on cooperative links for their success.

The Corporation for Education Network Initiatives in California (CENIC) is a non-profit organisation dedicated to enabling this kind of high-capacity networking and safeguarding

Almost 4,000 miles of optical fibre were required to link the participating institutions, and today around 10,000 sites connect to CalREN

California's future. Headed by CEO Louis Fox, CENIC's mission is to contribute to research and education by enhancing network capacity; one of the main ways in which this is accomplished is through the California Research and Education Network (CalREN), a high-capacity network purpose-built to serve an audience of students, educators and researchers. "From biomedical data to particle physics, today nearly all research and data analysis involves remote collaboration. In order to work effectively and efficiently on multi-institutional projects, researchers depend heavily on high-speed access to large datasets, scientific instruments and computing resources," Fox explains.

CALIFORNIA'S BACKBONE

The scale of CalREN is impressive. The physical fundament of this network – which connects members in every single one of California's 58 counties – is expansive in scale; almost 4,000 miles of optical fibre were required to link the participating institutions, and today over 10,000 sites connect to CalREN. What is more, whether they know it or not, 20 million Californians use CalREN, emphasising the great importance of this resource to society. The network is the backbone of CENIC's wide-ranging activities within the state, and acts as a vital support to the organisation's work. For this reason, the company recently completed an upgrade of the network, pushing its speed up to a huge 100 gigabits per second (Gbs⁻¹).

Opening the network up to libraries is currently an important goal for CENIC. In 2014, the organisation assessed the capacity of these public institutions, finding that 75 per cent had low-speed connections, two-thirds were operating at or above their capacity and that the total bill being paid for this poor service was US \$14 million. CENIC therefore decided to open CalREN to libraries, bringing them high-speed broadband that is 30 to 1,000 times faster than their current services at around one-third of the cost. Libraries will be able to join the project from September 2015 and over 1,000 libraries will be joining the library over the next two to three years.

THE RESPECT OF PEERS

"Peering is an important part of what we do," Fox affirms. Indeed, it is this practice that

allows CalREN to achieve such high capacity and speed with minimum expenditure. When two networks 'peer', they mutually agree to interconnect for the purposes of exchanging data between their users – and because the internet is composed of a huge number of interconnected networks, users generally need to send traffic across multiple nodes in order to achieve results.

"We peer with networks like Microsoft, Google and Amazon," reveals Fox. "The traffic goes from our network, which is a fibre network, throughout California and the west to their network, without ever going over the commercial internet." It is peering with these large private networks that allows CalREN to achieve such remarkable performance, and it also presents the option of offering novel cloud services that avoid the commercial internet. Another important resource in terms of peering is the Pacific Wave peering service, which is provided by the Pacific Northwest Gigapop, and allows for international connectivity. Pacific Wave is the main route by which advanced networks cross the Pacific Ocean and by which California research universities connect to the rest of the world.

A PACIFIC PLATFORM

Currently, however, some of the most exciting work being undertaken by CENIC concerns the Pacific Research Platform (PRP) – an ambitious project to integrate various networks including the US Department of Energy's Energy Science Network (ESnet) and its DMZ model into a high-capacity 'data freeway' for scientists and researchers. The National Science Foundation (NSF) has awarded a grant of \$5 million to support the project over five years, and more than 20 research-performing institutions have joined the partnership in order to be part of the developing network – including all 10 University of California (UC) campuses. Researchers at UC San Diego and UC Berkeley in particular have played a leading role in the project.

The PRP's data-sharing architecture allows for end-to-end connections throughout the network with a speed of not less than 10 Gbs⁻¹, although speeds of up to 100 Gbs⁻¹ are possible. Because it is a dedicated environment for science data and avoids the commercial internet, it is also highly secure and large amounts of data can be transferred without risk. These impressive capabilities make it the ideal tool for pursuing data-intensive collaborative research projects concerning topics from cancer genomics to climate modelling, and CENIC is working towards making it a reality for researchers across California, the Western US, and among international research and education network communities.

CORPORATION FOR EDUCATION NETWORK INITIATIVES IN CALIFORNIA (CENIC)

OBJECTIVES

- To connect California to the world and advance education and research statewide by providing the world-class network essential for innovation, collaboration and economic growth
- To operate the California Research and Education Network (CalREN), a high-capacity network designed to meet the unique requirements of over 20 million users

PARTNERS

Based in the US:

University of California (10 campuses)

California State University (23 campuses)

California Community Colleges (112 campuses)

Stanford University

University of Southern California

Caltech

California Department of Education (10,000+ schools)

California Public Libraries (1,100+ libraries)

FUNDING

CENIC is funded by its members, who also serve on its governing board.

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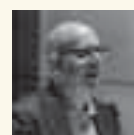
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DR LOUIS FOX is President and CEO of CENIC, a non-profit corporation that represents the common interests of California's education and research communities in achieving

robust, high-capacity, next-generation internet communications services. Prior to joining CENIC in 2012, he served for nearly three decades as a faculty member, researcher and senior administrator at the University of Washington and at Duke University, USA.





Securing data during computation

Between US \$375-575 billion is lost every year due to cybercriminal activities. **Professor Marina Blanton** is helping to improve this issue by creating systems so organisations can jointly compute on data without sharing their specifics, and by making sure that private data remain protected, even when being outsourced to the cloud

Why were you first drawn to information security, privacy and applied cryptography?

I started working on security-related topics during my Master's degree at Ohio University in the US. My research was highly empirical and allowed me to make only limited conclusions about the phenomena I was observing. As a result, for my PhD I was looking to explore areas better suited to formal analysis and rigorous scientific evaluation. My work on privacy-related topics and applied cryptography started early in my PhD studies. These topics are very important for modern society where many aspects of one's life are captured and stored in a digital form.

Can you introduce secure computation?

Secure multi-party computation refers to the ability of multiple participants to jointly compute on their respective private data without revealing information about those data to each other, except for the agreed upon computation outcome. A secure solution in this framework must guarantee that interactions are protected through provably secure cryptographic techniques, and it is not possible for any contributor or outsider to learn unintended information about other participants' data.

A range of applications benefit from such techniques; they include computation activities spanning sensitive databases that belong to different organisations (eg. medical records) and commercial applications (eg. testing for predisposition to a genetic condition without revealing one's DNA), among others.

How does this relate to secure computation outsourcing?

When such techniques allow computation to be performed securely by entities who are different from the data owners, they become suitable for secure computation outsourcing. In that setting, one or more clients utilise one or more external

servers to perform computation on their private data in such a way that it is not possible for the servers to learn anything about the data they handle.

Has the advent of cloud computing increased the need for greater privacy-preserving computation?

Cloud computing is an attractive mechanism for using abundant computing and storage resources of large service providers and lowering one's operational costs. The use of external resources, however, requires clients to relinquish control of their data to third parties. Because of a lack of transparency and inability to control what happens to one's data once it is outsourced to the cloud, there is a resistance to use cloud computing for computation with proprietary, private or otherwise sensitive information. The need for privacy-preserving computation has existed for a long time, but the ubiquitous use of cloud computing has taken this need to a new level and placed unique demands on the security objectives that must be met.

Can you introduce Private Distributed Computation Compiler (PICCO)?

PICCO is a compiler that allows a program written in the popular programming language C to be converted into a secure implementation of the same functionality. Our goal was to enable programmers without extensive knowledge of secure computation techniques to build a solution specific to their desired computational task.

Using PICCO, a programmer specifies what variables will hold private data. Our compiler then transforms the program into an equivalent in which all private data are fully protected. The resulting program can be used for secure joint computation or secure outsourcing with provable security guarantees. The compiler also supports optimisations that

help improve the runtime of the resulting secure implementation.

How does PICCO improve security of outsourced computation over conventional methods?

The current practice is to use no data protection when placing one's computation with cloud providers. Instead, clients sign a contract with the service provider that can include provisions for preventing data sharing of the client's data by the cloud provider. With PICCO, private data is never available in an unprotected form to any entity other than the data owner. Therefore, no employee at the cloud service provider will have access to clients' data. Similarly, if systems are compromised by an external attacker or malware, no one will be able to extract meaningful information about the data.

Can you provide a brief insight into your activities with biometric data protection?

Given a rapid recent increase in the use of biometric data in various applications and highly sensitive nature of such data, we develop custom solutions for securely computing with different biometric modalities or securely outsourcing such tasks. The security requirements are as strong as before, and the main goal is higher efficiency than what generic solutions provide. In addition, we develop techniques to efficiently verify that the result of outsourced computation is indeed correct.





Strong data protection

Data security is a prominent concern for businesses and governments alike, and it can prevent such organisations from making the most of the information they have to hand. Researchers at the **University of Notre Dame** are working on secure computation methods that allow outsourcing and collaboration without fear that data will be compromised

KNOWLEDGE IS POWER. Data on everyday citizens, consumers or patients has always been valuable, but in a digital world such records can be stored in quantities that would previously have been impossible. The rise of big data is a double-edged sword, in the sense that vast repositories of information represent a vulnerable target for malicious agents; indeed, there have been several high-profile cases of data theft in recent years.

And there is another challenge, too. It is very difficult to effectively mobilise data that are retained in silos. Take medical data as an example; patient records are commonly kept in disparate systems maintained by different organisations, effectively preventing them from being examined comprehensively. To compound the problem, even if collaborating organisations

computation – a processing method whereby participants can collaborate on computation without revealing their own private data. For example, imagine hospitals A, B and C each have patients with the same rare medical condition. Each on their own does not have enough data to determine the most effective treatment for the condition, but they would have enough data if they combined sources. However, because of privacy issues, legally they cannot freely share their patients' records. Blanton's work with secure computation would change this by enabling hospitals to participate in a joint computation through a secure system and share results without uncovering any private, medical details about the patients.

Secure computation must be absolutely watertight in order to be useful, because

were permitted and willing to share their information for joint computation, their information would be more vulnerable to attack during this process.

SECURE IN THE KNOWLEDGE

The solution, according to Professor Marina Blanton and her colleagues at the University of Notre Dame, is secure

end-users must be assured that nothing about their data can be discovered. Blanton and her colleagues have been pursuing a project that could make this sought-after ability a reality – unlocking much of the value that is currently locked away in data silos all over the world. The project has led to the development of the Private Distributed Computation COmpiler (PICCO), which is able to translate a general-purpose program, written in an extension of the C programming language, into a secure implementation. "As a community, we've made large leaps toward improving performance of secure computation and outsourcing techniques and developing necessary components to make general-purpose secure computation possible," Blanton summates.

KEEPING DATA IN THE DARK

There are many aspects to this challenging work that require the researchers' attention, but one factor that is particularly key is the development of what Blanton and her team refer to as 'data-oblivious' algorithms. With standard algorithms, many steps within the computational task depend on the original input – but this is not a secure way of handling that original input, because it allows the opportunity for data to be leaked at the processing stage. Data-oblivious execution bucks this trend by making computation steps independent of the data; the data can remain hidden with no loss of function.

The vast majority of data structures and algorithms are currently 'non-oblivious' and naive attempts to address this often result



SECURELY COMPUTING WITH PRIVATE DATA

OBJECTIVE

To enhance the frontiers of current knowledge for preserving data privacy and integrity through innovative research.

KEY COLLABORATORS

Dr Mehrdad Aliasgari, California State University, Long Beach, USA • **Dr Yihua Zhang**, University of Notre Dame, USA

FUNDING

National Science Foundation (NSF) • Air Force Office of Scientific Research • Air Force Research Laboratory

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MARINA BLANTON received her PhD from Purdue University in 2007. Her research interests are generally in information security, privacy and applied cryptography. Her recent projects span areas such as secure computation and outsourcing, integrity of outsourced computation and storage, private biometric and genomic computation, privacy-preserving systems for medical and social networks, authentication and anonymity.

in significant increases in computation time. The task for Blanton and her colleagues is to construct data-oblivious alternatives that are as close in time efficiency as possible to their traditional counterparts.

The researchers have already made significant progress in producing data-oblivious algorithms suitable for secure floating-point arithmetic and working with graphs; these algorithms have been integrated into the PICCO compiler. "The broader impact of this work includes societal benefits such as safer practices in handling private or sensitive data when it is being used in any type of outsourced and/or joint multi-party computation," Blanton enthuses. "This is directly applicable and useful to government, health, military and commercial sectors, to name a few."

THE DEAL WITH OUTSOURCED DATA

Blanton is also applying her work with secure computation to data when they are outsourced to the cloud or a storage service. "Current on-demand computing and storage offer attractive opportunities from the perspective of computing resources and infrastructure," she notes. Not only do these services enable organisations to meet their need for increased bandwidth or storage without having to build their own infrastructure, oftentimes these services are faster and cheaper. "However, significant security, privacy and result verifiability concerns are intrinsic to these services, making them outside the reach of organisations who work with sensitive data," Blanton warns.

To understand Blanton's concerns, one only needs to consider how data is handled when it is outsourced to the cloud. Not only are data put outside the control of the owner, but even in the context of best practices, data are likely

to only be encrypted while at rest; they have to be decrypted to be used in computation, meaning they can be retrieved from the computer's memory by someone with access to that system, or they can be altered. Therefore, if data owners want to use the result of an outsourced computation, they must then verify that the computations were performed as prescribed.

SECURE OUTSOURCING AND VERIFICATION OF RESULTS

Blanton and her colleagues are working on techniques to make sure that data are secure no matter what environment they are used in. One area in which they are applying these techniques is biometric data. Biometric research often involves running computation on large amounts of data, making cloud computing very appealing in order to reduce the burden on in-house memory and processing power. However, biometric data is extremely personal data; as such, medical organisations have not been able to seize on the benefits that cloud-computing provides in the interest of maintaining privacy. "The US National Institutes of Health (NIH) used to maintain a database of anonymised DNA sequences for researchers to use, but the database was taken down after it had been shown that the individuals whose DNAs were included in the database could be re-identified," Blanton shares.

Excitingly, her work in secure computation combined with her activities in secure outsourcing could bring the database's benefits back within reach and without patient re-identification concerns; her techniques would allow collaborative and outsourced computation on data from multiple sources where no information is revealed except the final outcome. Moreover, her techniques are robust enough to ensure that the results of the outsourced computations are verifiably correct.

A COLLABORATIVE ENDEAVOUR

Blanton's secure computation techniques are not only revolutionary, but they are enabling collaboration and computation that is not possible otherwise – one only has to look at her success in developing specific methods for iris images, voice recordings, fingerprints and DNA sequences to find this to be true. Even just considering fingerprints, Blanton has created protocols that allow for secure comparison of two fingerprints from different data owners in just a few milliseconds.

Blanton is excited to continue her working with colleagues to improve secure computation, secure outsourcing and data verifiability, as well as preserving data privacy in general. "We are at the point where secure computation and secure outsourcing techniques are efficient enough for complex and diverse computations, and I expect their adoption in practice to only increase," she concludes.

Tommy Frank was born with a hole in the heart...

Now he's one of the UK's brightest young boxers

Thanks to research into heart disease, congenital problems like the one Tommy had can now be routinely treated.

Heart Research UK has been funding research into the prevention, treatment and cure of heart disease since 1967, enabling more patients to benefit from advances in heart surgery and treatments.



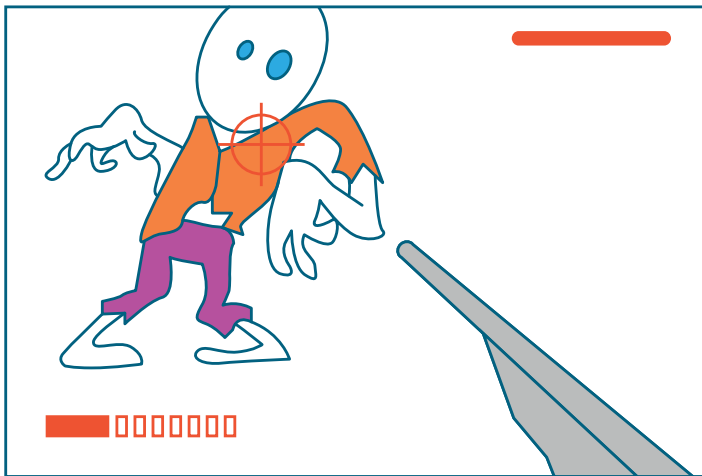
With your help we can continue funding this pioneering research so that more people like Tommy can live healthier, happier and longer lives

To find out how you can help HRUK, visit: www.heartresearch.org.uk or call: +44 113 234 7474



TECH ON THE MIND

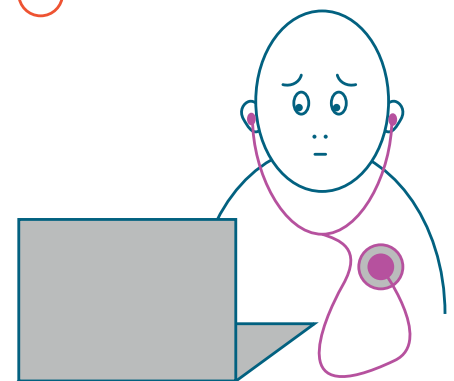
Recent years have seen our use of technology skyrocket. We spend more and more of our waking hours in a staring match with the computer screen and the psychological impact of this can be both good and bad



Technicolour dreams are a modern invention, secondary to the advent of colour television. Older adults who were exposed to black and white media, principally television, before experiencing colour media consistently report dreaming in a more greyscale palette. Conversely, younger adults first exposed to colour media typically recall dreams in vivid colour.

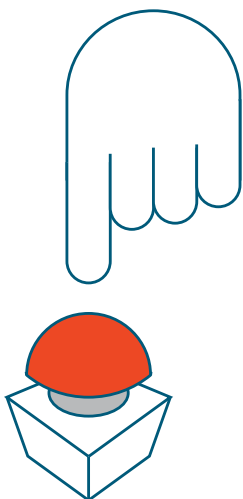
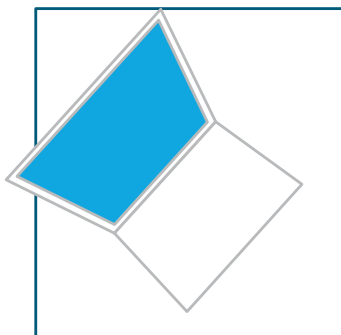


Decision making and visuospatial skills are put into practice when one plays a first-person shooter video game, recent research shows. In learning to respond to a given visual stimulus (eg. a Nazi zombie) with the appropriate action (eg. tapping the trigger), the player's ability to rapidly relate stimuli with calculated responses is trained.

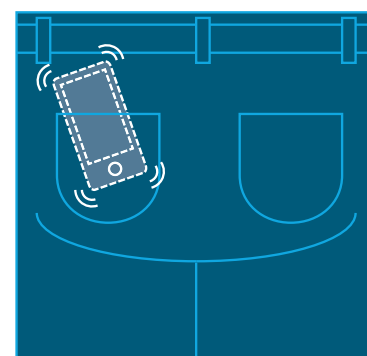


Cyberchondria is a newly-coined phrase assigned to those whose hypochondria is fuelled by the likes of WebMD and other online diagnostic resources. Intended to reduce the burden weighing on traditional healthcare services, these websites may actually represent a considerable problem for medical professionals, as we approach doctors ever more frequently (and hysterically) with our e-diagnoses.

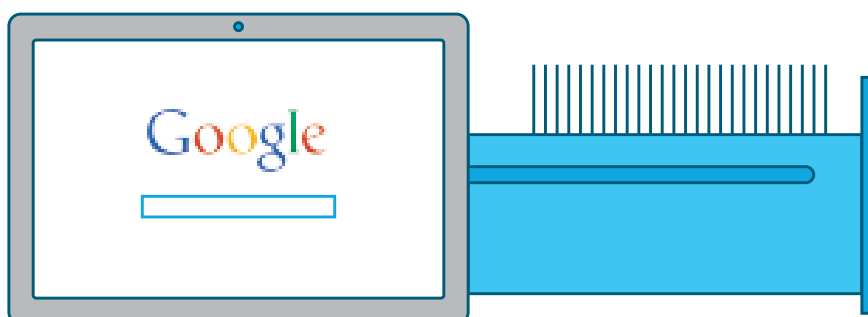
Sleep loss is a common consequence of late night screen watching. Blue wavelength light emitted by backlit screens disrupts the circadian rhythm, tricking the brain into thinking it is daytime. This effect is associated with a drop in melatonin, a hormone that promotes sleep. Regular night-time computing, and thus chronic melatonin deficiency, is not only a recipe for fatigue, but also a risk factor for some cancers.



Phantom Vibration Syndrome is experienced by 68 per cent of mobile phone users, reports a survey by the *British Medical Journal*. Aptly named, this term refers to the sensory hallucination of a vibrating phone in one's pocket. It is believed that the brain misinterprets unrelated tactile stimuli, triggering the familiar perception of a buzzing mobile.



Chronic gaming can have a detrimental effect on how we control impulsive actions. This 'proactive executive control' could explain why violent video games are thought to promote aggressive behaviours. However, a recent meta-analysis failed to support this latter point, corroborating instead reports of enhanced visuospatial cognition.



The Google Effect denotes our search engine-trained faculty of knowing where to find information, rather than recalling the information itself. Psychologist Betsy Sparrow of Columbia University sees this cognitive shift as no bad thing; merely an indication that our brains are adapting to new technology.

the last word:

Regreening Europe



Fresh from the 2015 EU Sustainable Energy Week, member of the European Parliament for Luxembourg's Green Party **Claude Turmes** discusses the need for Europe to regain its position as a world leader in renewables

You tweet a great deal about renewable energy. Do you believe the EU offers this sector adequate support?

I am passionate about renewable energy because it offers a potential solution to finally resolve climate change. In my eyes, renewables did not feature prominently enough in this year's Sustainable Energy Week. This is related to the pressure the EC is under and the fact that the use of renewables is therefore slowing down in certain member states. I believe I play an important role in reminding people of the importance of energy efficiency, interconnectivity, renewables and bringing those renewables to the market.

Is Europe a world leader in sustainable practices and technologies? What more can the region do to this end?

I think Europe certainly was the world leader and, indeed, still leads in wind technologies. However, we have lost ground, for example, in photovoltaics cells and modules (PV – a form of solar energy) to China. In short, we need to get our act together! We are in a unique moment in world energy history because new technologies such as PV and wind energy (which were basically developed in, and championed by, Europe) have now been taken up by the rest of the world. In 2014 alone, China installed 23 gigawatts (GW) of new wind capacity and more than 10 GW of new solar energy capacity. Similar trends are emerging throughout Asia and parts of Africa (South Africa) and South America (Chile).

Although many people realise that the future is all about renewable energy, its use is slowing because of the pressure of economic factors and the strength of longstanding energy companies. As a result, Europe wishes to continue using oil and coal rather than accelerating the transition to wind and PV. The continent requires the EC's leadership to improve the link between research and development – we tend to be weak in getting our research to market.

You are a member of the European Parliament Committee on Industry, Research and Energy and rapporteur on energy efficiency. To date, what impact has the Energy Efficiency Directive (EED) had on Europe?

The EED is in its early days when it comes to implementation. We have seen that most governments are on their way to implementing it, and we know that these results will be much more visible over the next three years. Denmark, for example, is a success story in terms of building

an energy efficient economy. The EED pushed many member states to establish successful energy savings measures.

It's important to understand that, generally speaking, Europe's energy demand is decreasing – electricity demand is flattening, for example. That is not only the result of the economic crisis; two-thirds of the reduction can be linked back to policy instruments such as the EED, the Energy Performance of Buildings Directive (EPBD), ecodesign and energy labelling directives.

In June this year, the EC reviewed progress towards hitting 2020 targets for renewables. Are member states on the path to meeting these targets?

We have a mixed picture. Countries like Sweden are advancing, and some Eastern European countries, such as Estonia, Lithuania and Romania, are already close to achieving their targets. This is linked to the fact that these European countries have very low national targets because they are mostly based on gross domestic product (GDP).

From examining the figures, we can see a slowing down of investment in renewable energy. This is especially clear in countries like Spain, which was a champion in renewables, with more than 23 gigawatts of wind installed from 2008-12. However, there has been no further investment in wind since the beginning of 2014. Spain will not be on track unless the new government takes action to alter the country's current position. It is a wakeup call, both for the EC to be more vigorous in implementation and take up new initiatives and, most importantly, for more pressure to be placed on certain governments to deliver on renewable targets.

In your view, how might challenges facing the implementation of renewables be overcome?

Sustainable Energy Week is this year's most important communication exercise on energy. The event provides an enormous forum for education, informing people about what is going on locally, nationally and internationally, and brings external input to Brussels. It solidifies the important link between European energy policy and the reality in local and national areas. It is a real catalyst for the transition of energy in Europe.

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