SCIENCE OMEGA REVIEW 03

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The Faculty of Medicine in Hradec Králové started its activities on 25th November 1945 as the first university faculty in East Bohemia. Being a part of the prestigious Charles University, it was possible from the very beginning to establish both a high-quality teaching staff and an effective departmental structure. Throughout its whole existence, the Faculty of Medicine in Hradec Králové has been among the top Czech university institutions.

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Introduction

Editors
Lauren Smith & Amy Caddick

Ireland played host to the EuroNanoForum in June, where industry and academia at the forefront of nanotechnologies, as well as government representatives, discussed everything big on the small scale. With a revolutionary impact on science and society, the widespread integration of such diverging technologies is likely to leave few sectors untouched.

Technologies are increasingly breaking down the traditional boundaries between sectors and, as a reflection, research programmes are becoming progressively more multidisciplinary, maximising the benefits offered by a diverse skill set. Novel materials offer one particularly fruitful area for growth, and this edition of *Science Omega Review* considers the full process surrounding innovation and commercialisation. With the regions particularly strong in discovery not necessarily correlating to those maximising the financial benefits, this is one aspect where economic elements deserve greater attention.

Life sciences developments, incorporated with pharmaceutical influences and healthcare, continue to dominate the social and scientific arena. As the population demographic changes, so too do the demands on the creation and development of knowledge in the sector to ensure a strong evidence base and, as a result, the best patient outcomes.

As all of these issues mature, moving to bi-monthly publication will allow *Science Omega Review* to explore developments at the forefront of global focus, particularly from the US and Canada, highlighting successful approaches, shared difficulties and priorities for future funding.

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ENF2013: the crest of a nanorevolution?

EuroNanoForum 2013 brought together key players from across the global nanotechnology community to discuss the challenges and opportunities facing this diverse field, as Editor Lauren Smith reports

Super simulations

In the second of a two-part special, Richard Walker shares with Editor Lauren Smith the aims of the Human Brain Project's work on the capabilities and limitations of supercomputers

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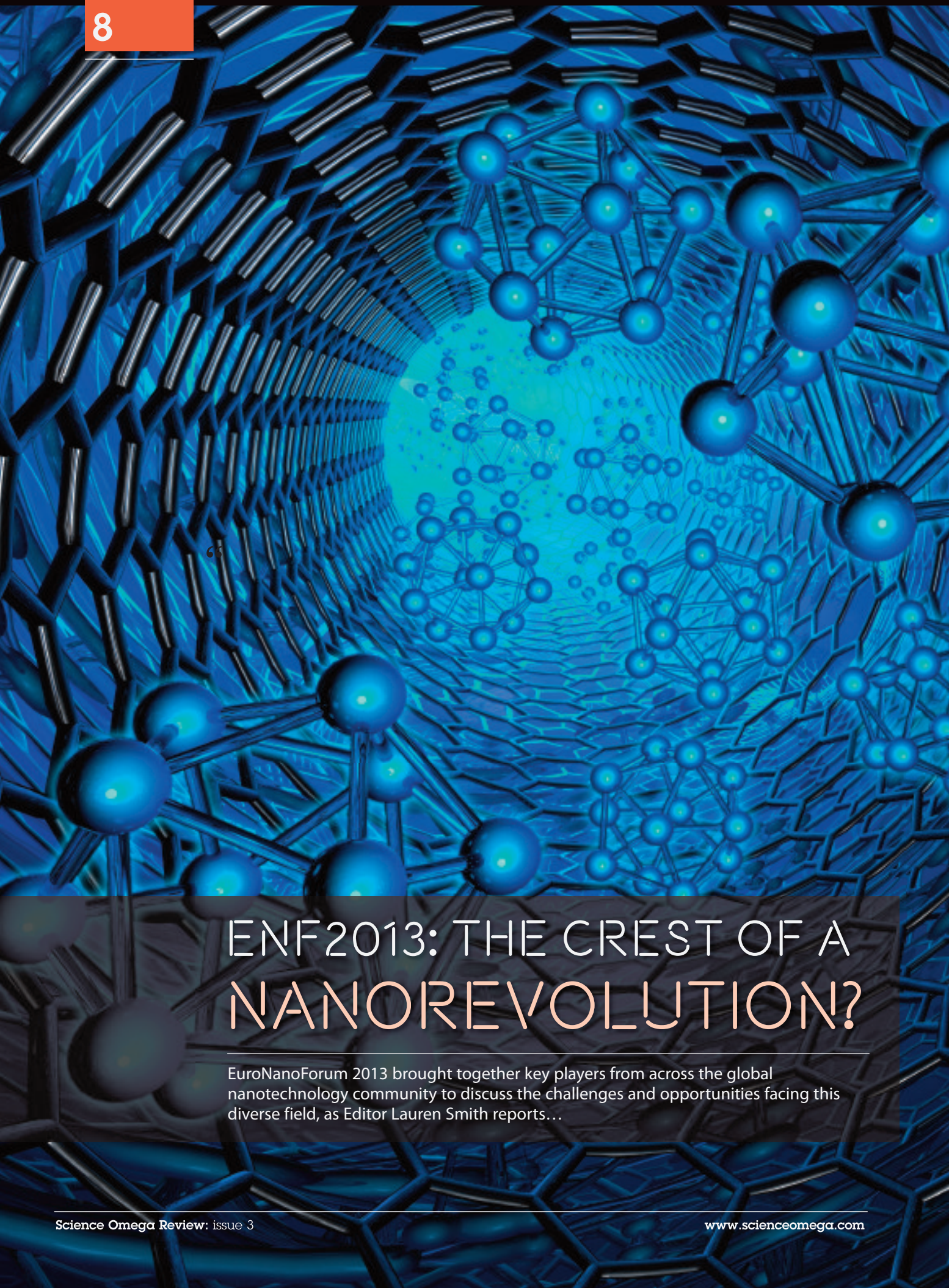


ENF2013: THE CREST OF A NANOREVOLUTION?

EuroNanoForum 2013 brought together key players from across the global nanotechnology community to discuss the challenges and opportunities facing this diverse field, as Editor Lauren Smith reports…

"EuroNanoForum 2013 will showcase a key example of new technologies – nanotechnologies – in which Europe has a leading interest and leading position. Indeed, in Horizon 2020, the European Commission has identified nanotechnologies as one of the EU's key enabling technologies (KETs). The Horizon 2020 proposals put KETs in a prominent position, through an integrated approach with strong support for cross-cutting KETs activities, including larger demonstration and pipeline projects for promoting innovation and deployment of KET-based products and processes in the marketplace." So said European Commissioner for Research, Innovation and Science, Máire Geoghegan-Quinn, in her video address to a packed audience at the Conference Centre Dublin in June.

As one of the final events under the auspices of the Irish Presidency of the European Union, Dublin hosted this year's EuroNanoForum (ENF2013), with around 1,500 delegates in attendance, highlighting cutting-edge nanotechnology and nanomaterials. The forum, co-hosted by Enterprise Ireland and Spinverse, emphasised the strategic importance of nanotechnology for societal and economic development, with a range of prominent speakers from government, industry and academia coming together to talk all things nano.

Nanotechnology and industry

Speakers discussed the significance of understanding industrial needs, along with focusing research and development through appropriate funding instruments. Over the three days of the event, broad consideration was given to the identification of areas where nanotechnology is most likely to have a vital impact: from healthcare to energy, manufacturing to communications, and beyond.

Herbert von Bose, Director of Industrial Technologies at the European Commission's DG Research and Innovation, discussed why EU leadership in nanotechnology is critical.

"Nanotechnology is an area that is very much at the forefront of the political arena worldwide," he commented. "If we look what is happening at the European Commission, in the framework programme, up to €3.4bn has been spent in nanotechnologies, and this covers the entire technology and economic value chain."

Noting how far things have progressed since the initiation of the ENF a decade ago, he continued: "The first nanotechnology conference was very scientific. Now we see many more industrial applications, and when you see industrial applications you immediately ask the question – what does the citizen expect? The citizens expect safe, environmental and sustainable products on the market and for that reason, since the very beginning, we have taken the approach of combining nanotechnologies with all of the surrounding questions about safety. We have already spent €200m for safety, environmental and regulatory related research."

Herbert von Bose: "Nanotechnology is an area that is very much at the forefront of the political arena worldwide"

This is something he went on to discuss in more detail at a focus session on nanosafety, which itself led to a lively debate about the perceived and actual risks associated with nanotechnology across a range of industry sectors.

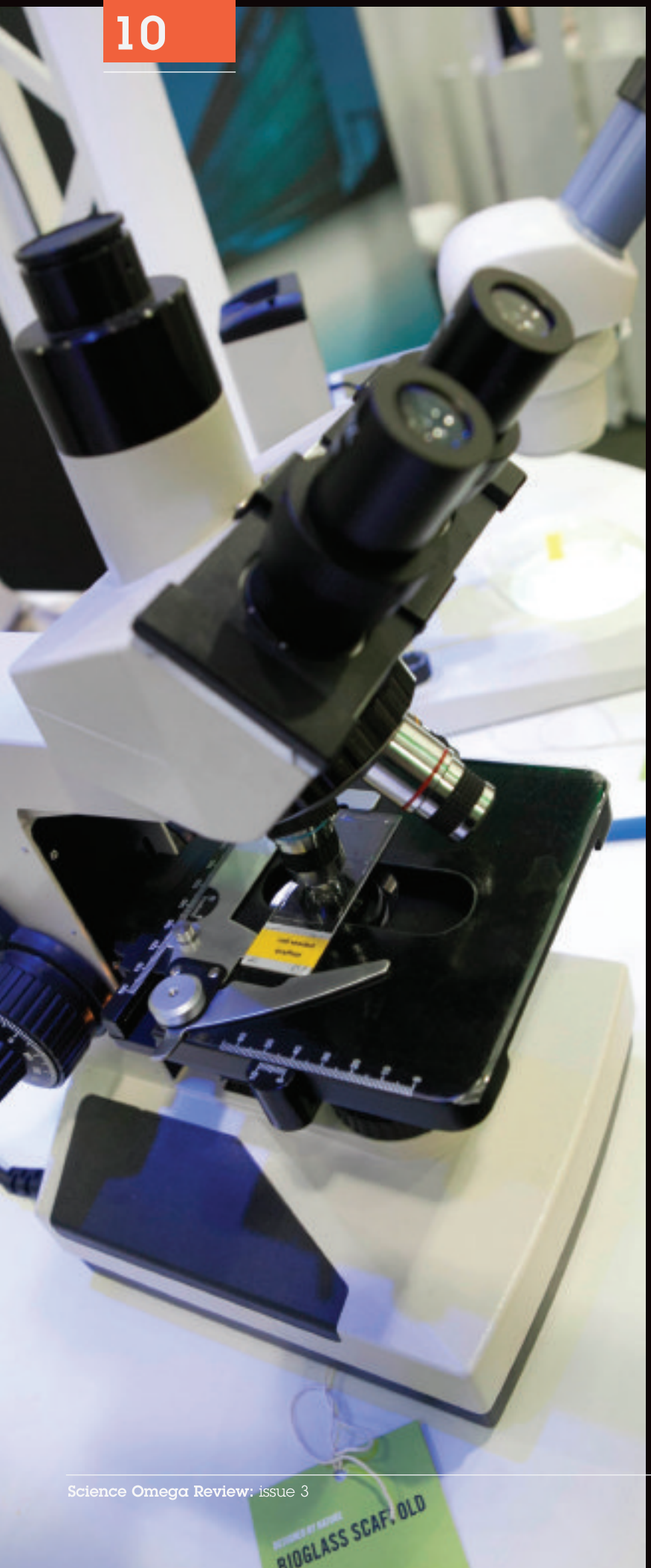
"The other important element for us," von Bose said, "is that we would like to see technologies in general, and nanotechnologies specifically, go nearer to the market. We have this problem in Europe that we are very good at research, in knowledge creation – that is true not only for nanotechnologies, but all different domains – but we are not so good at bringing it to the market."

He outlined how partners from across the Commission are working to improve upon this in order to successfully bridge the gap, but stressed that more work needs to be done.

Ireland's Minister for Education and Skills Ruairi Quinn followed this up with an explanation of the place of nanotechnology in the recent agreements

Ruairi Quinn: "The next generation of manufacturing industries require radical and continual innovation…"

"Nanotechnology will feature prominently in the return to growth and the industrial leadership pillar of Horizon 2020.



made under Horizon 2020. "Nanotechnology will feature prominently in the return to growth and the industrial leadership pillar of Horizon 2020. The scale of the budget for Horizon 2020 is testament to the importance attached to continuing to invest in Europe's science base," he told attendees.

Detailing the national role, he highlighted the positive impact that investment in the science base has had in Ireland's industrial development, by way of example.

"Firstly, we have sought to invest in people and also in infrastructure, to build the science base across many areas of scientific research in both our higher education institutions and indeed other public research organisations. Secondly, we have directly supported the enterprise sector to help individual companies to build their capacity both for research and development. This investment in scientific excellence has delivered many positive impacts. For example, it has influenced enterprise and economy – creating high-value jobs, attracting and nurturing business and science and ensuring that Ireland is connected and respected internationally," he said.

"Sustaining the manufacturing sector into the future in Ireland and across Europe is fundamental to economic prosperity. The next generation of manufacturing industries require radical and continual innovation focused on processing technologies and utilisation of novel or new materials."

This view was supported by Ireland's Minister for Research and Innovation Sean Sherlock, speaking at the forum's closing plenary address, who explained how nanotechnology would be promoted further under the industrial leadership section of Horizon 2020. The specific objective, said Sherlock, is to build and maintain global leadership in such enabling technologies and new production processes. He passed on these weighty targets to Professor Dainius Pavalkis, the Minister of Education and Science for Lithuania – whose country now takes over the baton of the Presidency of the European Union. Pavalkis committed to strongly supporting the scientific community and the interaction of researchers and business across the region.

Adding to the industry perspective brought by speakers from international corporations like INTEL down to the newest of university spin-off companies, Dr Gernot Klotz, Executive Director of the European Chemical Industry Council (CEFIC), expanded further on the need to have confidence in nanotechnology. "Europe is facing complex and unique societal challenges – with the ageing population, moving to a low-carbon economy, [the need for] more security, all these kinds of topics. They can only be found [by] mastering the technologies," he argued.

Going on to explore nanotechnology development in Europe, he pointed to the vital role it has to play in bringing value chains together and enabling integrated technologies that are at the heart of industry. It is essential, he claimed, to push innovation forward if Europe is to lead the global race on essential technologies, but also warned that "Europe is losing ground, with a stagnation of public investment" in many areas.

The rise of graphene

One of the recurrent topics throughout the forum was the role of what has been dubbed a 'supermaterial' – graphene. Renowned Nobel Prize winner Professor Andrea Ferrari, Director of the Cambridge Graphene Centre, took to the stage to discuss the Graphene Flagship Programme, which has received an award of €1bn over 10 years from the European Commission.

Describing the considerable beneficial properties of graphene that are open to exploration, he explained the many possibilities offered particularly by its strength, unique optical properties and flexibility. For every new material, he suggested, the key applications may not be what first come to light. "It's very important to link the academic research with industry," he said, "because often it is in industry where the real applications are developed and academia that will solve some of the problems that are present in industry."

The vision, he outlined, was to take graphene from the state of potential to the point of revolutionising multiple industries, stating that it is only the latest in a wave of such new materials that are ripe for investigation. "The reality is that there are a variety of these new materials and they are multidimensional in nature and their properties are different from one another," he asserted, with each having the potential to be tailored to particular functions.

Following his plenary address, Ferrari told members of the gathered media that one of the immediate challenges for the flagship was coming to an agreement with the European Commission about the best way to implement the programme and allocate the funding. Whilst welcoming this unprecedented level of funding in materials science, he warned against the dangers of getting overly tied up in bureaucracy and reports, or of spreading the funding too thinly – which would not achieve the maximum impact that the project is capable of. He warned of the "huge potential for disaster" in this respect, if bold moves are not taken in its implementation.

IP protection

Dr Martin Kemp, from the UK Technology Strategy Board's Nanotechnology Knowledge Transfer Network (NanoKTN), stressed that the protection of intellectual property for commercialisation is a complex matter. "If you look at something such as graphene," he said, "the number of patents filed by the UK is quite low, compared to elsewhere. But it's important to look at the value of the patents, as opposed to how many you have. It can be a slightly disordered picture, since one patent may be worth more than a hundred others combined.

"I believe that the UK is quite selective in the way it patents. I don't see that as particularly problematic, but it is almost impossible to measure this accurately, since patents are normally looking to future products and predicting a market value. Universities have thousands of technologies that they could patent, but they need to be selective. An ability to look ahead to be able to select the best ones will make money, otherwise it's just building a very expensive portfolio."

Looking at nanotechnology more broadly, he went on to say:

"Nanotechnology is a key enabling technology and advanced materials will impact on almost every market sector. In reality, there are many different nanotechnologies that are applied in many different application fields. However, each one will require its own commercialisation period before being introduced to the market. Although the UK is much stronger than many people realise, the key issue is making money out of nanotechnology and that is the challenge: to add commercialisation to the already impressive academic papers."

Enabling into the future

From considering the vast applications of nanotechnology in everyday life to the industrialisation and commercialisation of nanoproducts, what came to the fore was the importance of cross-disciplinary and international collaboration – balancing this with creating economic benefit for specific countries and regions may be one of the greatest challenges to be faced. Regardless, nanoscience and the resulting products and applications are set to have an even greater impact on society in the next decade than in the last – and further into the future, are set to revolutionise every area of life.

No innovation in isolation at the nanoscale

Dr Mihail C Roco, of the National Science Foundation, talks to Editor Lauren Smith about the need to strike the right balance in nanotechnology…

We have to support, in parallel, discovery, invention, innovation and the pursuit of commercialisation and societal needs, because innovation alone is not self-sustainable.

The first EuroNanoForum was hosted in 2003 in Trieste, Italy, and the event has progressed in scope and size in the intervening years. Dr Mihail C Roco, Senior Advisor for Nanotechnology at the National Science Foundation and an architect of the National Nanotechnology Initiative in the United States, was present at the first forum and has borne witness to a number of significant developments in the arena over this period, as he discusses with Editor Lauren Smith.

"Firstly, we have started to develop the foundational knowledge of nature to understand matter from the atomic and molecular levels, to understand life takes place at the transition of the nanoscale. We've started to have some control of matter at the nanoscale to create new products," says Dr Roco. "A second major development has been the formation of the global interdisciplinary nanoscale science and engineering community, which is focused on similar goals and built around a fast-growing research infrastructure and educational programme.

"Another important advancement has been the creation of a library of nanostructures, such as carbon nanotubes, quantum dots and sheets of graphene, which are the building blocks for future devices and systems. We are moving towards being in a position to build a periodic table for nanostructures based on the internal structures, not on the external boundary measurements."

Roco identifies as an essential element of progress the emergence of completely new skills in nanotechnology, some of which have resulted from the interface with other fields and others developing as spin-off domains of nanoscience, such as spintronics and plasmonics.

Other areas that have surfaced include plasmonics, nanophotonics, metamaterials, carbon nanoelectronics, molecular design to create hierarchical systems, DNA nanotechnology and nanophysics. But this is only the beginning.

"There are even newer fields that have started to become apparent in the last few years," Roco highlights, "like opto-genetics, additional branches of synthetic biology that are enabled by nanoscience, and nanoengineering in construction, amongst others.

"What is central is that nanotechnology was conceived in 1999-2000 as a broad-based technology that would create new fields of research, which is proving to be the case. In 2000, we defined nanotechnology as an intermediate length scale, between a single atom and 100 molecule diameters, where the fundamental properties and functions of materials and devices are established and can potentially be changed easily and economically when we have control at the nanoscale.

"We are now on the way to learning how to do it, but we are just at the formative phase. I think

that control at the nanoscale will require another 5-10 years in several areas, for example self-assembling, device quantum effects, nanosystem design and emergent behaviour of large nanoassemblies, to establish more general basic tools for direct measurement, direct and predictive simulation, and the basic principles for collective effects. However, progress in nanotechnology has been very fast so far, and it has been supported by an international community. Since the National Nanotechnology Initiative was established in 2000, more than 60 other countries have created nanotechnology programmes looking at using new properties and functions."

Research directions for societal needs in 2020 have been discussed in more detail in a recent report.[1] Roco is keen to stress the need to take a long view in technological development, based on new approaches to research.

"There are many people that have tried to ask universities to work in the traditional Pasteur's quadrant with goals that are defined in a particular way, such as a pre-selected application. What we're looking to do in nanoscience is to have vision-driven basic research, looking at novel targets that are beyond a predetermined application."

There are a number of approaches that can ensure international collaboration in science and technology, though Roco feels that nanotechnology in particular offers even greater opportunities for cooperation.

"What is needed, specifically in nanoscience, is to have multidisciplinarity in academic collaboration at the pre-competitive stage, with open source innovation in industry in the competitive phase," he outlines.

"Although there are many methods of interaction, there are just a few that are the most important. One is forming project-oriented networks with a combination of discovery, invention, and innovation goals that generally need to be cyber-enabled. Another is creating relatively large multidisciplinary university, industry and government centres. In Europe, there is the Grenoble nano-micro centre, the IMEC/Aachen/Eindhoven triangle, and more recently in Germany you have 'Silicon Saxony'.

"In the US Nanoelectronics Research Initiative, six companies, over 30 universities in 16 states, NSF and NIST are connected in a network that shares the medium and long-term goal of creating the next generation of logic and memory devices. Albany, New York state is home to the largest nanotechnology centre in the world based on the volume of activity, covering areas from discovery to commercialisation. This attracts collaboration from the industry around the world, NY state and US agencies. There is a college fully dedicated to nanoscale science and engineering.

"It's interesting – in Asia there are efforts to develop similar approaches implemented on fast-track through creating focal point nanocentres, such as Japan's Tsukuba Innovation Arena for Nanotechnology near Tokyo and China's Nanopolis in Suzhou.

"Such nanocentres are also another positive way to develop international collaboration because they all have partners from across the world. Collaboration is often connected to educational programmes, which are an increasingly prominent feature as long distance collaborations."

Roco contends that governments must pay close attention to the elements surrounding innovation, such as the development of commercialisation and societal application.

"By definition, the role of government is to create the conditions for the whole country to develop in new areas, with growth and responsible development," he explains. "This has five steps. The first step is to support scientific discovery. The second is to have inventions of new devices and new processes. The third is innovation – to use discovery and innovation in applications and other fields than originally intended for economic benefits. After that is where commercialisation and then broader societal implications come into the arena."

He underlines that innovation is just one of the steps in a string of activities. "If we focus on innovation alone for five years, for example, the whole system may become weaker because we will have fewer discoveries and inventions to serve as basic resources for the innovation process. We have to support, in parallel, discovery, invention, innovation and the pursuit of commercialisation and societal needs, because innovation alone is not self-sustainable. It's a risk to shift investment from discovery, invention and societal implications to soley innovation in the long run. This appears to be economically successful only for a short period.

"In the long term, there must be a balance between all of these steps," Roco concludes. "At this time, innovation is a key step in order to get societal recognition of the benefits of the new technologies, but it's very difficult to extrapolate the same methods from one country to another. In nanotechnology, as in wider scientific development, innovation itself cannot be sustainable in isolation, because you need the pipeline and the follow-up. Innovation is essential, but just one step."

[1] www.wtec.org/nano2

Read more from Dr Roco in the next edition of *Science Omega Review*.

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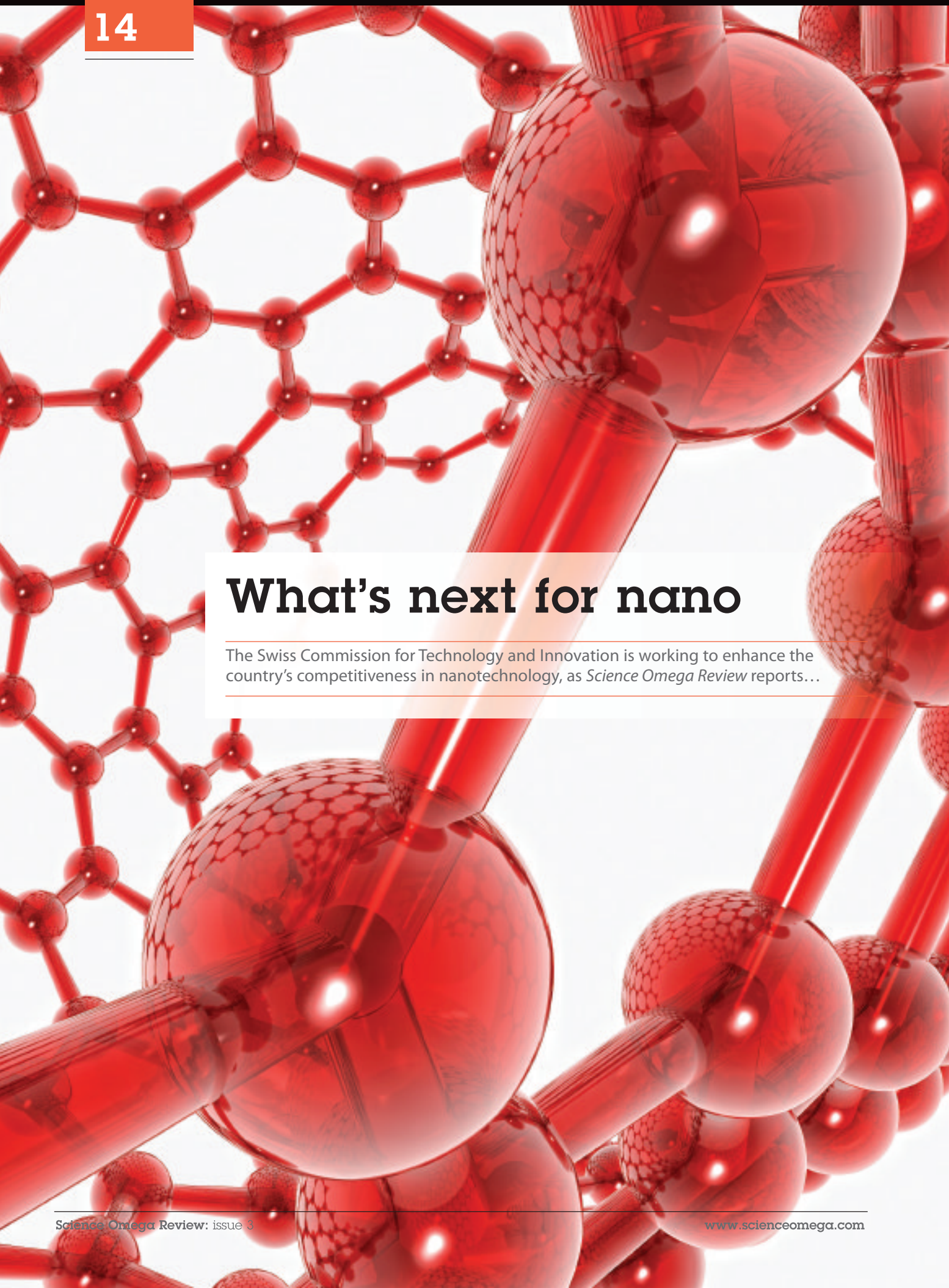

What's next for nano

The Swiss Commission for Technology and Innovation is working to enhance the country's competitiveness in nanotechnology, as *Science Omega Review* reports…

In 2010, a report carried out by a range of public and private sector organisations in Switzerland highlighted the capabilities and impact of its nanotechnology base. The Swiss Nanotech Report 2010 surveyed the recent developments in the industry and attempted to decipher how the country compares to other regions.

Whilst the report was unable to quantify the true potential of the field due to nanotechnology's use in a number of processes in industry, it did state that Swiss nanotech was 'healthy'.[1] It also noted that 'Switzerland was one of the most innovative countries within the field of nanotechnology'.[2] Given the potential of nanotechnology for the Swiss economy, there is little wonder that there has been increased support for the field.

The Swiss Commission for Technology and Innovation (CTI), the federal administration's innovation organisation, works to promote and enhance Switzerland's competitiveness with a bottom up approach, avoiding direct funding to firms. CTI also uses a number of methods to bridge the gap between industry and research institutes.

National thematic networks (NTNs) enable communication between business and academia. In 2012, there were eight of these NTNs recognised by the CTI:

- Carbon Composites Switzerland;
- Inartis;
- Innovative Surfaces;
- Swiss Biotech;
- Swiss Food Research;
- Swiss Wood Innovation Network;
- Swissphotonics;
- Logistics Network Association.

The NTNs began work in January this year.

Another is the use of innovation mentors (IMs). These contacts are available for SMEs to discuss challenges and assist in locating suitable research partners. IMs will 'create contacts and identify, specify and implement ways of encouraging innovation'.[3]

"CTI has carried out its activities successfully for the past 60 years," stated Walter Steinlin in his presidential statement. "The range of support measures has constantly been adapted to suit new circumstances. Innovation is a very dynamic and constantly changing endeavour.

"CTI has long encouraged companies to work with higher education institutions on joint R&D projects. In recent years, it has provided guidance and support to young entrepreneurs as well as assistance with the creation of start-up companies. It also works to establish networks that enable potential innovation partners to work together."[4]

In regards to nanotechnology, CTI encourages the development of this field through funding and supporting industry and academia.

Recognising the importance of maintaining and developing this relationship, the CTI has played a crucial role in ensuring this occurs, outlining its importance: "Nanotechnologies have emerged as key technologies for this century," it stated. "Microsystems technology takes them out of the labs of researchers and puts them into industrial products. Recently, the funding area of micro and nanotechnologies also extended the expertise in the innovation fields of energy research.

"CTI plays an important role in the promotion of this process. Its job is not only to effectively support collaborations between universities and industry in the area of micro and nanotechnologies, but also to promote synergies between their different sub-areas and sub-disciplines and solutions between various areas of application and industrial sectors."[5]

CTI mainly targets applied R&D and allows researchers and industry to target their own projects, covering some of the following areas in micro and nanotechnologies:

- Energy components, systems, conversion and storage;
- Optoelectronics and photonics;
- Microelectromechanical system;
- Micro-opto electro mechanical systems;
- Materials, surfaces and interfaces;
- Semiconductors.

In complex fields such as micro and nanotechnologies, where there are significant applications and the potential to revolutionise industries, substantial support from government agencies such as CTI is an obvious step forward. Assisting with funding opportunities and bringing industry and academia together is vital for the progression of nanotechnology, particularly if Switzerland wishes to remain at the forefront of innovation.

[1] www.swissinfo.ch/eng/science_technology/Science_of_the_small_has_big_potential.html?cid=8123020

[2] www.csem.ch/docs/Show.aspx/11445/docname/CP10-SwissNanotechReport-EN.pdf

[3] www.kti.admin.ch/netzwerke/index.html?lang=en

[4] www.kti.admin.ch/org/index.html?lang=en

[5] www.kti.admin.ch/projektfoerderung/00032/00036/index.html?lang=en

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Recognition nanomaterials

Nanomaterials for the detection and removal of undesired compounds from environment and industrial flow streams…

INOFEA is a Swiss hi-tech spin-off based in Basel that is active in the design, production and business development of innovative nanomaterials for the detection and removal of undesired compounds from environment and industrial flow streams. Historically, the spin-off originates from the collaboration of two scientists at the University of Applied Sciences (Fachhochschule Nordwestschweiz (FHNW)) back in 2009: Professor Dr Philippe Corvini, conducting research aiming at detecting and removing harmful compounds from the environment; and Professor Dr Patrick Shahgaldian, active in the development of recognition nanomaterials.

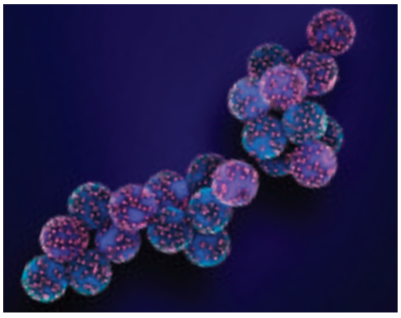
They started work on finding a way to design a completely different type of synthetic material to address the challenges brought by the specificity of viruses. They conceived the nanomaterial, hired a PhD student, Alessandro Cumbo, and after a few months of lab work, came up with an inventive nanoparticle with a virus imprinted surface. By that time Dr Yves Dudal, spin-off entrepreneur in the environmental service industry, had come into contact with the group and shared their vision of the potential of this technology. The idea of INOFEA was born and the company was legally founded on 23rd March 2011 in Basel.

Over time and thanks to other collaborative R&D projects INOFEA has taken shape as a company mastering the design and production of high value materials. The technology at the base of INOFEA consists of designing a recognition platform on the basis of a core particle, on which various chemical building blocks are assembled to produce a recognition site, i.e. a site that will specifically binds the target compound. Once bound, the target can be detected, removed or transformed, depending on the desired application. Our products are designed to be embedded in and drastically improve industrial processes dedicated to the detection, removal or transformation of target compounds in complex conditions.

The assembly can take various shapes and lead to a series of different products. For example, if the building block is made of enzymes (also called biocatalysts), the assembly consists of enzymes immobilised onto nanoparticles (the core particle), what we refer to as nanobiocatalysts. Our most mature product, GREENofea, is a formulation of laccase (an oxidoreductase enzyme, active in a broad variety of phenolic compounds) immobilised onto non-toxic nanomaterial. Immobilising biocatalysts onto nanoparticles provides a huge added value in terms of sustained activity, increased stability, possible recyclability and resistance to harsh environments compared with the free enzyme (i.e. extreme pH and temperature or the presence of contaminants). GREENofea can be used for the removal of polluting compounds (e.g. bisphenol A) from wastewater, in delignification of pulp (pulp and paper factory) and wood residues (biofuel production) or in textile industries for the decolourisation and detoxification of dyes.

By using a second enzyme, i.e. lactase, INOFEA is actively targeting the dairy market. Lactase is routinely used for the degradation of lactose from milk, in order to produce lactose-free milk. Unfortunately, impurities carried in the enzyme preparation and enzyme residues compromise the aroma and flavour of lactose-free milk. Immobilisation of lactase on particles (LACTofea) allows the removal of the enzyme from milk, thus preventing the release of unwanted impurities into milk and the development of unwanted aroma and flavour of lactose-free milk. In addition, the possibility of recovering LACTofea from milk and recycling it would reduce the enzyme costs of dairy industries. With a recently developed proprietary technology, INOFEA is able to produce these nanobiocatalysts on an industrial scale.

Besides the nanobiocatalysts line of products, INOFEA is developing a series of nanoimprints on the basis of the same platform technology (core particle and chemical building blocks to recognise a target). The first product, with the commercial name VIRofea, is a nanomaterial specifically designed to recognise viruses. The method for its production has been protected by filing a patent at the European Patent Office. We produce this nanomaterial with a surface imprinted method in three steps: immobilisation of the target virus on nanoparticles, surface growth of a polymeric recognition layer, and removal of the template virus thus leaving free binding sites at the surface of the particles. This nanomaterial has shown to bind selectively 80% of the starting amount of template virus after five minutes of interaction and almost 100% after 30 minutes. The first application of the nanomaterial is the virus detection in aqueous matrices.



Together with the University of Applied Sciences and the major worldwide leader in wastewater treatment, INOFEA is part of a European project aimed at the development of a kit for the early screening of waterborne pathogens. Recognition is also possible using other materials. By using cyclodextrin as the core unit, we are able to chemically decorate in various ways; we are able to produce a library of selective recognition polymers in a combinatorial and template-free fashion. These polymers have the commercial name of PHARMofea. This approach allows us to produce specific polymers that have inherent affinity for target pharmaceutical compounds, including diclofenac and propranolol, to name but a few. Selective binding properties of PHARMofea are used for the high-throughput screening of pharmaceutical compounds in water.

Based on the same platform technology and a similar production scheme, INOFEA has two product lines (nanobiocatalysts and nanoimprints) with a diversified portfolio of products: GREENofea, LACTofea, VIRofea and PHARMofea. INOFEA is actively developing solutions to embed these raw materials into high-value industrial solutions in order to offer functionalised nanomaterials for specific tasks in various industrial sectors. Indeed, these nanomaterials can be embedded in different industrial product formats, either on microplates allowing high-throughput screening capability, or on capture membrane for removal, or cartridge for the biotransformation of undesired compounds.

Various industries are faced with the challenge of detecting, transforming, recovering and removing specific compounds from different fluids, and are lacking simple, cost-efficient and fast methods to do so. Whether to remove lactose from milk, bisphenol A from wastewater, detect viruses or pharmaceutical in water, or transform lignin into valuable products, INOFEA's technology provides the industry with robust, eco-friendly, time and cost efficient, recyclable and reusable solutions exhibiting remarkable efficiency.

Such advantages available to the big industrial players will have tremendous implications for the environment and society in general. For example, the classic methods used to detect undesired compounds in water today are by far too complex and expensive for a frequent monitoring. A high-throughput screening kit that targets the water diagnostic market would have a high impact on water resource management and general trust in this precious resource by the public. Being able to quickly capture and detect viruses or pharmaceuticals in water, directly on site, would provide water resource management with new tools to quickly tune the sanitation procedure, and thus attenuating outbreaks of viral waterborne diseases and contamination of aquifer with active pharmaceuticals.

We are aware that there is a big concern associated with the effect of uncontrolled release of nanomaterials in the environment. The possibility of immobilising, entrapping and embedding INOFEA's raw nanomaterials in microplates, membranes or cartridges is eliminating the risk of leakage and release of our nanomaterials into the environment. Consequently, end-users are never in contact with the actual material and no risk is associated with the use INOFEA's nanomaterials.

INOFEA is actively developing by instituting a series of commercial partnerships with relevant European and worldwide industrial players, including wastewater treatment companies, biochemical processes companies, dairy industries and enzymes manufacturers. These partnerships give us the possibility of tuning our offer according to customers' needs. Our efforts were recently rewarded by the signing of our first contract with a major wastewater treatment industry. We are confident that this first sell will help increase INOFEA's credibility in the market and will trigger future commercial collaborations.

Currently, INOFEA benefits from strategic scientific advising and collaboration with Professors Corvini and Shahgaldian, and from a hosting agreement with the School for Life Sciences of the FHNW, which allows INOFEA to have access to strategic equipment for the characterisation of the final products. The headquarters and production facilities are located at the Basel incubator, where a dynamic team of young managers and technicians operate. INOFEA is now opening its capital by concluding its seeding round of investment. Financial resources will be used to increase the business development and production capacities focusing on the commercial deployment of the company.

INOFEA
Recognition Nanomaterials

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Surface skills

ISCST President Dr Andrew N Hrymak tells Editor Lauren Smith why understanding of the potential of coating technologies and material science needs to be increased…

The development of the science behind coatings has been diverse and, certainly in recent years, rapid. Coatings have traditionally been applied to enhance the surface properties of a substrate, such as appearance, adhesion, corrosion resistance and more, whereas many of the newer developments focus on the coating as an essential element of the finished product's function. Here, President of the International Society of Coating Science and Technology (ISCST) Dr Andrew N Hrymak discusses with Editor Lauren Smith the widespread application of coating technologies and the impact of this field across numerous sectors and society more widely.

"Coating technology is much more widespread than most people recognise," he begins. "There are many commodity applications such as paper coating, but coating technologies are also used in medical

devices, photovoltaic panels, displays for computers and televisions, aerospace and batteries, for example. Now they are expanding into some of the newer technologies like smart windows, where the coating on the surface may be responsive to different conditions."

The prevalence of such technologies is set to increase even further as the potential in more applications becomes apparent, with research and innovation being particularly enabled through collaboration between academia and industry.

"There is a fairly robust collaboration between universities and coating technology companies, certainly in North America," Hrymak says. "There are positive interactions in Brazil and Argentina, whilst Europe has a very robust coating community, particularly in the UK and Germany, with a number of others in France, Belgium, the Netherlands and Finland. There is also very active collaboration under way in Asia – with Japan, Korea, Taiwan and China all having strong interactions between the academic and industrial communities.

"One of my colleagues recently made an interesting observation that academics tend to interact more with the earlier adopters in coating technology than in more mature technologies, where the productivity gains are harder to develop through academic interaction. I certainly think this is the case."

Internationalisation in engineering research is vital and with larger companies already working with international vendors, Hrymak considers that this is well-established. However, he believes that support from government for internationalisation activities around fostering fundamental research in coating technologies may be beneficial for some of the smaller companies, to give them a more international perspective on what technologies can be utilised across the world. There are still several barriers that exist in the path of greater innovation in this sector.

"One issue is the change in government regulation and safety code," Hrymak explains. "Some of the changes are for safety and environmental reasons, but some of the changes aren't consistent with that and seem to be more about protecting certain product categories for companies within certain countries."

In addition to resolving these kinds of difficulties, internationalisation of funding for fundamental research into coatings would be helpful, he suggests. This would link in further to the interdisciplinarity required for the future of the technologies. There have been several critical developments in the field in recent years and Hrymak highlights two that he feels have had a prominent role to play.

"One has been the industries moving towards smaller, more flexible coating technologies that allow more rapid changes in product portfolio, as opposed to high-speed, dedicated commodity coating technologies," he suggests. "The other change has been towards discontinuous type coating, or complex coatings – specific examples of which are printed electronics and 3D printing. This is a very different kind of coating as opposed to sheet coating at high speeds with very uniform coating factors, with the level of complexity being much higher."

There are challenges facing the sector, particularly in terms of emerging applications, which must be addressed.

"When the industry was looking at large, commodity type coatings, there were certain large coating companies that had a lot of in-house expertise in developing new coating technologies and fresh innovation," he explains. "Many of those have now disappeared. The smaller companies don't have the capacity for research and development as much as they should, and this is where the linkage to academia is important.

"Also, with applications in printed electronics and 3D printing, commercialisation is running far faster than our understanding of the technologies. This means that we probably could have developed more efficient processes in terms of energy, material usage and productivity, but right now all of those new generation systems are being developed very quickly, with a lot of trial and error being used. It would be really helpful to try to have support for some fundamentals, both in academia and industry, to make more efficient processes."

One further consideration, Hrymak outlines, is that complex material systems are multilayered and multifunctional. "We need to understand better the microstructure that forms during coating and later in drying," he says, "which necessitates interdisciplinary working to increase understanding of coating technologies, materials science and the final product properties needed."

With many of the new precision coating products requiring the utilisation of such complicated functional materials, fostering greater links across material sciences could be crucial to success. This sector is set to expand into even greater arenas, with the impact of such technologies becoming increasingly evident in society. With this expansion comes further challenges that must be addressed through the spectrum of fundamental and applied research, through to industry application.

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Intelligent surface technology

Providing high performance industrial coatings worldwide…

With over 40 years' experience in the coating business, Accoat provides various industries worldwide with high performance industrial coatings. This means that both production processes and products within various industries are equipped with special properties using fluoroplastic surface solutions. Through this, Accoat contributes to the quality of life of the end-users that the various industries serve. Customers include pharmaceutical companies, the food industry, the heavy chemical industry and the oil and gas industries, amongst others.

The process

After receiving the customer's items, the treatment begins by cleaning them. Then the selected coating is applied and the items are baked in huge ovens, where the coatings transform into a tough, inert finish. In principle, Accoat can coat all types of components, but has decided to focus on high-build (multiple layer) corrosion protective coatings, as well as non-stick and low friction coatings. The company is a market leader in this field in the Nordic countries and ranks among the largest players in Europe.

Gains

The customers benefit from the fact that fluoroplastic coatings can improve the application, strength and product life of a number of products. For example, coatings can facilitate the cleaning of surfaces, reducing the use of detergents and water, and can save time. This also results in shorter production stoppage while cleaning takes place. Coatings can also make products and production oil and water

A tube plate coated by Accoat to be used at a refinery using the Topsøe SNOX™ technology

resistant, thermally and electrically insulated, or resistant to chemicals. In some industries, using coatings is necessary to comply with safety requirements. Customers have also realised that they can replace expensive materials such as titanium with other low-cost surface treated materials.

Research and development

Accoat improves knowledge and competences regarding the nature of surfaces through research and development undertaken together with universities, other companies and technological institutes. In 2012, the company completed a project within the EU's 7th Framework Programme (FP7) on CO_2 transport.

Case study 1: cleantech

Fertilisers dramatically improved agriculture productivity during the 20th Century. Sulphuric acid is a mandatory product in fertiliser production and can be made by treating the flue gas from power plants and refineries using the Topsøe SNOX™ process. Some parts of this process are coated by Accoat to prevent heavy corrosion.

- Problem: corrosion of steel during production;
- Solution: acid resistant coating;
- Product: Accoshield resistant to 260˚C acid.

Case study 2: energy

When oil is produced, the oil and gas industry uses downhole production tubulars to be able to pump the oil up. This process is made easier by using internally coated tubulars instead of non-treated ones. Accoat uses the DuPont™ StreaMax™ coating system to coat the tubulars internally. The coating has amazing non-stick properties, meaning that material deposits on the inner surface of the tubulars are avoided. This results in fewer production shutdowns and creates both economic and environmental benefits.

- Problem: blockages, material deposits;
- Solution: flow enhancement;
- Product: the DuPont™ StreaMax™ coating system.

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Microscopy: a window into inner space

Ian M Anderson, Secretary of the Microscopy Society of America, turns the microscope onto his own field to highlight its importance in 21st Century society…

Microscopy is the science of imaging things too small to be seen by the unaided human eye, and the 'aid' used to visualise these microscopic features may be generically termed a microscope. The simplicity of this description belies the vast scope of the field, which spans the physics of optics, the development of diverse instrumentation and techniques for microscopic examination, and applications fields in the physical, chemical and life sciences. Length scales relevant to microscopy range from approximately one-tenth of a millimetre to that of the atomic configurations in matter, but the richness of microscopy as a field of study derives from the manifold, often ingenious methods available to interrogate matter at these length scales.

Common features of any microscope can be illustrated by familiar household human vision aids, for example reading glasses or a magnifying glass. A 'source' of radiation (sunlight or a lamp) is used to illuminate an 'object' (say, a book) and an 'image transfer system' (the combined lenses of the instrument and the eye) magnifies 'features' (type) sufficiently to

be interpreted by the corresponding 'detector' (the retina). Microscopes typically comprise all of these components as a single integrated instrument; thus, optical microscopes found in today's science classrooms have their own dedicated source and detector, for example a high intensity light bulb and a digital camera.

A useful comparison can be made between the microscope and the telescope. Both instruments rely on image transfer systems to magnify objects not visible to the unaided human eye, but whereas the telescope is used to magnify objects that are unresolvable due to their great distance from the observer, the microscope is used to image proximate objects of small dimension. Just as a telescope is used to image objects of outer space, the microscope is used to image objects of inner space. Accordingly, both instruments provide fundamental insights into the natural world: the telescopes at the largest length scales – of solar systems and galaxies – and the microscope at the smallest length scales – of cells, microstructure, molecules and atoms.

A major differentiating feature between telescopes and microscopes is that while the source of radiation for the telescope is naturally generated by distant stars and galaxies, the microscope employs its own source of radiation to probe the microscopic object. Thus while we use a telescope to 'observe' the objects of outer space, we use a microscope to 'interrogate' the objects of inner space. This interrogation also points to the major differentiating feature between the two instruments' fields of application: in addition to natural objects, microscopy extends to man-made engineered objects, ranging from the microlithographic structures that give function to our portable electronic devices to nanotherapies for targeted cancer treatment.

Modern microscopes make use of every available kind of source radiation – electromagnetic waves such as X-rays and ultraviolet, visible or infrared light, as well as massive particles such as electrons and ions. The detected signal can be the source (primary) radiation, whose direction or energy may have been altered by the examined object, or secondary radiation excited in the examined object by the primary radiation, for example electrons ejected from the object under examination. The science (and art) of microscopy is the ability to generate contrast to image the salient features of the examined object.

Microscopy serves a singular role in science relative to other characterisation techniques, a role that has become more pronounced with the advent of nanoscale science, engineering and technology. While most techniques are used to derive precise average properties of a sampling of thousands, millions or billions of microscopic objects, microscopy is used to visualise a single such object. Microscopy's important role in scientific discovery, from van Leeuwenhoek's first observations of microorganisms in the 17th Century to Iijima's discovery of carbon nanotubes in recent decades, derives from this ability to resolve the features of a single microscopic object: as they say, 'seeing is believing' or 'a picture is worth a thousand words'.

When the differentiation of 'individual', rather than 'average' behaviour is critical, microscopy plays an essential role, and thus takes on the flavour of detective work when something goes wrong or something unexpected happens. To make an analogy, the average demographic captured by a poll or a market research survey is not germane to solving a crime, where atypical or singular behaviour must be understood. Microscopy is thus essential in the field of failure analysis; such techniques are used to examine the fracture surface of a critical component when a bridge fails, or what defect has caused a particular group of transistors to fail in a new generation integrated circuit. A single image is often all that is necessary to grasp an understanding of the problem, and to suggest a solution for fixing it.

Microscopy research is progressing on many fronts. In the area of electron microscopy alone, transformative improvements to each component of the microscope read like science fiction: sources producing spiralling electron 'vortex' beams to produce new sources of contrast; environmental cells that allow nanostructures to be visualised within liquids or gases; 'phase plates' that, like Polaroid sunglasses, allow vivid contrast without the glare; and high-frame rate cameras that allow movies to be recorded at ultra slow motion. Each of these advances is in its infancy; if these can be integrated, the electron microscope of the future will be an atomic-resolution observatory for nanoscale structures. Imagine seeing the atomic-scale mechanisms that make a catalyst work, or individual protein molecules fold, or lead to electrical conduction in graphene – each in its real-world operating environment.

Ongoing funding for microscopy instrumentation and techniques is critical to keeping pace with the challenges of technology development. Yesterday's solutions cannot fully address today's technological challenges, which will lead, in turn, to tomorrow's high-quality jobs. If we are to harness the remarkable behaviour of matter at the nanoscale as next generation technologies, we must be able to visualise what we make, and without microscopy, we would be navigating this process blindfolded.

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Seeing the invisible

Celebrating 15 years of the European Microscopy Society…

The European Microscopy Society (EMS) is a Europe-wide 'umbrella society' including national microscopy societies and individual members, with the aims of fostering scientific exchange between European countries and educating the next generation of microscopists across all fields of applied science.

At the suggestion of former CESEM President Wolfgang Baumeister, the EMS was inaugurated at the ICEM-14 meeting in Cancun in 1998, after the disbanding of the Committee of European Societies of Microscopy (CESM). Before this, when the committee was known as CESEM – the additional E standing for 'electron' – its focus was only on electron microscopy. Peter Hawkes (France) was elected the first President of the new EMS. Jose-Maria Carrascosa (Spain) was chosen as Vice-President, Eddie Wisse (Belgium) as secretary and Heinz Gross (Switzerland) as treasurer. More information on the history of CES(E)M and the EMS can be found on the EMS website (www.eurmicsoc.org) under 'EMS Documentation'.

In the early days, visualising individual atoms was still a domain of very specific physical enduring experiments, such as scanning probe microscopy and atom probe analysis on restricted surfaces, on tiny selected areas of only conductive material or by atom column projections by transmission electron microscopy (TEM). During the 1990s, major changes in electron optics, such as brighter and more coherent electron sources, monochromators and mainly, the development of optical correctors – a kind of 'correction glasses' for electron microscopes, elevated electron microscopy to an atomic resolving analytical method. Introducing electron microscopy into our research fields allowed measurements in crystals with picometre (pm) precision (pm=10^{-12} metre – the sub-atomic domain) and analysis of the elemental composition down to only a few atom numbers.

With further improvement of the optical performance, stability, high yield direct electron detectors and spectrometers, in parallel with dedicated sensitive sample preparation, electron microscopy becomes more and more a routine cross-discipline analytical method. Light microscopy was revolutionised by implementing so-called super-resolution techniques, allowing precision localisation down to 40nm closing the resolution gap between electron and photon microscopy. Allowing fast *in vivo* measurements with fluorescence, and highest spacial resolution and context information from electron microscopy methods to be combined. In combination with other imaging and microscopy technologies, correlative microscopy will speed up and even enhance the output of material characterisations.

Most of these improvements in the 1990s were driven by outstanding European scientists. From this burst of technology evolution, many scientific disciplines and industrial applications gained significant new insights into materials or increased their quality control, such as:

- **Quantum optics –** by analysis of quantum dots and quantum wells important for the next generation of computers, lasers and communication tools;
- **Digital storage technology –** by analysis of electromagnetic domains and electron potentials at the atomic level;
- **Nanoengineering –** by analysis of nanorobots and MEMS devices down to single atomic sheet devices (graphene);
- **Nanotechnology –** characterising natural and man-made atomic and nanometre scale devices;
- **New intelligent materials –** by analysis of biomaterials at the nanometre scale to mimic the design of next generation sustainable materials;
- **Materials science –** characterising new materials for more sustainable usage of natural resources;
- **Molecular biology/medicine –** by analysis of individual proteins and biomachines to near atomic resolution to decipher their functions;
- **System biology –** by analysis of the complexity and context of biological tissue and cells in 3D for deciphering nature's mastering of sustainable nanotechnology;
- Creating new prototyping devices on the nanoscale in modern scanning electron dual beam systems;
- Quality control in industry and science, mainly at the scale of atoms to a few nanometres.

These examples clearly point out that modern, state-of-the-art electron microscopy – TEM or STEM, with their different options, e.g. working at a temperature of -190°C or with pulsed electron waves etc. – has

become an indispensable analytical cross-technology for all experimental and engineering science fields.

Clearly, some of these fields will depend on developing the next generation of analytical tools for real molecular and atomic imaging across these disciplines. Some of them will start as research projects with an uncertain outcome, as was the case for the corrector project, and will need scientific freedom to develop without realisation or market pressure from the beginning. As in other technological fields, and as we've learnt from science history, surprising discoveries – often from unrelated fields – need a few generations to mature to their ultimate applications (e.g. lasers in medicine).

Finding a balance in supporting fundamental research, applied research and industrial development without exposing them in direct competition requires an open-minded discussion culture in our community and with supporting agencies.

A Europe-wide microscopy community is therefore important to help to educate the next generation of scientists in microscopy, and to foster European exchange, cross-linking and networking of excellent scientists in the field. This is a vital role in any society; allowing members to network in their home countries, across Europe and internationally to expose them to opportunities early in their careers. EMS provides and supports many of these possibilities, as can be seen from its achievements; providing added value in supporting microscopy throughout Europe. In addition, it is also crucial to give young or smaller European countries, such as the new Eastern European countries, the opportunity to be involved in European activities and be part of European research policy.

A society such as EMS is also responsible for communicating with the public, sharing findings enthusiastically and displaying our passion for research; both to the general public and the political sphere. This will help to attract the next generation of students, which we need to do more efficiently in future to cope with the challenges of the sixth technology wave – the so-called 'green wave' of sustainable technology development, based on using quantum and nanoscaled principles of nature – perfect domains for ultimate microscopy investigations.

There is much more work to do in bringing excellent microscopists together – both to solve urgent and important applications and to develop new instrumentation and methods. Positive steps already taken in this direction include the EMS European Microscopy Award and the Outstanding Paper Awards.

To help shape the future of European science and be ready to deliver a previously unseen view, insight, or realistically scaled models of the 'invisible' workings of natural or man-made machines, it is essential that EMS continues its work and establishes new efforts, such as:

- Creating standardised training for microscopy application in the educational curriculum for natural science;
- Establishing a repository for best experimental practice and standard operational procedures to enhance quality, speed and output;
- Maintaining a database of established methods and 'how to' guides from seniors in the field, to prepare the next generation and avoid 'reinventing the wheel' – technical methods for sample preparation and analysis are rarely published in peer reviewed scientific journals;
- Networking of instrumental projects and research for the next generation of analytical imaging tools;
- Integrating other imaging modalities into the microscopy community;
- Establishing a common communication platform (e.g. a webpage with a discussion forum or wiki) and an EMS journal.

The EMS needs the support of strong individuals, national organisations and the European scientific community to realise these essential initiatives, to benefit our future by supporting the 'green wave' and to continue its ongoing aim of 'seeing the invisible'.

About EMS

- Over 5,600 individual members and 50 corporate members;
- 23 affiliated national societies;
- Around 225 stipends for students since 1998;
- More than 55 EMS sponsored courses, workshops and conferences;
- 12 EMS extension events held to date and a European Microscopy Congress every four years – the next to be held in Lyon, France in 2016.

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A bright future for SLD

Richard Linke, Executive Director of the IEEE Photonics Society, discusses with Editor Amy Caddick the emergence of superluminescent diode technology…

Whilst photonics is hardly a new field – Albert Einstein laid the foundations for the development of the laser in 1917, and the optical fibre can trace its roots back even further – its scope has continued to advance immensely over the last century, bringing new, innovative technologies with it. From entertainment to manufacturing, photonics is increasingly becoming pivotal to a number of industries.

One sector that has benefited from advances in the photonics field is medicine. The use of photonics in healthcare is already prolific, particularly in clinical procedures. More recently, it has also been utilised in medical imaging.

The superluminescent diode (SLD) may not be as well known as the laser, the optical fibre or the photovoltaic (PV) panel, but this technology has wide-ranging applications and is enabling doctors to see further into the body than ever before through non-invasive methods.

"The SLD is a very interesting technology," says Richard Linke, Executive Director of the IEEE Photonics Society. "It falls right between two very popular photonic devices: the LED [light-emitting diode], which we're now seeing commercially available for illumination indoors, as well as in car headlights; and the laser, which has been very influential in science."

Like the LED and the laser, the SLD requires an optical medium that can be 'pumped' to charge particles to an excited state. However, in spite of a number of similarities in the three devices, they do work differently.

In the case of the LED, there is a p-n junction with a negative type semiconductor on one side and a positive type semiconductor on the other. A flow of electrons jumps across the p-n junction from the negative type side and fills holes in the positive type side. In doing so, the electrons change from a high energy state to low; this in turn causes a photon of light to be emitted.

With lasers, atoms are pumped from the ground state (the lowest energy possible) into an excited state (higher than ground state). This creates more atoms in the excited state compared to the ground state – called population inversion. The action of pumping the atoms creates excited electrons, which then release energy in the form of photons. Adding an optical resonator, such as 99% reflective mirrors, ensures some light is able to escape, but the majority is contained, enabling the continued creation of photons.

Describing the process further, Linke says: "An atom in the excited state will eventually drop down to ground state and produce spontaneous emission. In addition to this, if a photon of the right wavelength – meaning the wavelength matched to its emission wavelength – comes along from somewhere else and gets near enough to the atom, it will stimulate the atom to fall down to ground state.

"Now what you have is the original photon, and also a second one that came out of the atom. That's called gain. That means you amplified the first photon and made it into two. You can continue to make each photon stimulate another atom to decay, which results in stimulated emission. This is the essence of the laser. You could – and in fact do typically – just use the photons that are created spontaneously from some of the atoms, and run them by the other atoms to get a laser."

The SLD works similarly to the laser, but without the optical resonator. Instead, the device has to 'turn up' the gain, driving the current harder until it reaches amplified spontaneous emission. In order to do this there has to be high gain, to ensure photons are producing many copies before escaping the device. Superluminescence is caused by the amplification of photons from the spontaneously decaying atoms.

Linke explains that the reason the SLD is such a valuable device is that, unlike the laser, its light is not coherent. This means that no two sections of the beam will be the same, and it is this feature that makes the SLD so important in medical imaging.

"Typically, laser light is extremely coherent," he says. "That means one portion of a laser beam looks very much like another portion of that beam, maybe a metre away or sometimes even a kilometre away. One of the properties of a very coherent wave is that its spectrum is very narrow, so it only has energy at one wavelength, one frequency. That's why laser light looks so intense in colour.

"If you don't put mirrors on your semiconductor device, the wave becomes incoherent. The SLD will produce very intense light, but light that is not particularly coherent."

Optical coherence tomography (OCT) is one of the main imaging techniques in which SLDs are utilised. Like computer-assisted tomography (CAT), OCT works by taking three dimensional 'sliced' images of the body – in this case, the eye – without the patient undergoing an invasive procedure.

"A hundred years ago, tomography consisted of taking an organ or biological sample, cutting it into very thin slices and looking at each segment under a microscope to see how the structure changed between one sample and the next," says Linke.

Whilst other methods do exist to take images without being invasive, such as ultrasound, the high resolution of the images provided by OCT make the device much more useful.

"Coherence tomography is a way of getting this same three dimensional view, but by using light. It's a very convenient and non-destructive *in vivo* method. A doctor can look into somebody's retina without damaging their eye, while the person is in the doctor's office," Linke highlights.

Unlike the laser, which requires coherence to work, OCT thrives on incoherence of the light. In fact, the shorter the coherence length, the more effective the device, as this enables the OCT to view narrower slices within the eye.

"The superluminescent diode light has a very short coherence, which means it will only interfere with itself if it's within the coherence length. The goal is to make that coherence length as short as possible," he adds.

By moving a mirror inside the OCT, ophthalmology experts can scan slices of the eye, focusing upon the exact area required.

"It's a very useful diagnostic tool, but it only works with these very short coherence devices – they must have a coherence length of a few microns," says Linke. "A 10 micron coherence length is about one-tenth of the diameter of a human hair, so it's good enough that you're going to see very fine detail in the eye."

Like all technologies, whilst the SLD has many advantages, there are also challenges, as Linke describes.

"In order to make the SLD work, you need a high gain medium with no mirrors. Also, a lot of the light is going back towards the SLD in an OCT instrument. If that light gets into the SLD it will be amplified and can actually damage the device. More likely, it will act like a mirror outside of the SLD and instead of having a broad spectrum of incoherent light, it will form a laser, and it won't work at all as you'll have a coherent beam. You have to prevent any light from reflecting back into the SLD and that is the biggest technical challenge.

"You need an optical isolator, a device that allows light through in one direction, but not in the other direction," he continues. "There are such devices available, they're just not ideal. They do allow light through in only one direction, but they're bulky and they can be more costly than the SLD to begin with. It increases the technical challenge of using them, but it's doable – in fact, that is how it's done."

Overall, however, the SLD is another stepping stone in the advancement of the photonics industry, standing alongside other devices such as the PV cell, the optical fibre and the laser. The flexibility of light and the ability to change its properties to suit specific needs makes photonics extremely useful in science and technology.

"OCT itself has applications other than for biology," Linke concludes. "It can be used in manufacturing. If you want to measure details in a film that you're producing, you can measure the variations with a device like that. So there are a number of applications for OCT other than the biological one."

The strides already made in photonics are undoubtedly impressive and advances continue to be made all the time. What the future holds remains to be seen, but there is little doubt that the field still has much more to offer.

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Insight into superluminescent diodes

The high power and brightness of laser diodes combined with the low coherence of conventional LEDs…

Superluminescent light-emitting diodes (SLDs) are a specific type of amplified spontaneous emission semiconductor light source that combine broadband spectral emission, typical for light emitting diodes (LEDs), with a high brightness comparable with that of laser diodes.[1]

Similar to a conventional single mode laser diode, an SLD emission can be focused to a diffraction limited spot, collimated to a Gaussian beam, or efficiently coupled in a single mode optical fibre without considerable loss of energy. These SLD characteristics are due to a very high optical gain, efficiency of spontaneous recombination in semiconductor laser materials and their wide optical gain spectrum.

SLDs are based on semiconductor structures used in laser diodes and have a similar geometry. The main parameters describing the performance of any SLD are output power, central wavelength and the spectrum width, which also determines the coherence length. The SLD wavelength and spectrum width are defined by the material composition and the geometry of the semiconductor structure used.

SLD spectral broadening may be obtained by precise engineering of the SLD semiconductor material, which usually includes the use of quantum confined (quantum well) semiconductor structures. SLD geometry is carefully designed to achieve a very wide spectrum and high output power. It should be noted that SLD design varies slightly to that of laser diodes. A low threshold and high efficiency are important performance parameters. Wide optical gain spectra are a special feature of SLDs but are achieved at a cost to the highest possible overall efficiency.

In 1995, SUPERLUM made a breakthrough: scientists successfully used quantum well structures for essential spectral broadening of the SLD spectrum, combined with a high output power. Since then, SUPERLUM has delivered SLDs with, to our knowledge, the best combination of output power and optical spectrum width – in the 800-1000nm spectral range. Since 2000, SUPERLUM has been developing a series of SLDs with overlapped spectra. It allowed to achieve a total output spectrum width of up to 300nm. This resulted in a successful demonstration of ultra-high resolution optical coherence tomography using SLD-based sources, in collaboration with the group of Professor Fujimoto of MIT.[2] In 2004, Photonics Spectra magazine honoured SUPERLUM's light source based on this principle with a Photonics Circle of Excellence Award.

Another crucial parameter of any SLD is its residual modulation depth, which appears due to residual reflections from the end facets of the active region. The product of end reflections must not exceed 10^{-9} over the entire SLD spectrum in order to keep residual spectral modulation within a few percent in a high power SLD. This is difficult because end reflections of as-cleaved SLD semiconductor crystals are typically around 0.35 and SLD spectrum width may reach 100nm (3dB).

SUPERLUM developed and implemented a special technology for precise anti-reflective and protective coatings of SLD crystal facets. SUPERLUM was the first company to achieve a value below 5% residual spectral modulation depth with output power hitting 100mW in single transverse mode SLDs at 800-1000nm wavelengths. Today, single transverse mode SLDs with an output power of 50mW in free space (30mW in a single mode fibre) are commercially available. Free space versions emitting 100mW (single mode) and 200mW (spatially multimode) are in development.

With a lifetime exceeding 100,000 hours, SLDs are preferable for many different applications. Since the early 1990s, SUPERLUM SLDs have been widely used in commercial fibre-optic gyroscopes providing a number of advantages with respect to other technologies. SLDs are replacing laser diodes in various applications where lasers are used for illumination but 'speckles', due to their high temporal coherence reduce system performance, for example, in high end application of atomic force microscopy.

SLDs are also excellent for different types of spectroscopy by being compact, highly efficient white noise generators in the optical domain. SLDs open new possibilities in biophotonics, being an alternative to larger, more expensive and complex solid-state supercontinuum and other sources, the latter being used with the sole purpose of generating a wide optical spectrum.

Among other applications, time-domain and Fourier optical coherence tomography

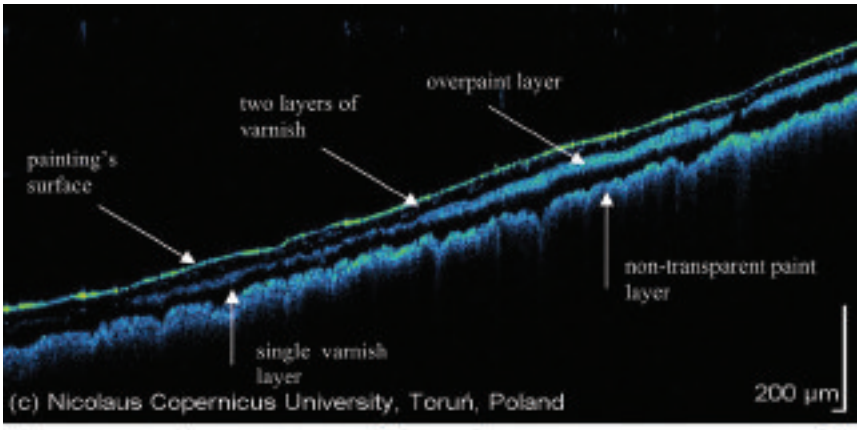

Fig. 1

(OCT) using SLDs as light sources may be currently considered as the most exciting. Today, OCT-based systems can be found in most ophthalmology clinics. The first systems were used generally for the early detection of dangerous conditions, e.g. cataracts and glaucoma. They are now used as diagnostic and control systems for complex laser surgery instruments in ophthalmology. Other medical systems exist allowing non-invasive diagnostics and early stage detection by OCT-based optical biopsy using SLDs as a light source. OCT, being an exciting, state-of-the art technology, now expands to other areas of technology, which require precise, high resolution and non-destructive 3D analysis. The range of possibilities OCT technologies offer may be illustrated by recently published results on studies of conservation and structural changes of Leonardo da Vinci's 'Madonna dei Fusi' by the group of scientists from the University of Torun, Poland (Fig.1).[3] One of the novel SLD-based light sources of SUPERLUM, namely BroadLighter T-860, has been used for these studies.

About SUPERLUM

SUPERLUM is an international group of companies who share research and development. The headquarters are located in Co Cork, Ireland. SUPERLUM manufactures SLDs and SLD-based light sources with state-of-the-art parameters covering the spectral range from 650-1650nm. SUPERLUM devices in 800-1000nm provide the best combination of spectrum width and output power among similar devices of competitors available on the market.

We deliver our products to almost 200 industrial and academic partners in more than 30 countries all over the world. We actively invest into the future by engaging in a number of European scientific research programmes, including participation in the Irish Photonic Integration Research Centre.

Having a core business focused on SLDs, we actively exercise other technology possibilities existing around them. We are offering widely tuneable external cavity lasers at 800nm band. The main advantage of our lasers is a very high setting tolerance and reproducibility of any wavelength within entire tuning range and its preservation during the whole lifetime of the device, thanks to a genuine design based on the narrowband acousto-optic tuneable filter and lack of mechanically moving parts in the external cavity. Our knowledge and experience in making SLDs and optical amplifiers allows us to get up to 100nm tuneability in a 750-900nm band, using a single semiconductor optical amplifier (SOA) chip in these lasers.

[1] Shidlovski V R, Superluminescent Diode Light Sources for OCT, in 'Optical Coherence Tomography', ed. Wolfgang Drexler, James G Fujimoto, Springer 2008

[2] Ko T H, Adler D, Fujimoto J G et al. 'Ultrahigh resolution optical coherence tomography imaging with broadband superluminescent diode source', Opt. Express, Vol 12, N 10, pp. 1212-1219, 2004

[3] Targowski P, Iwanicka M, Sylwestrzak M, Kaszewska E A, Frosinini C, 'OCT structural examination of 'Madonna dei Fusi' by Leonardo da Vinci', Proc. Of SPIE Vol 8790, 87900N-1, 2013

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An elemental force

Chemistry has a major role to play in helping to secure our future energy supply and in Europe's ambitious innovation plans, writes EuCheMS President Ulrich Schubert…

Horizon 2020 intends to stimulate 'smart, sustainable and inclusive growth' in Europe. These descriptors are what chemistry stands for. Most of the societal challenges put forward in the proposal for Horizon 2020 address chemistry directly or indirectly.

The knowledge and innovation created by the chemical sciences and the chemical industry in the past century have contributed to a vast extent to the present-day standard of living in Europe. Chemistry as an innovation motor will also be required for the decades to come ('smart growth'). Health and wellbeing for all, sufficient supplies of safe and high-quality food, a reliable and sustainable energy system, an environmentally friendly transport system, a resource-efficient and climate change-resilient economy and a sustainable supply of raw materials – to cite only some topics of Horizon 2020 – require continuing advances in chemistry. Europe is traditionally at the forefront of innovative chemistry. Strong support for knowledge-oriented, cutting-edge chemical research is necessary to keep this leading role.

We are experiencing a paradigm shift in chemistry due to a better understanding of ecological causalities as well as the awareness of dwindling resources. Transforming and modifying substances, and thus producing novel, more effective and cheaper compounds and products, is the essence of chemistry. A dimension with increasing importance, however, is resource and energy efficiency ('sustainable growth'). The question is no longer whether a compound or material with a certain set of properties can be produced under any condition, but whether compounds with the same or even better characteristics are feasible with a more favourable ecological footprint. This is a formidable challenge. An additional aspect is that fossil fuels, a number of metals and minerals and other resources will become depleted in the not too distant future. The chemical sciences will contribute not only to the economical use of such resources, which includes development

of efficient recovery methods, but also to finding efficient and ecologically sound replacements.

The key role of chemistry for technical and societal advancements is not always obvious. One of the biggest contemporary challenges, the development of new energy sources and transformation of our energy system, may illustrate this point. 'Secure, clean and efficient energy' may not immediately be associated with progress in chemistry. All energy issues, however, be it energy efficiency, production, storage or transportation, are closely related to chemistry.

Harvesting of the abundant energy of the sun can be done by photovoltaic or photocatalytic systems. Chemistry can contribute to much needed progress in photovoltaics by developing new materials to make the devices more efficient and stable, and to render them suitable for new fields of applications. The so-called 'artificial photosynthesis' is aimed at producing energy-rich compounds that can be stored and transported ('solar fuel') and requires efficient and economical photocatalysts. One possibility is water splitting for hydrogen production, with sunlight as the energy source. The ultimate solution would be the photocatalytic conversion of carbon dioxide in chemical compounds, which could not only be used for energy production, but also as an alternative chemical feedstock.

The use of intermittent electricity sources, such as wind and solar energy, requires high efficiency storage devices. In particular, the availability of rechargeable cells of medium to high energy/power remains inadequate, and substantial breakthroughs are needed in small-scale energy storage (e.g. batteries or capacitors). Chemistry can greatly contribute towards new devices by developing new materials for electrodes, electrolytes and structural materials to allow for demanding working conditions. The same is true for advancements in fuel cell technology, i.e. the conversion of combustion energy of fuels into electric energy.

The European Commission set a target of saving 20% of all energy used in the EU by 2020. Chemistry is the key science for accomplishing this goal in many areas: building insulation, energy-efficient windows and appliances, lightweight materials for transportation, superconductors, fuel additives, lighting materials, thermoelectrics (to convert heat in electricity) and energy-efficient processing, to name only a few.

These and other contributions to securing our future energy supply are examples of the problem-solving abilities of chemistry, both as a science and an industry. Chemistry, as a cross-sectorial discipline, is central to progress in many other fields and thus has a key role in achieving the 'Innovation Union'.

Spotlight on IUPAC

Smart growth in chemistry, utilising existing knowledge, in addition to new developments, does not stop at European borders. Developments in polymeric research are supporting more sustainable development, with input from a range of national and international bodies.

The International Union of Pure and Applied Chemistry (IUPAC), for example, works across the chemical sciences to advance the sector through enabling collaboration of academia and industry. With a longstanding history as a world authority on chemical nomenclature, terminology, measurement standardisation, atomic weights and related areas, it provides a forum for technical dialogue and exploration of the societal impact of the related sectors.[1]

Chemistry has intrinsically developed as an interdisciplinary scientific field, with broad interplay over the different elements of the scientific research. As such, the diversity of modern chemistry encompasses the generation of new knowledge in many vital areas, with organisations such as IUPAC in a strong position to strengthening the bonds of international chemistry and to promote the role of chemistry in global societal issues. Such multiplicity is reflected in the different projects supported by the organisation, which range from the enhancement of education in polymeric chemistry to enabling clean energy through chemistry; the impact on human health of nanoparticle technologies to pH measurements of seawater.

Bringing forward underrepresented groups in chemistry is one of the key strands of the IUPAC's work, which is reflected in a number of awards. For example, the 2013 IUPAC Prize for Young Chemists was awarded for five of the best PhD theses in the chemical sciences, with the majority of winners based in the US and one from Japan. In contrast, the IUPAC 2013 Distinguished Women in Chemistry or Chemical Engineering awardees hailed from much broader shores – representatives from Russia, Australia and Germany were amongst the 11 selected. Whilst the influence of different countries can be illustrated by impact factors and citations, indications of future influence can be gleaned from the support for the new generation of researchers and the investment in the ongoing skills set and knowledge base.

[1] www.iupac.org

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Synthetically speaking

Is this the golden age of polymer science and engineering? The Institute for Polymer Research's Professor Jean Duhamel shares his thoughts…

Over the past decade, polymer science and engineering has undergone a tremendous transformation, spearheaded by the advent of controlled radical polymerisations that are both easy to implement by scientists and robust to scale-up by engineers. Since the size of a macromolecule is a key parameter to predicting its properties, every polymer laboratory in the world is aware of and most likely practising atom transfer radical polymerisation (ATRP) or reversible addition fragmentation chain transfer (RAFT) to produce macromolecular architectures of increased complexity, while preserving an exquisite control over the size of individual macromolecular objects.

Considering the diversity of the synthetic toolkit now available, it is clear that a tipping point has been reached where the synthesis of macromolecules is no longer prevented by the absence of a suitable synthetic protocol, but rather is limited by our imagination. The impact of these synthetic advances was further enhanced by the introduction of instrumentation that could characterise these novel macromolecular objects having highly complex architectures at the nanometre scale. For instance, not only can atomic force, scanning electron or scanning tunnelling microscopes (AFM, SEM, STM) visualise individual macromolecules adsorbed on a surface, they can also demonstrate the existence of subdomains at the nanometre scale within a macromolecule, an assembly of macromolecules or in a polymer film.

Dynamic light scattering (DLS) is also ubiquitous in any institution conducting research on polymers to determine the size of macromolecules and their supramolecular assemblies in solution. Thanks to their resolution in the nanometre scale, these analytical tools could substantiate claims made about the expected features of their novel macromolecules.

The ability to synthesise macromolecules under controlled conditions and characterise them at the nanometre scale led to an explosion in the number of well-defined architectures that could be produced. No longer were dendrimers introduced close to 30 years ago the only objects found in the scientific literature having well-defined dimensions in the nanometre range. In the last 15 years, arborescent polymers, star polymers, multiblock copolymers, and polymer bottlebrushes have become ubiquitous on the scientific stage as these macromolecules can now be produced easily, with a high yield and level of control over their size. Of particular interest was the possibility to harness these efficient synthetic methods for the preparation of schizophrenic macromolecules built with polymer blocks having opposite properties. Indeed, polymer blocks can be prepared that are water versus oil-soluble, charged under basic versus acidic conditions, or thermally responsive versus athermal, and the macromolecules resulting from the covalent assembly of these blocks exhibit fascinating properties that can be triggered on demand by changing solvent, solution pH or temperature.

Their self-organisation into long range ordered patterns or their self-assembly in solution into block copolymer micelles has found numerous applications for array patterning widely used in nanofabrication for templates and moulds or drug delivery, which led some to announce the dawning era of polymer therapeutics. Most importantly, their existence did not remain self-contained within polymer science and engineering, but opened new multidisciplinary research venues to create novel materials via, for example, directed synthesis.

In summary, the advances in polymer synthesis and characterisation have recently led to an explosion in polymeric systems that can be prepared with an excellent level of control over their dimensions. This feature has placed polymer scientists and engineers in the enviable position of being at the interface of numerous disciplines with interests in medicine, catalysis, photovoltaics, nanolithography, detergents, and paints, to name but a few. This offering of new and exciting opportunities in conjunction with their intellectual and monetary rewards will appeal to the next generation of young scientists and engineers considering entering the field.

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Polymer research

Understanding the properties and commercial applications…

As anyone working with polymers is aware, the traditional disciplines found in science and engineering do not provide the basis that would allow one to understand the properties of polymers and apply them in a useful manner. Rather, the basic principles that govern polymer properties are found in polymer science and engineering, which constitutes a field on its own. It was thus natural that 35 years ago the polymer chemists and chemical engineers at the University of Waterloo (UW) gathered to form the Institute for Polymer Research (IPR).

The IPR currently has 15 active research faculty members and 80 undergraduate and postgraduate students. The core tenets of the IPR are to foster interactions between students and professors and facilitate mutually beneficial collaborations between industry and IPR researchers. These collaborations are essential to the IPR members as they bring new research and funding opportunities.

The IPR group of researchers offers an impressive range of expertise in chemical engineering, chemistry and physics. They range from polymer processing to polymer physics on thin films including polymer nanocomposites, membrane filtration, polymer synthesis and characterisation, photovoltaics, and interfacial phenomena. The students conducting research in these different fields gain both hands-on experience and a solid understanding of polymer science and engineering. The combination of these skills is extremely valuable in the job market as polymers are key elements found in a dizzying array of commercial applications, from the low-tech plastic bag to the hi-tech smartphone.

The understanding of polymer properties and their commercial applications has led to a clear recognition of the value of polymers and the advanced research expertise within the IPR. Numerous international companies have become industrial members of the IPR. IPR member companies have access to special research grade instruments operated by IPR researchers at discounted rates, as well as member in-house courses given by IPR academics on special topics in polymer science and engineering. Together, these initiatives create a collegial and fruitful environment conducive to creative research that benefits both academia and industry.

The IPR annual symposium is the highlight of the year, as it provides an up-to-date overview to the symposium attendees of the current research in polymer science and engineering being conducted at Waterloo. It is traditionally held in May on the UW campus, with well over one-third of the IPR student population presenting the results of their research to an audience consisting of fellow students, professors and industry researchers.

Frequently, the IPR symposium represents the first opportunity for graduate students to showcase their research to an educated and critical audience. Most importantly, it allows students to interact one-on-one with industry researchers and discuss their research challenges and ideas with industry experts who can offer a more applied point of view. These casual meetings can become informal interviews that result in a future hiring. Also, the interactions generated during the symposium often lead to collaborations between academic and industry members.

The merits of the environment enabled by the IPR are plentiful and are made possible through a high level of commitment by all involved. First and foremost, by the students who conduct the research and prepare oral and poster presentations at a professional level for the symposium; secondly, by the supervisors who oversee their students, in addition to actively participating in the IPR; and thirdly, by our industry members who continue to be engaged with the advanced research at the IPR.

It is eloquent testimony to the high level of dedication in research and academia that the IPR continues to thrive, due to the vitality of its members who lead and guide the next generation of expert researchers in polymer science and engineering.

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‘Cascading use’: a win-win scenario for biomass

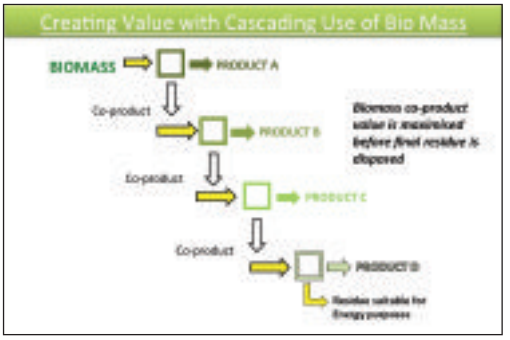
Charles Morris, of Pine Chemicals Association Inc, and the American Chemistry Council’s Kevin Moran, stress the importance of balance in the use of biomass…

In response to global climate change concerns, important new policies to advance the sustainable use of biomass resources have been initiated in many parts of the world. In particular, the EU and its member states have developed a new bioeconomy strategy.[1] One of the key facets of this strategy is the explicit requirement to increase sustainable biomass production and use ‘without compromising food security, adding pressure to primary production and the environment, or distorting markets in favour of energy uses’.[2]

This policy is comprehensive, encompassing all valuable uses of biomass resources including bio-based energy, chemicals, and pharmaceuticals. The policy is intended to be integrated within each EU member state as well, to ensure that every nation’s unique mix of biomass resources and manufacturing base can be utilised to maximum benefit.

Of course, the utilisation of biomass resources is not a new phenomenon. Wood and wood products, one of the primary segments of our available biomass, were the original source of artificial heat and light, as well as the basis for housing, medicine and myriad other essential uses. Biomass is, and always has been, a critical resource, and this increased policy focus is a welcome and positive development that will hopefully ensure Europe utilises its biomass resources more efficiently and with fewer potential impacts on the environment, as well as generating fewer conflicts between bio-based industries.

My industry – pine chemicals – was at the forefront of the bioeconomy long before the term was even invented. In the early days of sailing, pine tree sap was used to seal the hulls of ships, and terpenes from pine trees have been used in solvents and medicines for hundreds of years. Today, one of the primary raw materials for pine chemicals is crude tall oil (CTO), a co-product of the pulp and paper making process. CTO is essentially the sap of the pine tree, which is separated from the lignin and the



fibrous portions of the tree in the pulping process. CTO is collected, and through a complex distillation process, converted into a valuable array of chemicals used in products like inks, adhesives, paper sizing, paints and coatings and soaps and detergents. Beta-Sitosterol, a cholesterol-lowering food additive, is another co-product derived from the CTO distillation process.

The success of the bioeconomy strategy in Europe is highly dependent upon ensuring that maximum value is derived from available biomass resources. In order to accomplish this goal, the strategy must include the concept of ‘cascading use’. By systematically utilising biomass materials for their highest value products first, further refining remaining co-products for their value and then utilising any residuals for fuel, the EU can meet increasing demands for bio-based chemicals, products and energy without disproportionately increasing pressures on our natural resources. This methodology of ‘cascading use’ would positively reduce impacts on land and related services that EU member states provide to protect biodiversity and ecosystems.

The pine chemicals industry is a prime example of the value of ‘cascading use’. As noted before, co-products from the pulp and paper-making process are used to produce a number of valuable chemicals that are essential to literally hundreds of products. After the valuable chemicals are separated and

The success of the bioeconomy strategy in Europe is highly dependent upon ensuring that maximum value is derived from available biomass resources

utilised, the residual portion of the CTO is used as a fuel to produce heat and steam, thereby reducing our reliance on fossil energy. The industry is also continually engaged in research and development efforts to improve production and find valuable new uses for the distilled materials. 'Cascading use' makes business sense, serves the environment and the economy, and is therefore good public policy.

Properly employed, the 'cascading use' principle will reduce many potential conflicts between competing feedstock uses. For example, countries in the EU are promoting the production and use of bioenergy by using biomass directly in fuels. This has led to a significant conflict that has yet to be fully resolved, the so-called 'food vs fuel' debate. The impacts on food production and price caused by the diversion of certain feedstocks for bioenergy have been undeniably painful for many groups. Other potential conflicts between bio-based chemicals, pharmaceuticals and possibly other industries could be avoided in the future by diligent application of the 'cascading use' principle.

The biomass feedstock CTO, utilised by the pine chemicals industry, can be burned as a fuel or converted into transportation biofuels. The pine chemicals industry supports the use of renewable energy generally, and in fact, the forestry sector can be an important biomass source for fuel. However, if significant amounts of CTO are used directly or indirectly as a fuel source, thereby limiting supply for distillation and further processing, the current uses for pine chemicals will be replaced by fossil fuel derivatives. This, in effect, defeats the initial purpose of utilising biomass as a fuel to reduce fossil fuel use. Additionally, such a policy can negatively impact many jobs for workers engaged in the pine chemicals industry.

A well-designed biomass policy can serve the dual goals of promoting bioenergy and expanding the production and use of bio-based chemicals and other products. By employing the principal of 'cascading use' in the EU and its member states, we promote a win-win scenario. A bioeconomy policy that promotes bioenergy at the expense of other valuable uses is at best a win-lose proposition that can severely hinder the advancement of utilising alternative sources of feedstocks for bio-based chemicals and products.

[1] Innovating for Sustainable Growth: A Bioeconomy for Europe, 13th February 2012, European Union, Directorate-General for Research and Innovation, ISBN 978-92-79-25376-8

[2] Ibid, p. 10

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Green-grossing

World Green Building Council CEO Jane Henley highlights the business case for green buildings, and how sustainable buildings can improve bottom lines…

In the 1970s, when General Motors introduced the first airbags into the market, they were considered a luxury item. Today, airbags are routinely incorporated into most vehicles. In much the same way, sustainable design and green technologies that were once considered avant-garde are now 'business as usual'.

Many of the principles of green building – such as solar orientation, natural ventilation and use of renewable materials – are now simply considered 'good design'. At the same time, product and technology innovations have accelerated to lightning speed and everything from microturbines to green roofs, from smart meters to solar panels, are accessible and affordable.

Green building has transcended the category of high-end niche building, as the benefits across the triple bottom line have become too good to ignore. We now have a compelling business case for green building, which confirms that sustainable buildings make clear business sense.

The WorldGBC's Business Case for Green Building report, released in March, finds that green buildings are clear money savers. Green buildings routinely consume 30% less energy than non-green buildings – and often much more – which translates into direct reductions on operation costs. Energy savings in green buildings typically exceed any cost premiums associated with their design and construction within a reasonable payback period.

At the same time, a range of studies have found that 'green' and value are now inextricably linked, with a strong link between the green characteristics of buildings and the ability of these buildings to attract higher sale prices and rents. Just one example is the sale of the Pixel Building in Melbourne, Australia, which had achieved the highest ever score under the US Green Building Council's rating system for buildings, Leadership in Energy and Environmental Design (LEED), as well as the highest rating under the Green Building Council of Australia's (GBCA) Green Star rating system. Developer Grocon sold the building for AU$6m – nearly $1m more than a similar sized, similar quality office without a green rating. 'Green proves gold,' the headlines ran.

Green buildings routinely consume 30% less energy than non-green buildings – and often much more – which translates into direct reductions on operation costs

We also have compelling evidence that green buildings can be delivered at prices comparable to those for conventional buildings – and that the investment can be recouped through operational cost savings and a more productive workplace. An emerging body of evidence suggests that the physical characteristics of office buildings and indoor environments can influence worker productivity and occupant health and wellbeing, resulting in bottom line benefits for businesses. As just two examples, the Business Case for Green Building report found that improved ventilation can improve productivity by up to 11%, while improved lighting design can boost performance by as much as 23%.

Occupants of other building types also benefit from green design features. One study reported an 8.5% reduction in hospital stays when people had access to natural light, while another found a 22% reduction in the need for pain medication when patients were in rooms with bright sunlight. Other studies have found a 26% improvement in learning and even retail sales increasing by 40% simply due to good daylighting.

At the same time, governments around the world have recognised that green building programmes can deliver on their 'macro' priorities, such as climate change mitigation, energy security, minimising spend on new power infrastructure and reducing dependence on oil imports. Buildings offer the single largest opportunity to reduce emissions – and at the least cost. Scaling-up energy efficiency in buildings can also help governments to deliver on social priorities such as employment and health, while maintaining economic growth and improving the quality of life in our cities.

It is for all these reasons that green building – and adoption of the green technologies within the buildings – has escalated, as it is recognised as a long-term business opportunity. The latest World Green Building Trends report, released by McGraw-Hill Construction in conjunction with the WorldGBC and US Green Building Council, confirms this. While just 2% of professional services firms were dedicated to green building in 2005, this has grown to 28% of firms in 2012, and is predicted to reach 51% by 2015. The survey captured the sentiments of professionals in more than 60 countries.

So, what's the next step in the evolution of green building? We know that few companies make the decision to build green based on technical information about photovoltaics or wind turbines. Companies are interested in how our products – buildings – can improve their bottom lines. Once people understand that green buildings make business sense, the choice is simple.

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Self-learning technology

Significant energy savings through heating control…

From the fire in the cave, through underfloor heating in Roman villas to the modern, eco-friendly apartment, the effective use of energy to provide heat has been a challenge that has always greatly exercised the ingenuity of man. In recent decades, pre-programmed heating controllers that generate a 'heat curve' have dominated heating technology, and these devices have even evolved a measure of intelligence and adaptability.

However, in the face of mounting climate concerns and the associated need to reduce CO_2 emissions, not to mention occupants' increased discernment regarding comfort and cost, it is found that such controllers are generally too coarse and inflexible to truly optimise heating energy provision while ensuring comfort. Even the most advanced controllers available today, with their predefined heating curves, struggle to cope with the non-linear and dynamic thermal behaviour of a building.

In addition, heat curves are extremely difficult to tune. It is impossible to estimate their parameters (mainly slope and offset) without measuring outdoor and indoor temperatures over a long period. Thus, in most cases, no tuning is done and default parameter values are used that often lead to poor performance in terms of energy and/or comfort.

A significant technological advance is needed, and that advance comes in the form of adaptive and predictive HVAC control technology from the Switzerland-based company Neurobat. Its novel approach exploits neuro-fuzzy techniques to significantly improve comfort levels in buildings, decrease energy use and reduce CO_2 emissions.

A single-family house in the canton of Zürich, Switzerland

© Neurobat

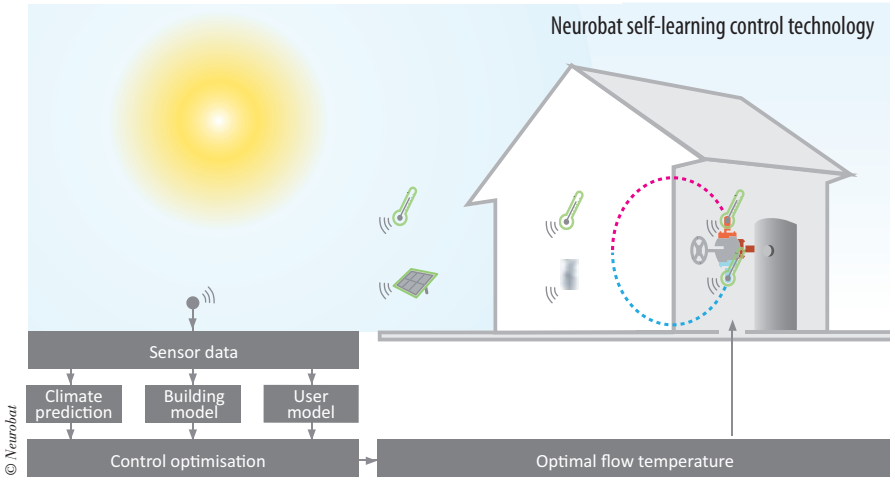
Heat of the moment

The heating controllers currently in use are often equipped with modern electronics and may sport the latest LCD display, but their control philosophy has not changed much over the decades: You pre-programme them, switch them on and they will faithfully turn the heating on and off as instructed. Too bad, then, if the sun decides to shine through the windows for an hour or two during one of the heating phases. Or what about that crowded regular group meeting in the conference room (we've all been in them)? Does the heating really have to come on exactly then? Does no-one know how to change it? And why is the heating on when that photocopier beside the coffee room is producing enough heat to melt a glacier (which, in an indirect way, it actually is doing)?

Ideally, you would stick a box of tricks on top of the heating controller that would take account of all this. Maybe this magical box could even predict the weather and anticipate the sun coming out. This is precisely what Neurobat's award-winning, adaptive and predictive HVAC control platform does.

Neurobat's patented algorithms exploit all the advantages of neuro-fuzzy technology to make sure that exactly the right amount of heat flows to exactly the right place at exactly the right time. Whether it is a commercial office or a private apartment, the controller learns and anticipates the thermal behaviour of the building – what its occupants do and when; how the building itself heats and cools; what happens when the sun shines.

It can even consult the weather forecast, turn down the heating in advance of a sunny period and exploit all that free solar energy. Even seasonal changes are easily picked up, like when shady trees lose their leaves or are felled to let more sunlight and heat into the building. The optimisation



target is to achieve a good level of comfort with the lowest possible heating flow temperature.

The consequently smaller temperature difference between the heating system flow and that of its environment results in less heat being released where it is not required. This is not a standard approach: while the traditional goal is to reduce the energy provided to the building, Neurobat optimises the flow temperature provided to the heating zone. The main argument for this is that when thermostatic valves are installed (a very common occurrence), it is impossible to influence how much energy is released to the building, as the thermostatic valves decide this according to their setting. Controlling 'heat availability' through flow temperature, however, makes suitably regulated energy release possible.

This all results in no overheating and no underheating, reduced bills, improved occupant comfort and reduced CO_2 emissions and carbon footprint. The proof of the pudding, you might say, is in the heating. The technology has been exhaustively tested in a wide variety of building types and the results were dramatic: energy savings of up to 35% were recorded when compared to a traditional controller's performance.

Brain box

OEM customers can use Neurobat's NBM product to complement their own controllers. NBM monitors the same inputs as the controller, works out the optimal control values and supplies these to the controller. It is like the brainiest kid in class whispering all the answers in your ear. The controller then commands its valves, pumps and so on as before, but now with the certainty that the best use is being made of the heating energy. The OEM need not change his own product, except to modify the software so it delivers the data needed to the NBM module. This way, the costs of installing and commissioning the heating system are minimal and significant energy savings are made from the outset.

If you already have a controller, then Neurobat's NIQ merely takes over the sensor inputs, processes them through its patented algorithms and sends an appropriately conditioned signal to the controller, which then instructs the valves and pumps accordingly. Put simply, NIQ adds a very clever brain to the existing controller. If neither of these two solutions suit, there is an online service, NOL. NOL extracts the relevant data from the building system, sends it to an off-site Neurobat server and returns the appropriate commands to the building system.

Easily installed and maintained

Despite the sophistication of its neuro-fuzzy technology, Neurobat requires only one configurable parameter at commissioning time: the optimal indoor temperature set point. Just plug it in and set the desired temperature, and the self-learning technology will figure things out for itself as it goes along. The parameters relating to the heat curves, the trickiest ones, no longer have to be tuned as they are determined by the self-learning facility. A traditional installation may require the input of many dozens of parameters – the elimination of this procedure is one of Neurobat's major advantages.

Awards

The value of Neurobat's approach has been recognised. In 2005, the fledgling technology won the Swiss Technology Award, which is the most prominent prize given in Switzerland for technological innovation. In 2012, the mature product won the prestigious Swiss Environmental Prize.

Neurobat technology is now coming onto the market. "The arguments for the technology are very convincing and are summarised very clearly at the bottom of your gas or oil bill," says Sohail Malik, Neurobat's CEO. "Not only that, but heating buildings consumes around 40% of primary energy in developed countries, so Neurobat's devices are essential if you want to achieve large energy usage reductions and reduce CO_2 emissions significantly."

NEUROBAT
INTERIOR CLIMATE TECHNOLOGIES

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Green technologies for aviation

The Clean Sky initiative…

Flying has become an essential part of modern society; a means of bringing people together as well as an instrument of global trade and economic growth. At the same time, the industry has shown itself to be sensitive to environmental concerns such as air and noise pollution, and climate change.

In collaboration with partners from the aviation industry, the Fraunhofer-Gesellschaft has set an important objective within the European Joint Technology Initiative 'Clean Sky'. The researchers are hoping that their work will help to significantly reduce CO_2 and NO_X emissions, as well as perceived levels of aircraft noise. The main issue at stake is 'ecolonomy', or ecological economics – in other words, the question of how to steadily make aircraft more eco-friendly without incurring excessive costs. In addition to reducing emissions and noise, other key strategies include improving energy efficiency and promoting a sustainable life cycle.

The Clean Sky initiative consists of six technology areas, the so-called integrated technology demonstrators (ITD). These are ecoDESIGN®, Green Regional Aircraft, Smart Fixed-Wing Aircraft, Green Rotorcraft, Sustainable and Green Engines, and Systems for Green Operation. They are connected by the Technology Evaluator, where they are evaluated in terms of environmental objectives. Under this initiative, it is expected CO_2 emissions will be reduced by 50%, NO_X emissions by 80% and noise by 50%. The Fraunhofer-Gesellschaft leads activities in the research area of ecoDESIGN® on the use of current and future materials, processes and technologies, amongst other areas.

Numerous studies predict a sharp increase in both freight and passenger traffic in the coming years. In order to reduce the impact on the environment in spite of the rising volume of traffic, it will be necessary to conduct research into new, eco-friendly design concepts and to optimise existing processes. In order to support the fulfilment of the goals of Clean Sky, the ENDAMI project was launched.

ENDAMI stands for Environmental Data Models and Interface development in Aviation. It supports the Clean Sky goals by quantifying environmental impacts of aviation specific products and processes. The method used for this quantification is Life Cycle Assessment (LCA), which is standardised in ISO 14040/14044 and widely applied in industry and academia for the quantitative assessment of environmental impacts of products and systems.

In cooperation with the Department of Life Cycle Engineering (GaBi) at the University of Stuttgart, the Fraunhofer Institute for Building Physics (IBP) has created an aviation-specific database with process and component information based on information from aircraft manufacturers and material suppliers. In addition, a specific ecoDESIGN® tool has been developed for use in the aerospace industry.

The tool provides a comprehensible, intuitive interface with which, for example, aircraft designers without specific knowledge can calculate complete LCA results for various design alternatives. The underlying models are created by experts in the GaBi LCA software. In the interface, materials and processes can be varied, as well as various scenarios for production, and manufacturing processes can be created so the environmental impacts of the different alternatives can be compared directly. With this tool, the expert knowledge that is necessary to create complex LCA models in the appropriate software is made available for design teams to enrich the field of application of the LCA method.

To perform LCAs in aviation, major process routes and their interdependencies with environmental impacts were identified. The major dependencies were parameterised in generic aircraft LCA models and, finally, the link between the components and the setting of process parameters was made.

In this way the Life Cycle Inventory (LCI) modelling is transferred to a central server,

providing aviation specific background data, which is maintained by LCA experts and so ensures a high data quality. The LCI models can be extended and new aircraft parts can be added. The server, a pool of parameterised LCI models for aircraft parts, relies on the comprehensive GaBi database. The ecoDESIGN® software tool is an extension of GaBi LCA software and supports Design for the Environment (DfE).

To model the environmental impacts of different aircraft types, designers are able to modify components by varying weights, surfaces, material properties and production processes – partly in predetermined range. Next to a 'reference airliner', different scenarios can be modelled to compare the environmental impacts of different design alternatives of aircrafts and their components.

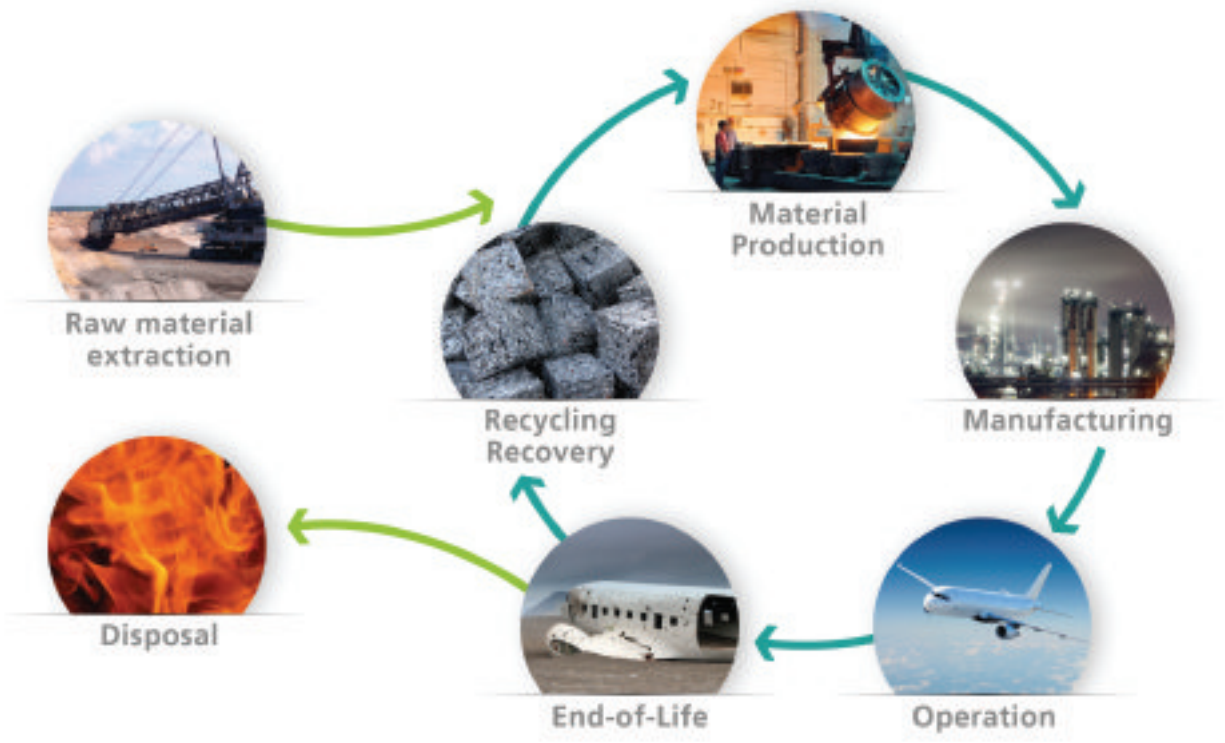
The results are available as inventories with a detailed list of various individual selectable emissions, or as aggregated environmental impacts, and new impact methods can be added as proposed by ISO.

ecoDESIGN® software tool: the advantages

- Easy-to-use interface;
- Complex expert LCA model in the background;
- Compliancy to LCA standards;
- Evaluation of different scenarios;
- Detailed LCA from cradle to grave, based on expert background models;
- Comprehensive, high-quality data;
- Aviation specific datasets integrated.

Client-server architecture: benefits of central data storage

- Transfer of complex LCI modelling to a central server that is maintained by LCA experts;
- Pool of parameterised LCI models for aircraft parts;
- Central data storage and maintenance ensures data consistency;
- Updates are available for every user (in real time);
- Define access rights for different design teams.



Due to the expected growth in the aviation sector and the long life cycles of aircrafts, the accompanying assessment of the development processes is extremely important for the systematic reduction of the aviation sector's environmental impact. The use of LCA and the ecoDESIGN® approach allows the investigation and quantitative evaluation of the potential ecological value of different materials, processes and technology methods. The activities of the Fraunhofer-Gesellschaft under Clean Sky are important elements on the path to sustainable aviation.

The Fraunhofer-Gesellschaft has a seat on the Governing Board of the Clean Sky initiative, next to leading companies in the aviation industry such as Airbus, Alenia, Dassault Aviation, EADS CASA, Eurocopter, Liebherr-Aerospace, Safran, Agusta Westland, Thales, Saab AB and Rolls-Royce.

About the Clean Sky Joint Technology Initiative

Clean Sky is a five year old public private partnership that keeps its promises and demonstrates commendable achievements. To date, more than 20 large demonstrators are being developed at high maturity level and some 2,000 people are working on projects financed by Clean Sky.

It is projected that some 10,000 (full-time equivalent) highly skilled people will be involved in the overall implementation of this programme. Clean Sky's result-driven approach delivers highly mature solutions in line with business requirements and contributes to the achievement of the ACARE 2020 goals by developing technologies that offer an approximate 30% reduction in CO_2 emissions and perceived noise and an 80% reduction in NO_X emissions.

Building on Clean Sky's initial successes and its proven and effective governance approach, Clean Sky 2 aims to achieve a higher level of technology integration at aircraft level and to raise the maturity level of systems incorporating these new technologies. Clean Sky 2 is a vital enabler to develop and mature breakthrough innovations in Europe's aviation sector. With a foreseen budget of €3.6bn funded by the European Commission and the aeronautical industry, it is the force that will ensure the vital step changes required in technologies, systems and architectures. Clean Sky 2 will pursue the efforts to fully meet the European Aviation Research technology goals in ACARE 2020. The programme will pave the way for a new wave of technology breakthroughs in line with the ACARE Flightpath 2050 objectives concerning carbon emissions, noise, societal challenges relating to enhanced mobility, and fundamentally, European industrial competitiveness, for which innovation is the key word.

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Bolstering the basins

The European Geosciences Union's Gerrit H de Rooij looks at the causes of the 2013 floods in the Danube and Elbe basins and asks how future episodes can be avoided…

Economically, ecologically and aesthetically, scattering empty reservoirs in often pristine landscapes seems unappealing. In contrast, capturing in reservoirs the rainwater that falls in cities is both attractive and feasible.

In June 2013, the Elbe and the Danube rivers and their tributaries flooded towns, city centres and roads. These floods were unexpectedly severe considering the rainfall that triggered them. Why did this happen, can such floods be prevented and, if not, can we minimise their damage to life and property?

The Elbe originates in low mountain ranges. It is fed by rain and, in spring, by snowmelt. The Danube catchment has a glaciated alpine region, but nevertheless mainly discharges rainfall and snowmelt. The floods occurred well after snowmelt and before the autumn rains, at a time of year in which the vegetation takes up large amounts of water and thus funnels water that precipitated earlier back into the atmosphere before it can reach a river.

Heavy rains in late spring and summer are often associated with a north-eastern air flow from the Mediterranean that carries moist air to the central European mountain ranges. This was the case in May and early June 2013, but why was the river response so extreme? The answer lies in the terrestrial part of the hydrological cycle. It starts when a falling raindrop (or snowflake) hits the vegetation or the soil surface. If it is not locked up in a glacier for centuries, there are various pathways the water can take. Some of it evaporates straight back into the atmosphere. Whether the water remaining on the soil surface will infiltrate depends on the soil: when the soil is unsaturated (as it often is), the air-filled portion of the pore space can be occupied by infiltrating water, to be transported to deeper soil layers later. In saturated soil, the amount of water that can enter the soil is limited by the flow rate of soil water to larger depths.

In sandy and loamy soils, the pore space takes up 30% to 50% of soil volume. Clay and peat soils have more, but most of their pores are filled with water throughout the year. Only the air-filled pore space is available for rapid storage of infiltrating water. If earlier rains filled up this pore space, water in excess of the soil's capacity to absorb it will collect in puddles that will grow and eventually discharge into the discharge network of ditches and brooks. This surface runoff provides a rapid pathway to the river. Surface runoff is erosive, and the soil particles it carries along turn the river water murky, something that was clearly visible from the footage of the floods.

When there are air-filled pores available, water can infiltrate. A fraction of the water infiltrating into the soil can escape back into the atmosphere by evaporating from the soil surface when the rain stops. It can also be taken up by plant roots and be transferred back to the atmosphere by the leaves. This pathway through the plant supports life on Earth by allowing plants to grow, thus sustaining terrestrial ecosystems. In middle and northern Europe, precipitation exceeds the sum of evaporation (from the soil) and transpiration (through the plants), and a portion of the infiltrating water will escape the roots and eventually replenish the groundwater. Even there it can be taken up by specialised plants with deep roots tapping into the groundwater, or flow up, back into the soil, during dry periods and become available again to plant roots. But most of the groundwater feeds the rivers. This long travel path through the subsurface generates a damped flux of water into the rivers: it exhibits seasonal fluctuation (often with a delay of up to several months), and its trend over the decades reflects changes in land and water use, and in weather patterns. But it is much less sensitive to very intense, short episodes of heavy rainfall.

With this, the chain of events leading to the floods becomes tractable: snowfall in late winter melted and wetted up the soils. A wet and cold spring further filled up the soil pore space, while simultaneously delaying plant growth and budding. This limited transpiration and less water was taken up from the soil than usual. The extra water in the soil elevated the groundwater levels, which in turn increased the pressure in the groundwater, leading to a larger influx into the rivers. Much more important though was the storage in the soil pore space. There was hardly any available for the rain in late spring,

The 2013 Danube basin flood led to emergency action from the Hungarian and Slovakian governments and halted all shipping along the Austrian stretch of the river

which therefore had to be discharged largely by surface runoff. To handle all that water, rivers had very high water levels and occupied a much wider area than usual.

The generation of surface runoff; exacerbated by the ever-increasing paved area as urban areas expand and the road network gets denser. Most of the water falling on pavements and roofs is channelled into ditches or sewage systems and efficiently delivered to the river system. Increasing urbanisation thus makes river responses to rainfall more spiked.

The weather that generated the floods was unusual, but not highly improbable – the sequence of events will probably repeat itself. Building better dams sounds like an obvious protection measure, but constriction of the river bed by buildings in the floodplain, combined with high discharge spikes caused by urbanisation, would require very high dams to contain the water in a narrow cross section. The failure of such a dam would be disastrous. Instead of squeezing the rivers into a narrow channel enforced by massive dams, a combination of mitigation measures seems prudent.

There has been enthusiasm in some quarters for building storage reservoirs in the mountain regions from which the main river branches originate. These would fill and then gradually empty, thereby flattening the discharge peak. The Elbe and Danube have tens of tributaries, many of which would require such reservoirs. These need to be empty most of the time, only to be filled in a narrow time window: fill them too early, and the storage capacity won't be available when it is needed, fill them too late and the high-water wave will propagate downstream undamped. Economically, ecologically and aesthetically, scattering empty reservoirs in often pristine landscapes seems unappealing. In contrast, capturing in reservoirs the rainwater that falls in cities is both attractive and feasible.

Alternatively, sparsely populated areas further downstream could be designated to store rain by keeping the groundwater low and the soils permeable (through tillage or, for instance, by planting trees, the root networks of which create conductive channels once they die and perish). These areas store rain (and river water if they are permitted to be flooded), while at the same time allowing the soil to be productive between floods.

Instead of storing the water and releasing it gradually, it can also be carried downstream more effectively. Increasing the river cross-section by clearing the floodplain of obstacles or compensating for those that have to stay by deepening the river bed reduces the required water level to accommodate high discharge rates. Such measures must first be executed downstream; otherwise, the more efficient water delivery from upstream will increase the chance of flooding in areas where such measures are not yet implemented.

Finally, areas could be designated for controlled flooding. In these regions, houses and towns may be protected by surrounding dams or rebuilt on artificial hills (as done near the North Sea Coast in the 2nd and 3rd Centuries). This last resort measure is to be preferred over an uncontrolled breach of a dam, which carries a much higher risk for those behind it.

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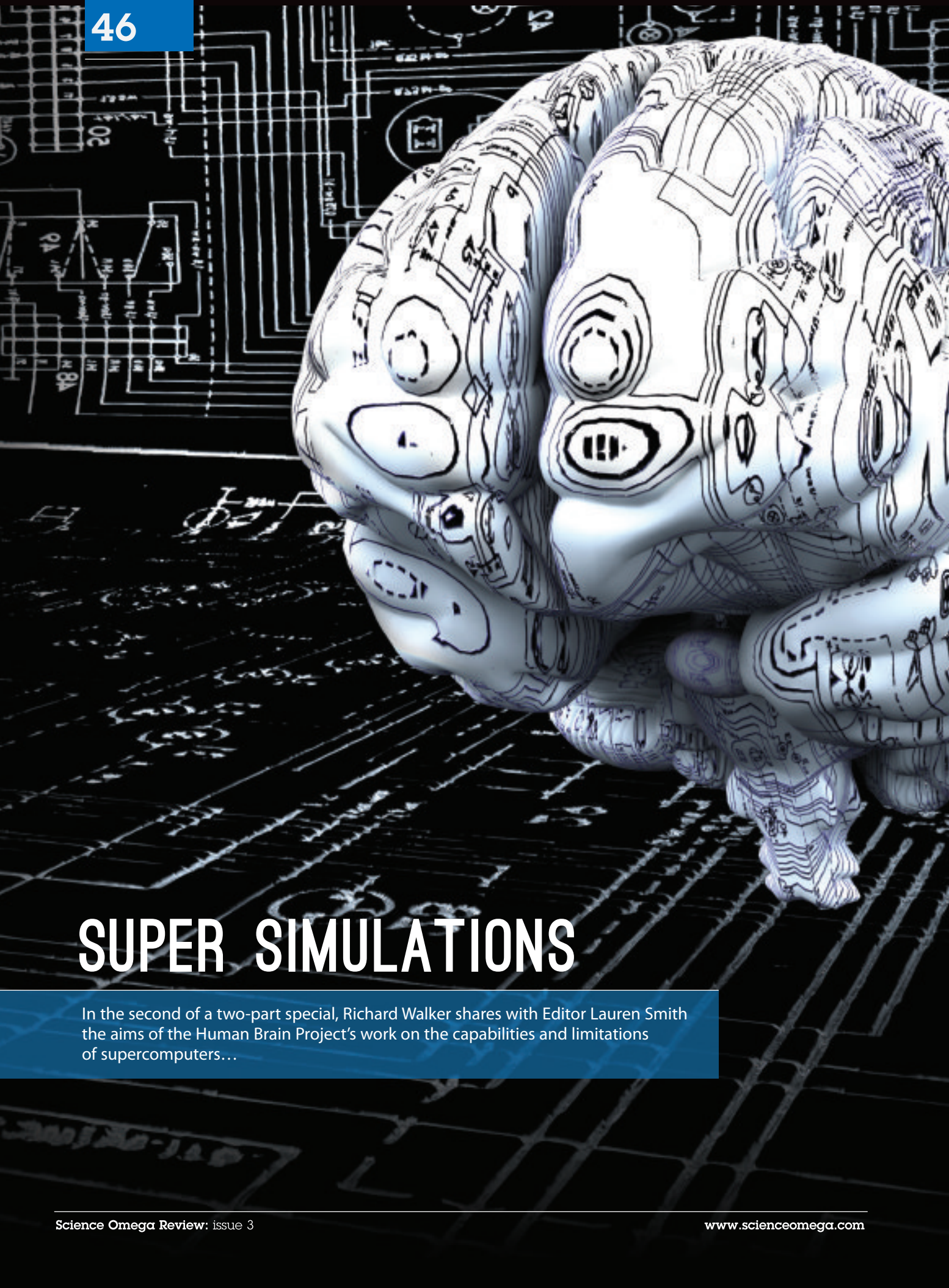


SUPER SIMULATIONS

In the second of a two-part special, Richard Walker shares with Editor Lauren Smith the aims of the Human Brain Project's work on the capabilities and limitations of supercomputers…

The European Commission announced two EU Future and Emerging Technologies (FET) flagship programmes in January to drive forward radical scientific research across the continent and enable greater understanding of key elements in our society. With each to be allocated €1bn in funding, one focus area was the wonder material graphene, the other the vast Human Brain Project (HBP), which hopes to gain profound insight into the nature of humanity, to develop new treatments for brain diseases and develop revolutionary computing technologies.

In June's edition of *Science Omega Review*, Human Brain Project (HBP) Spokesman Richard Walker spoke to Editor Lauren Smith about the vast scope, expectations and hopes being placed on the initiative. In the second part of our feature interview, he this time focuses particularly on the possibilities for, and implications around, the use of supercomputing.[1]

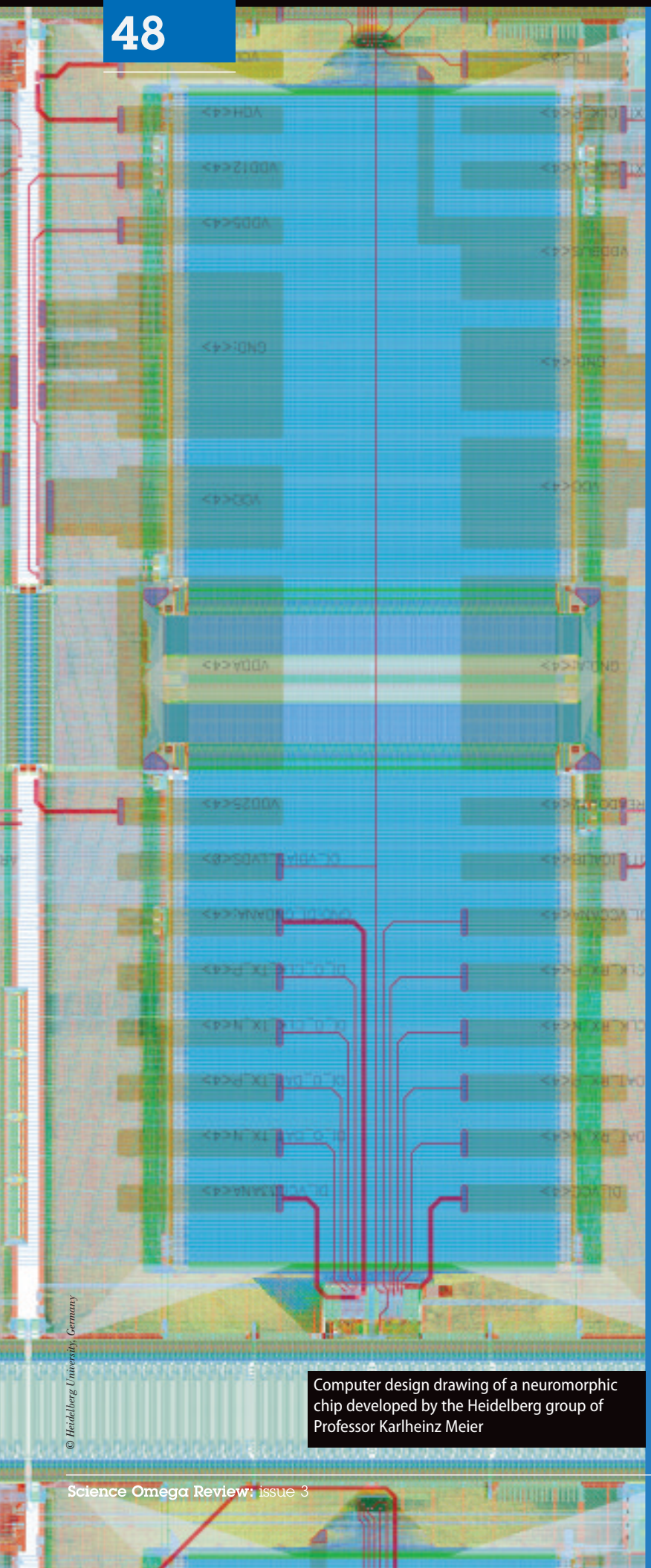
The project will require a massive amount of computational power on which to develop the proposed models, and it is acknowledged in the outline plan that the supercomputing capacity needed to continue to pursue this task in the long term does not yet exist. However, Walker does not feel that this will be problematic, suggesting that the systems will develop in sufficient time for their needs.

'There are plenty of problems that human beings and animals resolve easily on a regular basis that computers find hard to resolve.'

"Supercomputing has very well established roadmaps showing where it is going," he explains. "It is fairly clear that sometime between 2020 and 2022 it will be possible to get exascale computers. We're not currently building models of the whole human brain – at the moment we have models of parts of the rat brain and will be scaling these up and moving onto models of the whole mouse brain. The computing power that we know will be installed by about 2016 will be sufficient for that. We know from our current work how much we need and we can extrapolate from that.

"We believe that the computers we will have by 2022 will be sufficient to build a whole human brain."

Walker is keen to explain that this doesn't mean that they are aiming to create an artificial human,



© Heidelberg University, Germany

Computer design drawing of a neuromorphic chip developed by the Heidelberg group of Professor Karlheinz Meier

since there will be several key differences between the brain models and the real organ.

"Our simulations work much more slowly than the real brain – currently about 100 times slower," he elucidates. "So, for one day of a human's life we would need 100 days in the simulation. Additionally, our models are what we call 'snapshot' models. We take the average brain as it is at a certain age, in a child, adult or an elderly person, but it will not reflect the experiences of a whole life that you would see in an actual human brain."

There are some moral and ethical implications of developing ever more advanced and emotionally complex artificial intelligence that need to be considered under the project's remit. To this end, it will incorporate a major Ethics and Society Programme. Walker describes that they are keen to address any public concerns about morality, along with any potentially more significant ethical considerations that have already been recognised.

"We would like to have a dialogue with the public, where we can perhaps dispose of some fears," he says. "Some people may be concerned that we are creating an artificial human being, which is not the case. At the same time there are genuine ethical issues. There are common ones, such as with animal research, but then there are also ones that people think of less, such as about building neuromorphic technologies with very great computing powers and potentially flexible cognitive capabilities that we don't have in current computers.

"For instance, if you put this in the hands of the military it could have unsettling complications – do we want our drones to become really intelligent?"

Walker doesn't believe such examples are a justifiable reason to stop research, but highlights that they want to investigate such implications to provide early warning of any impending issues that may arise. The intention is then to publicise the information and lead a wide-ranging debate about any repercussions, giving opportunity for input from social, legal and political realms.

Whilst computing plays a central role in the project development, in turn, the HBP is likely to have extensive influence on future computing models and hardware usage. Although modern computing is extremely effective, Walker suggests that what is likely to be learnt from the human brain could bring revolutionary additions to the field.

"We have incredibly powerful, fast machines at present, but they have a number of limitations," he says. "There are plenty of problems that human beings and animals resolve easily on a regular basis that computers find hard to resolve. For example, if I

look out of my office over Lake Geneva, I see the mountains on the other side. You could ask me a random question about what I see and I could answer it with no effort – as could a five year old child. No computer in the world can do that today. Even with something like IBM's Watson; it does very well, but that requires a massive programming effort, whereas a child could do some of the same things with very little effort at all."

Although computers obviously do some things much better than a brain, such as calculations and word processing, the lack of flexibility to respond to new things is a major limitation. Computers also consume huge amounts of energy and, as Walker explains, a supercomputer will have hundreds of thousands of processors running simultaneously, all consuming energy – whereas the brain, activating all of the normal functions and processes – is likely to consume a million times less over the same period. Although many more differences could be cited, another significant one is that the brain is considerably more reliable, starting to work as it develops in the womb, and in most cases continuing to work for many decades – a feat that no computer has even come close to emulating.

"The reason the brain can do all of this is that it doesn't work like a computer," Walker outlines. "It isn't programmed – it learns. It has very effective neurons and makes a huge number of parallel, imprecise and slow calculations. Although neurons function much more slowly than modern micro-processors, we would like to learn from the way that the brain does computation and build computing devices that work that way, to actually produce the circuitry, low-energy usage and reliability of the brain.

"We don't think that this will replace modern computing, which is wonderful at what it does well. Instead, it will complement modern computing by doing things that it can't – working faster, more efficiently and reliably. We all know that predictions tend to go wrong, but if I was to speculate what future computing would look like, I would suggest that in 20 years time we will have comparable computers that are even more powerful than those we have today, side-by-side with computers inspired by the architecture of the brain."

Walker cautions that we shouldn't expect miracles, highlighting the decades it's taken to develop from the early 1950s transistor – through basic technologies, to what we have today.

As he concludes, "I'm very confident of the developments we will enable, and that either we ourselves or people following on top of what we've done will be able to make notable contributions to technology."

Richard Walker
Project Spokesman
Human Brain Project
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Why basic biochemistry needs a funding boost

Dr Lars Rask, of the Federation of European Biochemical Societies' Science & Society Committee, calls for improved funding support for European biochemistry…

The landscape of funding for public life sciences, including biochemistry, has changed dramatically during the last three decades. Traditionally, most of the public funding within these areas consisted of three year grants to individual scientists. In Europe, the main exception was EU funding to groups of scientists from different countries, which aimed to promote research collaborations between the different EU member states.

The evaluations of grant proposals by national research councils and research foundations were almost exclusively based on criteria that focused on funding proposals of the highest possible scientific quality. The evaluators were selected to have high competence within the area of evaluation, e.g. applications within biochemistry were evaluated by high ranking biochemists; this meant that important research problems might be funded, even though they might have been considered to be esoteric by non-biochemists.

Today, the pattern of research funding has partly changed. It is still possible for individual scientists to apply for research funding from national research councils, research foundations and within the EU from the European Research Council (ERC); however, a large amount of research funding goes into different kinds of 'synergy grants' for groups of researchers – often with different but complementing competencies that are important in solving the research questions in the applications. In many cases, these grants are supposed to solve research problems of industrial or societal importance, not necessarily of high scientific interest.

Another emerging pattern within research funding is the investment in large-scale '-omics' projects, like genomics, transcriptomics, proteomics and metabolomics. These projects usually result in numerous scientific leads, identified mutations, transcripts encoding proteins, proteins or metabolites potentially involved in diseases, or valuable traits within animal or plant breeding. The investments in these types of studies are, as such, commendable. However, there is a fundamental imbalance between the amount of money spent on these large-scale projects and the funding of the necessary biochemical characterisation of the proteins and metabolites identified in them.

The problem is that detailed biochemical studies are usually carried out by specialist research groups with high competence in a specific research field, such as a type of metabolites and their physiological effects, a metabolic chain or even a specific protein and its post-translational modifications. The large-scale -omics studies might result in interesting ideas for numerous research projects, each one demanding the attention of several research groups within biochemistry, physiology and cell biology. In addition, high-quality experiments are definitely facilitated if the 3D structure is available for the protein under study, which necessitates studies by X-ray crystallography or NMR. That means for each euro or dollar spent on -omics projects, maybe 10 to 100-fold more euros or dollars are needed to fully exploit these investments in new knowledge. At present, financing on such a scale for these types of projects is not available, at least not in Europe. It is also clear that even applied areas like clinical medicine, plant breeding and husbandry benefit from high-quality basic research in biochemistry.

The lack of sufficient project financing for biochemistry and other areas like physiology also hampers the recruitment and education of next generation biochemists. The number of research groups with both high competence and good economical resources is continually diminishing, at least in Northern Europe. Instead, research groups that are active within a much broader area, such as a combination of biochemistry, cell and molecular biology, are increasing. In reality, these groups obtain their reagents, like antisera or recombinant proteins, from commercial sources. Very few of these groups have

***Science Omega Review* comment:**

Support for biochemistry, and life sciences more broadly, is strong in Europe and creates many vital research networks for knowledge and innovation across these fields. Part of this success can be attributed to collaboration, not only at the level of individual researcher or researcher group, but also at organisational level. The Federation of European Biochemical Societies (FEBS) is due to hold a joint life sciences conference next year in partnership with the European Molecular Biology Organisation (EMBO), and alongside the French Society for Biochemistry and Molecular Biology. The FEBS-EMBO 2014 Conference is planned to be an international event that brings together many leading researchers to discuss the latest scientific findings in the field, offering unparalleled scope for the entire range of the molecular life sciences.

"I believe the strengths of each organisation will contribute to an outstanding event for all life scientists," Israel Pecht, Secretary General of FEBS, comments. "It will also be an ideal opportunity to celebrate the achievements of all three organisations over the past decades."

Maria Leptin, Director of EMBO, remarks: "High-calibre conferences where scientists of all ages have access to the very best speakers are an essential part of building a research community," that will "help to increase the impact of our efforts to create a research environment where scientists can achieve their best work."[1]

EMBO promotes excellence across the life sciences, supporting talented researchers at all career stages to stimulate the exchange of scientific information and enhance the European research environment. With a broad geographical reach encompassing approximately 1,600 members (or associates), both within Europe and globally, the organisation assists the development of vital research and collaboration from genomics to biochemistry, systems biology to virology and beyond, including fellowships, young investigator funding and relocation grants.

[1] www.embo.org/news/press-releases/press-releases-2013/febs-embo-and-the-french-society-for-biochemistry-and-molecular-biology-to-hold-joint-conference-in-2014?

the competence and/or the tenacity to purify and characterise proteins, carbohydrates, lipids or other compounds *de novo* from a tissue, be it from plant or animal origin.

In reality, this means intricate secondary modifications that are absolutely essential for the function of the proteins in question are easily overlooked. PhD students in the biochemistry labs, in order to save precious time, rely more and more on commercial kits for their experiments, with the unfortunate result that they sometimes neither understand exactly what they are doing, nor can evaluate the results obtained in a proper way. There is, however, no way back. Commercial kits will increasingly be used in the future and all modern techniques, such as the various modes of mass spectrometry and NMR analyses, should be used whenever applicable.

The development of national platforms that offer education and access to these types of expensive equipment, together with ample advice on how to utilise them, is very good. It is also important to educate young biochemists in biophysical techniques, and in the isolation and characterisation of macromolecules and low molecular weight compounds. There is still time to educate a new generation of biochemists in all the modern techniques available today, but the time to achieve this is limited. Therefore, it is essential that funding for basic areas, such as biochemistry, is increased substantially in the near future.

However, biochemists should by no means work in isolation from other life science researchers. On the contrary, they should, when needed, collaborate with scientists skilled in, for example, molecular biology, cell biology, imaging, structural biology or physiology. Such collaborations are usually scientifically stimulating and fruitful. They might even be essential in order to publish in high ranking scientific journals. In many cases, to be successful with a manuscript's submission, it is now necessary to offer the journal – even journals specialising in biochemistry like the Journal of Biological Chemistry, Biochemistry, or European Journal of Biochemistry – a 'complete story', in which data is presented in a broader context. In reality, that means the biochemist has to collaborate with scientists skilled in other areas. Even though each scientist within such a collaboration has contributed only part of the results presented in the article, he/she would be responsible for its total content. In well-established and tight collaborations, this would not be a major problem, since the collaborating scientists will undoubtedly develop a good insight into the scientific areas of their counterparts. However, without increased and stable funding for biochemistry, skilled biochemists will be rare in the future.

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The (blue) sky's the limit

Lunenfeld-Tanenbaum Research Institute's Jim Woodgett warns that neglecting basic research in favour of applied science is a mistake…

Modern societies invest in research for the compelling reason that history has repeatedly shown that it pays off with economic growth and prosperity. Societies without abundant natural resources, such as Japan, Taiwan and Singapore, have formalised investments in science and technology and protected these, even in times of economic and natural disaster. Emerging mega-economies such as India and China tend to plan for three or more times the rate of scientific investment than more mature economies.

Recognising its utter dependence on government support, scientific communities around the world have willingly promised their respective governments significant returns on investments in exchange for greater funding. For example, the $3bn cost of the Human Genome Sequencing Project has been claimed to generate economic returns in excess of 140 times the initial investment. It is hardly surprising, therefore, in a time of bloated budget deficits and high unemployment, that governments are looking to cash in on their investments and these previous promises. The obvious consequence is a shift towards more applied science, an increase in partnerships with industry and emphasis on lower risk development – leading (it is hoped) to new products and wealth creation.

There has also been a perceptible shift in the priorities of non-governmental agencies such as charities. In the health charity sector, there is increasing demand for donors to see the results that impact their loved ones sooner rather than later. Ever since US President Richard Nixon's declaration of a 'War on Cancer', hundreds of billions of dollars have been

spent on research. There have been significant developments, better therapies and improved outcomes, but the number of people dying from cancer has hardly been affected, even when ageing demographics are taken into account. Donors, and by extension fundraisers, are right to demand better results. Surely, we know enough and it's only a matter of translating that knowledge into better drugs and treatments? The same is true for heart disease, diabetes, Alzheimer's, mental health, etc. Indeed, there are plenty of scientists and fundraisers willing to promise new cures in the foreseeable future.

These developments are all perfectly reasonable on the surface and, in times of fiscal pressure, entirely predictable. Governments and charities are in the business of improving the lives of their taxpayers and donors, not in keeping scientists employed. Why not accelerate the process, focus on products and generate new jobs, businesses and cures? Without new funding, such efforts necessarily redirect money previously targeted towards basic science, also referred to as 'blue sky' or 'discovery' science. Is this such a bad thing and, if so, why?

To answer this question first requires an admission of guilt by the research community. We have, either directly or by omission, given our benefactors the distinct impression that basic science behaves in a manner that is at least partially predictable. In other words, we have effectively bluffed what we do and how we operate, at least in terms as understood by our funders. The fact is that basic science cannot make reliable forward projections. There may be some exceptions, such as the Large Hadron Collider, which has provided such a technical advance in high-energy physics as to allow meaningful prediction of results, but in most cases, what we recognise as genuine breakthrough discoveries are largely serendipitous. That is not to say that basic science is random – clearly, there are environments and behaviours that favour success. The density of Nobel Laureates from the Laboratory of Molecular Biology in Cambridge defies the logic of pure chance in scientific impact. But it is also a truism that the most important work a scientist does is typically done before she/he is 40, at least in the life sciences. The reasons for this are complex, but also relate to reduction in risk and adaptation to mainstream dogma (not 'rocking the boat') that is a natural survival tendency in a world where research support is divided in three to five year increments with ever-decreasing chances of approval.

Indeed, the modern research machine is in danger of suffocating that upon which it depends most dearly: not funding, but originality of ideas. As funding has become tighter, funding agencies have demanded greater accountability and reporting. Peer review, the cornerstone of scientific adjudication that is meant to recognise the best quality ideas, has become cynical and conservative. Truly new ideas are typically shot down as being ridiculous or counterintuitive. We cling to our current models of the universe and only allow subtle, pedestrian refinements. Surely, the bulk of human knowledge cannot be wrong? Meanwhile, funding agencies, under direction from their masters, insert provisions and assessment criteria to encourage and reward characteristics such as 'relevance', 'impact' and 'socioeconomic benefit'. If we were being honest, basic scientists would point out that relevance is an incredibly poor predictor of original discovery. Major discoveries rarely have immediate use or benefit. They are often stumbled upon while asking completely distinct questions. Often, the significance is not fully appreciated by their discoverer, it is doubtful, for example, that Fire and Mello perceived the subsequent revolution in biomedicine enabled by their discovery of RNA silencing in the nematode worm (Nobel Prize in Physiology and Medicine, 2006).

The greatest threat to basic science is therefore not increased emphasis on translation or application of science. These are valuable and essential products of basic science, which feedback and provide future support. There has always been a broad spectrum of research, from the most basic of ideas to the most useful. What is far more dangerous is our arrogance and fundamental misunderstanding of the nature of ideas. That we generate more bioinformatics data each year than in all previous years combined reflects efficiencies in data generation, not understanding. The sheer volume of our knowledge base is not an indicator of its accuracy or utility. In other words, we have no idea how much more there is to be learned. All we can know is that it's immensely more than we currently perceive. As a single, obvious example, pharmaceutical development remains an impressively inefficient process where the vast majority of drugs fail at enormous cost. Is that due to big pharma incompetence (from each and every company) or the fact that our basic understanding of physiology remains woefully lacking?

In our race to squeeze faster fruits from science, we must be extraordinarily careful not to take shortcuts that asphyxiate our tenuous and ill-understood methods of birthing true discovery. We must avoid programming out the risk and initial absurdity that accompanies new ideas. We must be patient. We must, above all, stop expecting basic science to conform to our own inherently limited and established perceptions of the universe.

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Discovery science and clinical synergy

Maximising impact nationally and internationally…

The Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital (Toronto) is a landmark in the Canadian biomedical research landscape. Home to 50 core investigators and 60 clinical researchers, the institute is small, but mighty. While seen as a top tier leader in discovery research in its own right, the institute also effectively synergises with the clinical programmes of the hospital, creating value for patients, researchers and the community.

The Lunenfeld-Tanenbaum (formerly the Samuel Lunenfeld Research Institute) has a short but storied past. In 1985, its Founding Director, Dr Lou Siminovitch, a Canadian research pioneer and master architect of the modern Toronto research landscape, fused the disciplines of genetics and molecular biology in the institute. A decade later, the institute was already ranked within the top 10 research institutes worldwide, with peers such as the Salk Institute and the Whitehead Institute, based on citation analysis in the field of genetics and molecular biology (Science-Watch, papers published 1994-1998).

More recently, the institute has strategically expanded its focus. Scientists such as Andras Nagy, Janet Rossant and John Roder steered the institute in the late 1990s as a powerhouse for embryonic stem cell science and mouse transgenesis – areas that continue as strengths today.

In the early 21st Century, cancer biologists, including Jeff Wrana, Frank Sicheri and Jim Dennis, introduced high-throughput methods and robotics infrastructure as key to systems biology, while recruitment of investigators such as Anne-Claude Gingras, Dan Durocher, Laurence Pelletier and Fritz Roth has maintained the institute at the cutting edge of large-scale data analysis, visualisation and imaging.

Today the institute's lauded productivity continues, with researchers publishing 600+ research articles in peer reviewed journals each year. Its $100m budget positions it in10th place in size among research hospitals in Canada, but its research intensity, as measured in $ per investigator, ranks it easily in first place (www.researchinfosource.com).

Lunenfeld-Tanenbaum researchers have been internationally recognised for their research impact; lauded researchers include Tony Pawson, pioneer in understanding modular protein interactions, winner of, among others, the Gairdner Foundation International Award, the Kyoto Prize and the Wolf Prize in Medicine, and one of seven worldwide 'Citation Laureates' (Medicine) named by Thomson Reuters in 2012. The institute is also home to four 'Highly Cited Researchers': Jeff Wrana (molecular biology), Tony Pawson (dual awardee: biology and molecular biology), and Eleftherios Diamandis and Edward Keystone (both clinical medicine).

The institute's leadership and extensive collaboration in biomedical research is shown in the large range of multi-institutional clinical trials it has led, with participation in 70 large clinical trials and research consortia, and collaborations with nearly 1,000 institutions in 60 countries.

For example, Irene Andrulis heads the Ontario Familial Breast Cancer Registry, part of the international Breast Cancer Family Registry, and recently helped launch the Canadian-American LEGACY Girls Study tracking how lifestyle, environment and biology affect development. Neonatologist Shoo Lee established the Canadian Neonatal Network (27 hospitals and 16 universities) and the International Neonatal Collaboration, and is involved in collaborations with 200 hospitals internationally. Mark Silverberg has been involved in leading several international efforts in inflammatory bowel disease, including the International IBD Genetics Consortium, the NIDDK IBD Genetics Consortium and the CCFA Microbiome Initiative.

Research at the Lunenfeld-Tanenbaum falls under the following broad disease or discipline-based umbrellas:

Cancer research

Representing the largest disease areas in terms of funding, the cancer programme is broadly defined and embraces a range of approaches from molecular and structural biology-based discovery programmes and high-throughput systems biology through clinical trials to population-based studies. Of particular note are the breast cancer and sarcoma programmes.

Systems biology

The myriad of processes that cells and tissues employ to communicate and function act in coordinated and consequential patterns that can only be discerned by analysis that accounts for multiplicity and complexity. The systems biology group is

Lunenfeld-Tanenbaum's Bernard Zinman (left) played a key role in the 25 year international Diabetes Control and Complications Study. Daniel Drucker has developed two new drug treatments for Type 2 diabetes and has recently obtained FDA approval of a new drug to treat a bowel condition associated with colon cancer and IBD

developing and employing state-of-the-art mass spectrophotometric, imaging and robotic technologies to capture datasets that reflect the layers of controls and outputs of biological systems – and developing the computing technologies to make sense of the data.

Diabetes research

The Lunenfeld-Tanenbaum's potent diabetes team boasts remarkable expertise in tackling the challenges of this devastating, costly and pervasive chronic illness. Bernard Zinman, Daniel Drucker, Bruce Perkins and Ravi Retnakaran, working with the Leadership Sinai Diabetes Centre, have been at the forefront of new therapeutic interventions and glucose control studies for Type 1, Type 2 and gestational diabetes.

Neuroscience

The sheer complexity of the human brain presents an immense scientific challenge and researchers have therefore relied upon model organisms in order to simplify analysis and determine fundamental principles. The nematode worm and genetically engineered mouse models are employed to better understand neurological disorders such as depression, schizophrenia and dementia.

Genomic medicine

As the cost of whole-genome DNA sequencing plummets (achieving increases in efficiency that dwarf advances in microprocessor technologies) to sub-$1,000, the future is clear: genomic information will be fully accessible to healthcare and will become an important baseline tool for patient care. Moreover, while the technology is essentially in place, efficient methodologies for sifting through and understanding the reams of data (2x3 billion nucleotides per individual, much of which has low information content) is still in its infancy. Lunenfeld-Tanenbaum's Kathy Siminovitch is leading a provincially funded pilot programme in personalised medicine that combines genomic information with clinical data to enhance clinical decision-making.

Stem cells and regenerative medicine

By developing techniques such as tetraploid aggregation and isolation of mouse embryonic stem cell lines that are used around the world, Lunenfeld-Tanenbaum scientists were pioneers in embryonic stem cell science and mouse transgenesis, and, more recently, induced pluripotent stem cell technology that allows adult tissues (such as skin cells or blood cells) to be reprogrammed to an 'embryonic state', which in turn allows their reprogramming into essentially any other cell type. Other Lunenfeld-Tanenbaum researchers apply regenerative medicine techniques to produce cartilage, bone, small blood vessels and beta-islet cells with potential for tissue replacement.

Women's and infants' health

Mount Sinai Hospital is home to Canada's largest clinical programme in obstetrics and gynaecology with ~7,000 births per annum and the institute has a complementary and equally high performing research programme in this discipline, along with its close ties to physiology and developmental biology. Researchers study pre-eclampsia, intrauterine growth restriction, preterm birth, gestational diabetes and placental insufficiency, as well as elements of reproductive health, including *in vitro* fertilisation, stem cell differentiation and ovarian health. A key building block is the newly launched Ontario Birth Study, a longitudinal study conceived by Stephen Lye and Alan Bocking that will follow thousands of babies *in utero* and throughout childhood.

Prosserman Centre for Health Research

The results of studies of populations with different propensities to various diseases have firmly established the field of genetic epidemiology at the Lunenfeld-Tanenbaum as a key methodology for identification of behavioural and genetic factors associated with health, including vitamin D and breast cancer risk and identification of causal associations between disease and gene variants.

From its founding to the present day, the Lunenfeld-Tanenbaum's strengths have arisen from the conjunction of a world-leading discovery research platform twinned with centres of clinical excellence. Multiple institute and hospital-led studies – the Personal Genomics project, the Ontario Birth Study – as well as leadership and participation in international consortia, attest to this. Going forward, the institute's goal is to continue to align and enhance these programmes, maximising its impact nationally and internationally.

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Making gains in pain management

Chronic pain is an epidemic that has been neglected for too long, and this must change, urges Professor Dr Hans G Kress, President of EFIC®…

While acute pain may be understood as a symptom of a disease or injury, chronic and recurrent pain should be considered a disease in its own right. Typically, chronic non-cancer pain cannot be referred to as a tissue injury, has no biological warning function, and its end is unforeseeable for the patient and the physician. As a result, chronic non-cancer pain has severe psychosocial consequences and is notoriously difficult to treat because of its complex, all-encompassing nature.

The challenge

Chronic non-cancer and cancer pain is not only a relevant cause of suffering and reduced quality of life, but it has a huge medical, economical and societal burden on developed countries: some 80 million Europeans – one-fifth of the adult population – are suffering from chronic pain.[1] Thus, chronic pain is one of industrial civilization's most disabling disorders. Pain affects more people than heart disease, diabetes and cancer combined, but pain is still inadequately recognised as a major challenge, not only by primary and secondary healthcare practitioners, but also by the social security and healthcare systems. Chronic pain poses a substantial burden to the individual sufferer, inducing a complex set of physical, psychological and social changes that have been underestimated or neglected by political decision-makers.

The development of access to innovative analgesic drugs is still needed, urges Professor Kress

Non-cancer pain is a major reason for visits to physicians and for taking medication, a significant cause of disability and a key factor in reduced individual and societal productivity. In 2005, chronic pain resulted in over 500 million sickness days in Europe – costing the European economy more than €34bn. Being a major reason for absenteeism, discontinuation of labour and receiving disability benefit, chronic pain is also the number one or at least the number two cause of early retirement in most European countries.

Where is pain medicine in Europe today?

In 2001, the European Federation of IASP® Chapters (EFIC®) published its 'Declaration on Pain' in the European Parliament and called on European national governments and EU institutions to recognise chronic pain as an individual and societal challenge. 10 years later, pain continues to be an under-recognised and under-treated epidemic and imposes a substantial burden on societies and healthcare systems. In addition, public funding of pain research has remained negligible compared to the huge amounts provided for cardiovascular or oncological research projects in the EU.

The development of new (and free) access to innovative analgesic drugs is still needed, mainly for patients suffering from chronic mixed nociceptive/neuropathic or neuropathic pain that cannot be sufficiently relieved by available simple painkillers. The reimbursement of such innovative drugs and therapeutic systems (e.g. intrathecal drug application via implanted pumps or electrical spinal cord stimulation) is not warranted in all European countries and healthcare systems. Even if pain therapy is available but not adequate, many patients continue to suffer from psychosocial and socioeconomic sequelae, which by themselves reduce quality of life dramatically.

Recently, in collaboration with EFIC® and Mundipharma International Ltd., the European Expert Task Force on Placing Pain on Undergraduate Medical Curricula has started to analyse the current status and deficits of undergraduate pain education in 15 European countries. Based on this robust data and their in-depth analysis, which will be published by autumn 2013, educational strategies and recommendations for the implementation of pain management are to be developed in the undergraduate curricula of as many medical schools across Europe as possible.

In parallel, based on the Pain Management Core Curriculum for Medical Schools proposed by the German EFIC® Chapter (Deutsche Schmerzgesellschaft eV), and in close collaboration with the EFIC® Committee on Education, EFIC® has very recently developed 'The Pain Management Core Curriculum for Medical Schools in Europe' to facilitate future improvements in undergraduate education on pain management.

Call for action: the EFIC® Roadmap

To improve the still unsatisfactory public funding situation of academic basic and clinical research in pain medicine, and to provide best practice pain management in the EU, EFIC® has launched the 'Europe Against Pain®' and 'Societal Impact of Pain (SIP®)' initiatives at the EU level, mainly to use the EU institutions and programmes in the field of public health and to influence awareness, public opinion and policy on pain at both pan-European and national levels.

The Societal Impact of Pain (SIP®) symposia – organised in collaboration with Grünenthal GmbH – unite pain professionals, patients and industry to work toward the common objective to raise the profile of chronic pain on the future health agenda in Europe. An important outcome of the 2011 SIP symposium was 'A Road Map for Action', with seven key issues:

- Acknowledgement of pain as an important factor limiting quality of life;
- Availability of information and access to diagnosis and management of pain;
- Increased awareness of the medical, financial and social impact of pain;
- Increased awareness of the importance of prevention, diagnosis and adequate management of pain;
- Enforcement of pain research;
- Establishment of an EU platform for the exchange, comparison and benchmarking of best practices;
- Trend monitoring in pain management by using the EU platform.

EFPIA: controlling pain

Pain can be debilitating for the sufferer, particularly chronic pain. Many health conditions require significant management for individuals to lead a normal and pain-free life. For instance, in the European Union alone, 35 million people a year consult their GP because of back pain.

The European Federation of Pharmaceutical Industries and Associations (EFPIA), the organisation that brings together members of the pharmaceutical industry, states that 'the sensation of pain is complex and this gives considerable scope for developing medicines that act by new mechanisms, or on different parts of the nervous system'.[1]

Whilst a number of quality analgesic products exist on the market, the pharmaceutical industry is actively working on developing new, innovative medications that can tackle pain. EPFIA lists a number of developments in analgesics that are in the pipeline. These include:

- The use of adenosine to adjust pain perception;
- Creating NSAIDs with fewer side effects;
- Discovering new types of opioids, particularly transdermal patches.

'There is much research devoted to pain relief and the complex mechanisms of pain perception are becoming better understood,' believes the EFPIA. 'With the parallel search both for more effective pain control and a reduction in side effects, the prospects for medical control of chronic pain especially should be significantly improved within a few years.'

[1] www.efpia.eu/diseases/97/59/Pain/#content3

Finally, besides the often misdiagnosed or inadequately treated chronic pain patients, the healthcare system – not to mention society as a whole – has to pay a price for the fact that the need for systematic academic pain research and adequately developed pain medicine has notoriously been ignored. In these times of financial crisis, civil communities must come clean about their healthcare priorities. How chronic pain patients are treated will tell us a lot about societal ethical values: adequate pain management should be considered a fundamental human right.

[1] Reid K J, et al., Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. Current Medical Research & Opinion 2011, Vol 27, No 2, pp. 449-462

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Challenges in analgesic drug development

Problems in providing pain relief…

Unrelieved severe pain is an unfortunate condition suffered by millions of people and can be associated with numerous clinical conditions, such as surgery, trauma, arthritis, diabetes and migraine. Severe pain is often not manageable with conventional analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs), and can be debilitating. Significant quality of life issues include missed school and lost productivity.

A recent report by the Institute of Medicine estimated the value of lost productivity secondary to pain at around $300bn in 2010. 40% of the population reports that pain interferes with their mood, activities, sleep, ability to do work or enjoyment of life, and two-thirds report interference with any of these. 19% of the population suffers from chronic pain, i.e. pain that lasted for at least three months; another 34% complain about recurrent pain and 44% about acute pain. The most common site for pain is the back (25%), followed by knee (12%), head (9%), shoulder and leg (both 7%). Although six in 10 have taken prescription drugs for pain, 41% experienced 'just some' or 'hardly any' pain relief, putting the efficacy of prescription drugs at the same level as prayer.

Currently available analgesics are either based on mechanisms of action that have been known for decades or re-purposed drugs, e.g. anti-seizure medications such as the pentinoids that happen to have an analgesic effect. All of which have potential disadvantages such as dependence with opioids, or gastrointestinal and cardiac side effects of NSAIDs. The FDA

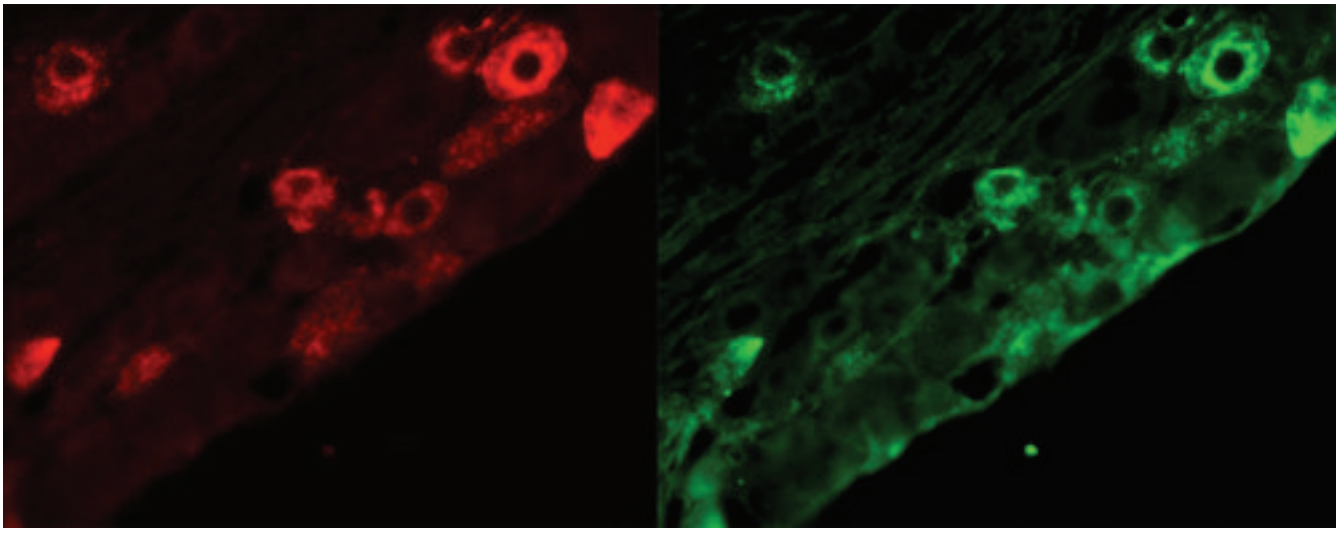
stated that the numbers of deaths secondary to narcotic pain reliever overdosing has quadrupled in the last 20 years.

Most analgesic 'innovations' being brought to the market are optimised formulations of already introduced substances yielding a somewhat improved side effect profile, e.g. oxycodone/naloxone combination to reduce opioid induced bowel dysfunction, a faster onset of action, e.g. transmucosal fentanyl applications or intravenous acetaminophen, abuse-resistant hydrocodone, or extended release formulations, e.g. once daily hydromorphone. Unfortunately, all of these still come with much of the same baggage of previous versions.

Therefore, it is clear that there is an enormous need for truly innovative pharmaceutical approaches to treatment of pain. However, there are several challenges that need to be overcome: there were about 50 approvals for new molecular entities (in total, not only for pain) in 1996, but only 16 in 2000, although the expenses for research and development almost doubled. This fact mirrors that the demand for safety and tolerability by regulatory authorities has markedly increased. As a matter of fact, it is questionable if some of the analgesic drugs that are already on the market and have been prescribed for years, such as acetaminophen or aspirin, would get approval in the current regulatory environment.

Another problem that arises from the upping of regulatory standards and the accompanying dizzying increase in the cost of drug development is that pharmaceutical companies tend to be very risk averse, attempting to improve patent lives or pharmacokinetic properties of existing drugs rather than developing something completely new and potentially groundbreaking. This fear is being nourished by fiascos with COX-2 inhibitors (e.g. Vioxx®), Substance P antagonists and TRPV1 antagonists, all of which had billions of dollars/euros/pounds spent on them by many companies, but which were shown in humans to have significant side effects or a lack of efficacy.

The reorganisation of drug companies, leading to closures of well-established research sites, e.g. Pfizer in Kent, UK and AstraZeneca in Montreal, Canada, is also not helpful for promoting groundbreaking research. Similarly, the degradation of funding from governmental agencies for pain and analgesia research would seem



short-sighted – the positive financial impact for these governments in returning pain sufferers to productive work would be substantial.

Despite the adverse conditions, there are many, usually small start-up innovative biotech or biopharma companies that investigate potential new targets for pain relief. Truly promising technologies are frequently acquired by the large pharma companies to finish the development process that the biotech has begun. This kind of symbiotic relationship may well be the future for most drug development. For example, a start-up called Rinat came up with the idea of using monoclonal antibodies directed against nerve growth factor for the treatment of arthritis pain. This technology was acquired by Merck and, as is typical for large pharma, mimicked by other companies once preliminary clinical trials showed much promise.

Unfortunately, larger trials, while still showing excellent efficacy, also exposed a potential downside in a small portion of treated patients – sufficient to put all trials on hold. Hopefully this issue will be resolved soon, but it illustrates some of the risks of drug development in the current environment – negative effects in a sub-population can cause risk averse regulatory bodies to terminate projects where they likely would have been allowed to continue in the past.

Other small companies are investigating innovative administration routes for potentially analgesic molecules, thus limiting potential side effects, decreasing time to onset of action and ultimately improving patients' acceptance and satisfaction. For example, Trigemina, Inc., is utilising a direct pathway from the lining of the nose to the trigeminal nerve, which supplies all pain information from the head, to the polypeptide hormone oxytocin – for which there are specific receptors on trigeminal nerve cells (see image above).

Pilot clinical trials have demonstrated that application of a particular formulation of this molecule using this approach is highly efficacious in the treatment of chronic migraine headache. Chronic migraine, defined as experiencing 15 or more headache days per month, is particularly difficult to treat, but appears to respond well to nasally applied oxytocin. This approach is likely to be helpful in a variety of head pain conditions, such as trigeminal neuralgia and tooth extraction pain.

Although companies like Rinat and Trigemina can be highly efficient in their development process, they still require large amounts of capital to see their ideas through to the point where a larger company might want to work with them. That capital traditionally came mainly from venture capitalists. Unfortunately, this model too has suffered of late – the funding cycle of venture groups is too short for how long it usually takes to deliver a molecule to the point where they can make money.

Thus, although a biotech to larger pharma model seems to be a relatively successful approach, there is still the problem of getting the biotech started with funding. One emerging model is for pharmaceutical companies to set up incubators to help the process along (and get first peek at discoveries). However, this is frequently a necessarily limited approach. Government platforms sometimes can be very helpful, such as the NIH's small business innovative research (SBIR) programme. This kind of programme, which is merit-based and peer reviewed, is somewhere that governments can support biotechnology in their constituency and foster not only the growth of good jobs, but perhaps provide the seed for a new innovative therapy to ease the suffering and financial impact of pain.

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Driving development: from patent to patient

Dr Keith Bragman, of the Faculty of Pharmaceutical Medicine, highlights how the pharmaceutical industry is innovating for patients…

The pharmaceutical industry is responsible for over half the funding for medicines research and development (R&D) in the UK (approximately £4.5bn)[1] and employs more than 72,000 people, including 27,000 highly trained scientists and doctors, thus making a substantial contribution to the economy and healthcare. Worldwide, the industry currently spends approximately £89bn on R&D (2012) and this investment is projected to rise to £99bn by 2018 (EvaluatePharma® 'Embracing the Patent Cliff', 2012).[2]

This compares to worldwide total prescription drug sales of £466bn (2012), which is projected to rise to £590bn by 2018. The R&D investment, excluding generic medicines, is approximately 20%. The development of novel medicines is an extremely expensive exercise, which is partly explained by the high attrition rate (failure) in early development; by a high rate of failure in some therapeutic areas, e.g. neurology-psychiatry, at a late stage in clinical development; and by the cost of developing and validating new technologies.

Clinical trials include a number of stages and it may take over 10 years, and typically costs in excess of £1bn for all the R&D required, before a new medicine can be licensed for use by patients. This investment in R&D can be as high as £2.5bn per new molecular entity.[3] For every licensed medicine, not unusually about 1,000 chemical compounds will have been screened and tested, and only approximately 25 of these will have gone into mid to late stage preclinical development and then only a few will be tested in clinical trials in human subjects. Research is led by clinical need and advances in understanding of pathogenesis and the identification of novel targets for drug development. Oncology is currently one of the most researched therapeutic areas, with twice as many drugs in the overall pharmaceutical/biotechnology product pipeline as other areas. Diabetes mellitus, chronic inflammatory diseases like rheumatoid arthritis and neurodegenerative diseases like Alzheimer's are also critical areas of activity.

Standards, efficacy and safety

Maintaining professional standards in clinical research and other areas of pharmaceutical medicine is a high priority. The General Medical Council (GMC) sets out standards for doctors involved in clinical research.[4] In the UK (and some other countries), pharmaceutical medicine is now a recognised medical speciality alongside areas like oncology or cardiology. The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the UK is the organisation that maintains and develops competence and professional standards in the practice of pharmaceutical medicine. The faculty helps oversee the training of pharmaceutical physicians and onto specialist registration with the GMC.

The development of medicines is a multidisciplinary activity in which pharmaceutical physicians – clinically trained doctors who now apply their medical knowledge to medicines development – have a key role. Their responsibilities include the translation of fundamental research into novel new medicines: the design, running and interpretation of clinical trials; the safety and wellbeing of research participants; and understanding the safety profile of medicines and their benefit-risk balance for patients.

Pharmacovigilance is the science of identifying the hazards associated with medicines and minimising the risk of harm to the patient. Before a medicine is approved for general use, it must undergo a thorough appraisal of its benefit-risk profile by regulatory agencies. After a new medicine is approved for use by patients, safety is closely monitored; e.g. information from patients and healthcare professionals in the UK is collected by the UK Yellow Card scheme and fed through to the Medicines and Healthcare products Regulatory Agency (MHRA).

Usually a considerable amount of safety data is required before drug approval. However, the safety paradigm may be evolving for medicines to treat life-threatening diseases with limited treatment options. There is increasing interest in adaptive licensing, with less data required for initial market authorisation but more afterwards. The balance of risk versus benefit is therefore shifting to favour earlier access to potentially life-saving treatments.

Challenges

In the 1980s and 90s, the pharmaceutical industry enjoyed a fertile period of rapid scientific advancement in a favourable financial environment. However, since the millennium, the industry has had to overcome a number of challenges: many of the known drug targets has become exhausted and the low hanging fruit have been taken with the provision of novel medicines. There has been a slowdown in novel treatments coming to market as physicians and scientists have been compelled to innovate and establish new approaches to research.

Mergers and acquisitions have strengthened the industry with companies increasingly focusing on a small portfolio of drugs, reducing costs and head count. Many 'blockbuster' drugs developed in the 1990s have reached the end of their patent life and many companies are suffering significant falls in revenue with the 'patent cliff' (for example Viagra® [5]). The industry has also not been immune to the recent global recession, as governments seek cost reductions in the purchase of medicines, thereby reducing the funds available to support research in new areas.

Compounding these problems has been the increasingly negative perception of the industry in recent years. A series of high-profile cases has involved large fines and penalties over misrepresentation of data, illegal marketing practices and failing to report safety data.[6] As a result, despite already being a highly regulated industry, there has been demand for greater transparency and independent scrutiny of clinical trial conduct and data. This has been coupled with increased restriction of marketing activities and a publicly transparent relationship with healthcare professionals in clinical practice, patient groups and charities.[7]

The issue of transparency of clinical trial data is currently receiving considerable attention. It is widely reported that both commercial and academic organisations are often poorly compliant with existing guidelines and requirements for clinical trial registration and dissemination of results.[8, 9] Whilst company attitudes towards data transparency and commercial sensitivities are shifting, questions remain about the practicality of providing access to historical data, how to balance the benefit of sharing data with third parties versus clinical trial patient confidentiality and how to prevent inappropriate use of data.

Studies have shown that there is a correlation between lack of belief in a medicine and low adherence; not taking a prescribed treatment as intended is linked to poor health outcomes and an economic loss for society (thought to cost the NHS £1bn annually).[10] Greater transparency should engender greater patient belief in medicines and thus greater adherence. The industry must play a leading role in helping patients through the development of novel technologies to monitor adherence and better communicate the benefit of medicines in patient information leaflets.

The future

Despite all of the aforementioned, the outlook for the innovation-led industry is generally positive. Rapid progress in understanding diseases at the molecular level (pathogenesis of disease) has led to the identification of new disease targets and underpinned a biotechnology revolution. A biological or biotechnology product includes medicines such as a vaccine, genetically engineered protein, stem cell therapy (blood derived products) or gene therapy.

Old models of drug development are being overtaken by innovative science and clinical trial design. New treatments, such as gene therapies, are starting to be realised in healthcare. Biomarkers are increasingly being used to predict treatment effects. However, and in parallel, some novel biologics will be replaced by biosimilars as these medicines lose their protective patent status. Innovation will be led by pharmaceutical companies in partnership with academia.

Based on an understanding of molecular disease and individual genetic profiling, personalised medicine is a model that customises healthcare, with clinical decisions and medicines being tailored to the needs of the individual patient. Rather than an empirical or trial and error based approach where medicines are switched if no clinical improvements occur, the goal of therapy is to get the patient on the right medicine early on and derive maximal benefit from treatment. Pharmacogenomics (genetic markers), proteomics and metabolomics (protein and metabolic markers) are other terms used to describe how a disease can be more accurately characterised and how the therapeutic effect of a medicine can be measured over time in the individual patient. In tandem with novel medicines, diagnostic tests are often developed to identify patients who are most likely to benefit from treatment.

For the moment, personalised medicines are relatively uncommon. Well-known examples include trastuzumab, a monoclonal antibody that interferes with a target called the HER2/neu receptor in breast cancer, and, more recently, cystic fibrosis now has a genetically targeted drug for individuals with a gene defect called the G551D mutation.[11] We are already moving away from simply classifying patients as having either Type 1 or 2 diabetes mellitus to a better understanding of the genetic heterogeneity of the disease. Patients with mutation in the KCNJ11 gene, which codes for a protein in the pancreatic ATP sensitive potassium ion channel, have been shown to respond better to sulphonylureas than insulin, and genetic testing in the diabetes clinic may soon be a standard procedure.[12] This is especially important for those patients who can be treated with an oral pill and can be spared treatment with insulin injections.

Understanding the genetic basis of complex conditions, e.g. schizophrenia and other psychiatric conditions, may well lead to the identification of genes that convey a risk for developing schizophrenia.[13] Asthma and chronic obstructive pulmonary disease

are also seeing a greater understanding of the genetic basis, though ready availability of truly personalised medicines and diagnostic tests for these conditions still appears some years away.[14]

Genetic profiling also helps with knowing who not to treat; the KRAS mutation in patients with metastatic colon cancer can be used to identify those patients less likely to benefit from some of the newer targeted monoclonal antibody treatments.[15] Another challenge to the development of personalised medicines is that only a small number of patients within a specific disease category may benefit, and how should treatment be reasonably valued, relative to the cost of high R&D costs. In addition to the contribution by industry, R&D is also funded by charity and public funding. This speaks to a need for industry to increase collaborations with academic groups in the future, and there are signs that industry is increasingly dependent on the efforts of academic health science centres.

In conclusion, the industry is adapting and responding to the challenges associated with developing cutting-edge technologies and the needs of society. Research from academia has contributed and led to novel technologies that have become the basis of young biotechnology companies. Alliances with academia and an increasingly research focused NHS provide new opportunities for collaborative research in medicines development. The landscape is changing and personalised medicines and the science of genomics are becoming increasingly important. Industry must continue to nurture the relationship with academia to ensure that society benefits from the new technologies that are driving medicines development.

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***Science Omega Review* comment: Pharmaceutical industry innovation**

The pharmaceutical industry has made many strides in recent decades. Partnerships between industry and academia are becoming more important than ever in increasing innovation and ensuring quality research enables quality products.

The changes that have been implemented across the NHS have presented challenges for all services, and the pharmaceutical industry is no different.

In the UK, the Association of the British Pharmaceutical Industry (ABPI) supports biopharmaceutical companies that are involved in innovative research. Speaking recently at the APBI's Annual Conference, Chief Executive Stephen Whitehead recognised the problems facing the industry due to NHS reform.

"The NHS in the UK is undergoing dramatic change, the English system more so than that of Wales, Northern Ireland or Scotland," he said. "We, the R&D-based industry, are struggling to understand the nature of that change, the emerging influencers, the appropriate business model to adopt to ensure we are commercially successful, the right tone to ensure our innovations are a cornerstone of healthcare delivery.

"We are looking at our emergent pipelines and our existing portfolios alike to see how they can best be positioned in an increasingly complicated and diffuse operating environment."[1]

Innovation has undoubtably been affected by reform and austerity. How the pharmaceutical industry, academics and physicians in the field overcome these current hurdles remains to be seen, but with the announcement that the European Federation of Pharmaceutical Industry Associations (EFPIA) plans to extend its Innovative Medicines Initiative (IMI), it is apparent that working together to advance the field is the way forward.

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Beyond open innovation: the CQDM

Addressing the pharmaceutical productivity crisis…

The lack of productivity in the pharmaceutical sector over the last decade can be attributed to many factors: lack of basic scientific understanding of clinical targets, most easy wins have already been made, increased industry consolidation and dependence on in-licensing, limited risk sharing between pharmaceutical companies, increased regulatory hurdles, etc. This gap in innovation has led to the introduction of new R&D models, in an attempt to address this productivity crisis.

Strategic partnerships, interactions with academic research centres and open innovation are becoming vital in this new ecosystem. The currently ongoing cultural transformation differs from what the industry experienced over the last decades; the pre-competitive space is undergoing expansion by public and private actors, so that scarce resources can be pooled to focus on elucidating and more efficiently identifying treatments for diseases.

The challenges are numerous:

- How to bring pharmaceutical companies to the same table to express what their common needs are and have them co-invest in solutions in order to reduce the risk of development, R&D costs and time to market;
- How best to seek innovation, new therapeutic approach opportunities and new research avenues;
- How to keep SMEs and academic researchers aligned with the needs of the pharmaceutical industry and those of the patients;

- How to get all the actors of this ecosystem: patients, charities, governments, funding agencies and biopharmaceutical corporations, to invest time and money for the good of the patient population.

Birth of CQDM

It is with those considerations in mind that the CQDM was created in 2008. CQDM has operated in the pre-competitive space with great success for the last five years. It was founded with the goal of opening new research avenues to provide solutions to the lack of productivity faced by the biopharmaceutical industry.

CQDM's mission is to identify, fund and support breakthrough technologies that will significantly enhance biopharmaceutical R&D productivity and accelerate the development of new safer and more efficacious drugs. CQDM is also a neutral ground that brings patient groups, academia, governments, biotech and the pharma industry together to work collaboratively on complex medical challenges. CQDM's unique business model is designed to bring added value to the entire scientific community. CQDM's funding promotes strong ties with the pharma industry, a key success factor for translational research.

CQDM was created as a partnership between three pharmaceutical companies (Pfizer, AstraZeneca, and Merck) and the Quebec and Canadian governments. Since its inception, CQDM has launched 10 competitions, established five funding programmes and reviewed over 375 projects, totalling over $420m in funding requests. CQDM programmes address various productivity issues associated with new drug R&D, yet they all focus on scientific excellence, innovation and technologies to solve pressing challenges of biopharmaceutical research. Over the past years, CQDM has warranted interest and has added additional pharmaceutical industry sponsors (Eli Lilly, Novartis, GlaxoSmithKline, and Boehringer Ingelheim) to its consortium.

A unique business model

CQDM promotes the co-creation of value through synergies emerging from a collaborative network of researchers across universities, hospitals, biotechnology companies and the pharmaceutical industry. CQDM's industry partners co-invest in technologies that none of them individually would support, which brings them a financial leverage of up to 20x. As a pooled research consortium, CQDM's industry partners also share all project results and are entitled to use the technology for research purposes.

The programmes are meant to generate clear deliverables (enabling tools, technologies and platforms) with applicable results that can be implemented by the pharma members immediately after completion of the projects.

The mentorship programme is unique to CQDM; it was implemented to ensure that the funded research is continuously aligned with the needs of the industry. It provides a significant number of relevant industrial resources that are of great value for investigators. Most of the mentors on CQDM funded projects are future end-users of the results.

It is expected that by using the CQDM results, the pharma members will also bring large-scale validation of the technology, a critical step towards its successful commercialisation. This is especially true in the medical device market, which is difficult to penetrate without several large-scale validation studies.

The CQDM model clearly addresses the needs of the life sciences ecosystem and helps SMEs and academia engage in early R&D activities to provide solutions to the pharma industry's problems. Only five years after the initial funding of research projects, amazing results are already having impact on the pharma industry:

- To design better agonists or antagonists for GPCRs, Dr Michel Bouvier, from the Université de Montréal, developed a high throughput screening biosensor toolkit for multidimensional GPCR signatures. The technology has already been transferred into three large pharma research laboratories, has attracted close to $1m in additional funding from one large pharma group and was spun out into a small company;

- Dr Jocelyn Dupuis, a cardiologist from the Montreal Heart Institute, has developed a new imaging probe that is already in Phase II clinical validation for early diagnosis of pulmonary hypertension. This technology is so promising that Merck is already validating a PET version of the probe in primates;

- Dr Michel Maziade, a psychiatrist from the Université Laval, has pioneered the use of electroretinography as a non-invasive tool to help stratify patients with major psychiatric disorders for clinical trials. He has obtained clinical proof of concept of his method for schizophrenia, thanks to CQDM funding. He is pursuing additional clinical studies with CQDM's pharma sponsors. A spin-off company was created to commercialise the developed biomarkers;

- Dr Eustache Paramithiotis from Caprion Proteomics has developed a new panel of proteomic biomarkers to directly measure/follow the B-cell function for Type 2 diabetes. This unique panel of biomarkers is readily detected in blood and can be used to identify pre-diabetic subjects and follow their disease progression;

- CQDM funding was also used to fund Encycle Therapeutics and to help it develop a proprietary platform technology that enables the rapid synthesis of small to medium macrocycles. Under this collaboration, the pharma sponsors are actively involved into the development of the technology through the mentorship programme, and are also the first 'clients' to validate the drug library for some of their internal programmes;

- Under CQDM's leadership, a new research project involving Montreal-based Biospective, Merck and Pfizer, took place. This initiative undertook in-depth characterisation of animal models for Alzheimer's disease, with the goal of improving predictive models. In this project, Pfizer and Merck are developing two new animal models, while Biospective performs a high-level and comprehensive characterisation of the animal model using its unique magnetic resonance imaging and quantitative immunohistochemistry image analysis platforms.

Conclusion

CQDM is now well-recognised as a reference and a key player in the Canadian life sciences ecosystem. Its role as a unique drive belt gathering Canadian multiple actors in drug discovery and development brings substantial added value to support innovative and translational research.

As exemplified above, CQDM funded projects are already impacting biopharmaceutical R&D productivity. Other tangible benefits of CQDM's funding include:

- New job creation;

- Creation of new start-up companies;

- Development of new products or services with high commercial value;

- New contracts, partnerships and funding opportunities for CQDM's members.

CQDM's vision is to be a global leader actively involved in creating Canadian and international networks dedicated to the advancement of next generation technologies, with the ultimate goal of bringing better cures to patients.

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A meeting of minds

Scientists in academia and the pharmaceutical industry must unite to tackle the global health priority of MNDs, urge IFPMA's Ali Karami-Ruiz and Mario Ottiglio…

An umbrella term for a wide range of different conditions, mental and neurological disorders (MNDs) have a common challenge: gaining a deeper knowledge of how the brain works and affects the human experience. For the research-based pharmaceutical industry, there is a clear need to advance progress in this area. According to the World Health Organization (WHO), MNDs affect on average 700 million people a year, and the direct and indirect costs of these disorders impose heavy burdens on people and society.

…11.48% is the percentage attributed to disability adjusted life years caused by MNDs, yet WHO reports governments globally allocate on average only 3.76% of their health budget to mental health.

Making these disorders more visible, better understood, and yet less feared is a pivotal step that we need to collectively address to spur innovation. The self and social stigma of MNDs makes many patients very reluctant to seek treatment. By falsely assuming that it is all subjectively 'in their heads', they can spend months and even years suffering in silence, not disclosing their conditions to their doctors, families and employers, and failing to receive treatment at an early stage when disease management could make a tangible difference. This is a phenomenon that affects populations in both low and middle income countries, as well as in high income countries. Greater focus on raising awareness of MNDs, reducing stigma and encouraging governments to provide a more targeted primary care response to these disorders are solutions that can help stimulate more public and private funds into brain research.

Today, research-based pharmaceutical companies also face challenges in finding new solutions to many intractable MNDs. In contrast with other areas of scientific innovation, brain research requires the mastery of both the clinical world – defined by a complex mixture of subjective assessments and indirect measures – and the molecular world – defined by objective molecular parameters. By its very multidisciplinary nature, brain research also calls for collaboration both inside and outside research labs. Not only is brain research complex, it is also time consuming. Findings from the Tufts Center for the Study of Drug Development point out therapies require on average 35% more time to obtain regulatory approval compared to medicines for other disease areas. Looking to the future, the intricacies and connections of studying the brain, as well as human behaviour, are a challenge particular to MNDs that R&D innovation needs to overcome to be successful in this area.

Scientists agree that the brain is by far the most complex organ in the human body. 100 billion nerve cells in the human brain and their connections regulate many functions in the body – from muscle movement to hormone secretion, from memory to emotions. Its complex folding structure makes it extremely difficult to observe directly. Compounding this challenge is the connection between the brain and behaviour. It took neuroanatomy researchers many centuries to demonstrate how specific areas of the brain are responsible for emotions, speech and movement.

Today, our neuroscientists have moved to a molecular level, a task that defies direct observation. Unlike studying the heart, kidneys or liver, which pose their unique challenges as well, tackling brain research requires indirect observation. In other words, neuroscientists must rely on a combination of subjective assessments and indirect measures given by molecular markers and a new wave of advanced imaging techniques. Additionally, brain research requires a high level of cutting-edge expertise. Advances in genetics have made a stride forward in this disease area.

Incentivising research is important to find new ways to effectively treat these disorders. The World

On average, treatments for brain disorders take 35% longer to obtain regulatory approval compared to medicines for other disease areas

Health Organization estimates that by 2030, major depressive disorder will be the largest disease in terms of burden worldwide. Other neurological disorders like Alzheimer's disease are on the rise as well – Alzheimer's Disease International estimates a total of 115 million people will be affected by this disorder by 2050. However, there is a clear gap between the burden of MNDs and the budget for mental health at the government level. 11.48% is the percentage attributed to disability adjusted life years caused by MNDs, yet WHO reports governments globally allocate on average only 3.76% of their health budget to mental health.

Greater focus on raising awareness of MNDs, reducing stigma and encouraging governments to provide a more targeted primary care response to these disorders are solutions that can help stimulate more public and private funds into brain research.

Progress on research and policies should be achieved by tapping into the expertise of research-based pharmaceutical companies, other medical devices and diagnostics sectors, academia, and policymakers in the areas of health, social, economic and education policy.

One such example is to strengthen industry liaison offices so basic science can be transferred to experts carrying translational research. Industry scientists can likewise support academia by feeding appropriate knowledge to foster basic research into the brain. The Alzheimer's Association calculated a new treatment that could delay the onset of the disease by five years would almost halve the number of people affected by it. This would not only reduce suffering, but also save billions of dollars in direct and indirect costs.

We need a new mentality towards MNDs. As a society, we have come to conceptualise and judge these conditions by their most obvious symptoms: behaviours. However – and as Thomas Insel at the National Institute of Mental Health in the US has stated in a previous TED talk – behaviour is usually the last thing one sees in the progression of the disease. We need to incentivise others to have a new look at the brain and find innovative therapies and collaborations to go forward.

To illustrate the cross-disciplinary and multi-sectoral mindset that is needed to break down the silos, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has developed the 'Do You Mind?' campaign,[1] a dynamic website that puts people in the shoes of different stakeholders to illustrate how they cope with MNDs and the solutions available to them. In this way, whether one is a policymaker, an employer, a patient or carer for someone with one of these conditions, or a scientist, the website provides thought provoking stories and facts on how everybody can reduce suffering.

[1] www.doyoumindcampaign.org

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The power of synchrotron X-ray powder diffraction

A state-of-the-art technology opening doors to new horizons for the characterisation of pharmaceuticals and other complex materials…

X-Ray Powder Diffraction (XRPD) is a powerful technique that exploits the interaction between X-rays and matter to study the structural and microstructural properties of materials. Its power lies in the **direct** and **unique** relationship between the X-ray powder diffraction pattern of a given substance and its structural order and/or disorder. The position and intensity of the peaks in a diffraction pattern (so-called Bragg peaks) reflect in fact the solid state symmetry of the substance and, in powder mixtures, XRPD can determine the percentage in weight of the components. Furthermore, the diffraction peaks' width and shape unveils further precious information on the substance microstructure.

The high brightness of synchrotron radiation sources enables X-ray characterisation of pharmaceutical products and chemical compounds with a quality much superior to that achievable with lab-based X-ray sources. The Paul Scherrer Institute is home of the Swiss Light Source (www.psi.ch/sls), providing unique facilities and services for single-crystal, powder diffraction and chemical analysis to both academic and industrial users. We have a long tradition in providing services to industry and are proud supporters of our spin-off companies Dectris, Eulitha, Expose and Excelsus Structural Solutions (ESS). With the advent of ever more sophisticated X-ray detectors with fast readout, detailed in-situ kinetic of phase transformation studies of chemical processes have become possible. It is my prediction that the volume of industrial analytical services at synchrotron radiation sources will grow significantly during the coming years.

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Swiss Light Source Powder Diffraction Station

In the field of pharmaceutical powders, XRPD is thus considered as the **gold standard method** for the identification and quantification of solid forms (i.e. polymorphs, solvates, hydrates, salts, co-crystals, amorphous).[1] However, it is the quality of an XRPD pattern that defines the accuracy and reliability of the technique, and therefore the wealth of information that can be extracted. When it comes to data quality, nothing competes with **Synchrotron X-Ray powder diffraction (SR-XRPD)**, which is widely superior to laboratory XRPD in terms of angular resolution, counting statistics, energy tunability and fast acquisition time.

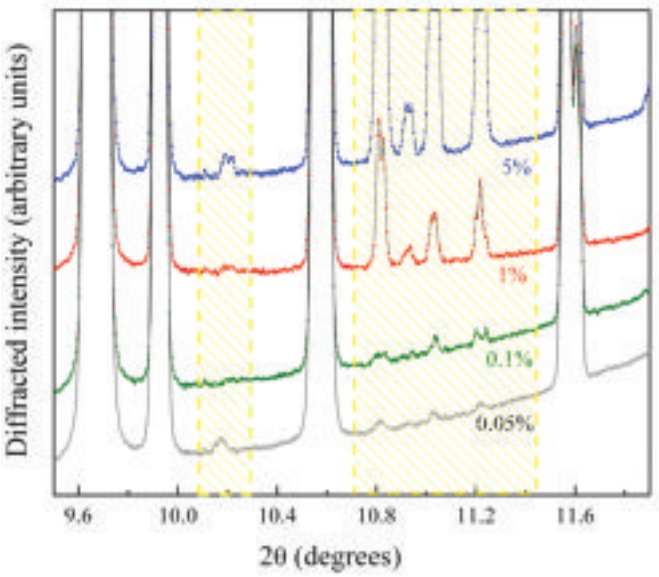
In SR-XRPD, X-rays are generated by a synchrotron facility and are at least five orders of magnitude more intense than the best X-ray laboratory source. When combining SR-XRPD with the new generation of solid-state ultra-fast and efficient detectors,[2] level of detection (LoD) smaller than **0.05% wt** are obtainable even when only micrograms of powder are available. Such an efficient data collection with acquisition times ranging from milliseconds to few minutes allows one to control the inevitable radiation damage of organic compounds and perform kinetic studies of structural changes during chemical reactions or under temperature and pressure variations.

Synchrotron radiation facilities have traditionally been accessible only to expert scientists due to their intrinsic complexity, and are characterised by long waiting times not compatible with the speed requested by private companies. **Excelsus Structural Solutions SPRL (ESS)** is a spin-off company of the Paul Scherrer Institute founded in March 2012 with the mission of providing industry with fast and easy access to SR-XRPD, including data interpretation and design of non-standard experiments.

SR-XRPD is a key tool to support research, development, manufacturing and life cycle management activities for (bio)pharmaceuticals. Drug substances can exist in different crystalline forms (**polymorphs**), solvates/hydrated forms (**pseudo-polymorphs**) and **amorphous** forms, as a result of the manufacturing and storage conditions. These different forms can have a profound effect on the quality or performance (e.g. solubility, bioavailability, efficacy, safety) of the drug products.[3] For example, therapeutic failure has been attributed to uncontrolled hydrate formation in tablets during storage.[4] For this reason, it is now a **regulatory requirement** to conduct a detailed analysis of the polymorphism of the drug substance and drug product during technical development, including screening, characterisation, property determination and setting of acceptance criteria for the different forms. Typical

BASF has been working with Excelsus Structural Solutions (ESS) since its inception. Synchrotron X-Ray Powder Diffraction has always been an elemental part of our analytical toolbox, but in the past the effort of accessing beam time and collecting data was exorbitant. Since our collaboration with ESS, this has become as simple as a phone call. We do not have to concern ourselves with all the details of the experimental setup, which can be impressively, but also dauntingly, complex. It is a great pleasure for us to work with a company so dedicated and professional as ESS has proven to be. ESS is our first choice when it comes to accessing SR-XRPD Data.

Bernd Hinrichsen, Research Scientist, BASF SE, Ludwigshafen, Germany



SR-XRPD patterns recorded on pharmaceutical binary mixtures of similar elemental composition ranging from 0.05% to 5% weight (wt) of the minority phase. The small XRPD signal is directly detectable down to 0.05% wt with a signal-to-noise better than 10, allowing the quantification of the minority phase

applications include:

- Structural solution of a new solid form;
- Development of formulation and screening of excipients, including co-crystals;
- Characterisation and quantification of all polymorphic forms in a drug substance and product, including in fully opaque blisters;
- Detection of impurities down to a trace level (<0.05% wt);
- Optimisation of manufacturing processes;
- In situ non-ambient kinetic studies at the millisecond scale;
- Stability studies of polymorphic forms;
- Troubleshooting activities and investigations during commercial manufacturing;
- Patent application for new materials and patent-life extension;
- Detection of counterfeits even with minute differences.

SR-XRPD data quality is appropriate for both **qualitative analyses** (e.g. structural identification, structural solution and refinement, detection of crystalline traces in amorphous, microstructural analyses) and **quantitative analyses** of complex mixtures of active pharmaceutical ingredients (APIs) and finished products.

SR-XRPD is a powerful technique in several other areas where the properties and performance of products are dependent on their crystalline structure and relative distribution of their polymorphic forms, such as: food and aroma compounds, cosmetics, pigments, catalysts, cement.

Novartis owns strong technical and scientific capabilities allowing us rapidly assess and resolve problems that might arise. Each material has the potential to present different challenges and technical features. Some may be straightforward and routine, others may be complex. We have further enhanced our analytical capability by forming a partnership with Excelsus Structural Solutions (ESS). For complex tasks requiring a creative, technical or logistical solution, a specialist service such as SR-XRPD was not available worldwide. Faced with exceptionally challenging deadlines our partnership with ESS has been very successful in improving our ability to deliver quick solutions. ESS brings energy, pride and passion on everything they do, they innovate and improve. This partnership has been found to ensure a smooth transition of products during drug product development, underpinning more conventional routes.

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Reconfiguration nation

Minister for Health and Social Services Mark Drakeford sets out his vision for the NHS in Wales to reliably deliver safe, high-quality, effective patient care…

Following my appointment in March this year, I have come into my new post as Minister for Health and Social Services at a time of great, and necessary, change. I bring with me a sense of determination to see completed many of those changes begun by my predecessor.

The process of reconfiguring health services in Wales is under way and my aim is to bring that process to a conclusion. By completing this tranche of change, we can ensure services are safe and sustainable for the future, and provide a sense of certainty for all those who work within the NHS, as well as those who use it.

Change is needed, but we sometimes talk about change as though it has never happened before and is something to be feared. The NHS has been in a constant state of change since it was founded by Aneurin Bevan in 1948. By growing and adapting to the needs and demands of our population, we will have a National Health Service in Wales of which we can be proud.

Our vision for the NHS in Wales is one that remains true to the principles of Bevan, rather than relying on the marketplace and competition. Our approach focuses on collaboration and cooperation, using clinical leadership and transparent reporting to drive up standards.

'Together for Health', the Welsh Government's strategy for the NHS, was launched in November 2011. Developed with the help of clinicians and the trade unions, it describes how we will respond to the challenges we face and create something better for Wales – better health for everyone and an NHS that can reliably deliver safe, high-quality, effective care and best outcomes for patients.

The focus of our vision is to move care from hospitals into primary and community care wherever possible, with new technology such as telemedicine playing a major part. While district general hospitals will retain an essential role, 'Together for Health' sets out the intention to establish centres of excellence, such as for cancer surgery or stroke care, to ensure the very best skills and equipment are on hand round the clock for the most complex, life-threatening conditions.

I also firmly believe our nation needs to start taking responsibility for its own health. Instead of concentrating the NHS on trying to put right what has gone wrong, we should be looking towards keeping ourselves as well as we can for as long as we can.

Our population is ageing, and this is something we should see as an achievement. Our next step is to ensure we live a healthier longer life, and that can only be done by taking vital steps towards eating a more balanced diet, drinking alcohol within sensible limits and discouraging smoking as a society.

While health in Wales is improving overall, the average gap in healthy life expectancy between the most and least deprived parts of the country is 19 years for men and 18 years for women. We know that only 6% of adults follow healthy lifestyles in the four main risk areas – maintaining a sensible diet, not smoking, drinking sensibly and taking regular exercise.

We need to act and the Welsh Government has been seeking views about whether it should introduce a public health bill; legislation is amongst the most powerful levers we have. We are now reviewing the results and deciding on our next steps.

Improving our health and wellbeing to match the best in Europe means we all have a part to play, including third sector organisations and local authorities.

In Wales we face big health challenges, including obesity, high rates of smoking and low levels of physical activity. However, inequalities in health between the most and least deprived parts of Wales also play a part.

The ability to feed a family is driven by the price and availability of food and many of the products high in sugar and salt are the cheaper products.

While district general hospitals will retain an essential role in Wales, 'Together for Health' sets out the intention to establish centres of excellence, such as for cancer surgery or stroke care, to ensure the very best skills and equipment are on hand round the clock for the most complex, life-threatening conditions, says Drakeford

There is no quick way we can turn that around but I think we do need to raise awareness of this and find alternative approaches.

I am sure the rest of the country will be watching Wales closely as we enter an important period in the future of the Human Transplantation Bill. The Health Committee's Stage One scrutiny report has been received, and as expected, it raised some important questions and issues for discussion. One of those is the role of the family in deemed consent cases, clearly an emotional issue and one that we are currently working to clarify.

I am keen to steer the legislation we have under way to a successful conclusion. Deemed consent is a further important step, amongst other measures, to increase the number of organs available for donation. This in turn will vastly improve the lives of hundreds of people currently on the transplant waiting list.

I do not come into this job with a naïve belief that absolutely everything in the NHS in Wales is as we would wish it to be. The very fact we are reconfiguring our services means we know this is not the case.

Over the past few months our accident and emergency departments have experienced the pressures of very high and increasing demand. This in turn has had a real impact on our ambulance service.

I am aware of the situation and I will be making it a priority to find a workable way to improve it. I cannot be drawn into micromanaging the NHS, but I am the person responsible for getting the messages to the people whose job it is to manage it.

That said, I think it is vitally important to pay strong tribute to the women and men who work tirelessly, day in day out, to make sure our health service is there for us.

It is sometimes too easy to forget, amongst the negative headlines and sound bites, that our NHS works 24 hours a day, seven days a week, 365 days a year. It never sleeps. It never stops. And for the vast majority of the hundreds of thousands of people who need it, it saves lives.

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Filling the prevention gaps

King's College London's Professor Dr Nigel Pitts, Public Health England's Sue Gregory and Leeds Dental Institute's Professor Dr Paul A Brunton address dental caries prevention…

…despite the emergence of minimally invasive or tooth preserving operative care, there is an urgent unmet need for new innovations to extend the reach of secondary prevention and avoid the need for caries cavities to ever occur.

The localised destruction of susceptible dental hard tissue by acidic by-products from bacterial fermentation of dietary carbohydrates,[1] the dental caries process is the dynamic sequence of biofilm-tooth interactions, which can occur over time on and within a tooth surface.[2] These bacterio-chemical interactions may result in some or all of the complete spectrum – or stages – of damage, ranging from initial outer surface demineralisation at the molecular level, through subsurface demineralisation producing enamel white spot lesion formation, through macroscopic lesion cavitation, to dentine and pulpal infection, to complete tissue destruction. It should be appreciated that relentless progression through all these stages of disease severity is not, however, inevitable and that the disease process can – in the initial stages – be arrested and even reversed.[3]

The economic and social burden of caries is still significant across Europe and many other regions of the world, and inequalities in oral health still persist.[4] The need to prevent and control the so-called silent epidemic of caries has been reinforced recently by changes in ways in which the dental profession – through the FDI World Dental Federation and its July 2012 policy on caries classification and management, and governments, such as the Department of Health in England with its Delivering Better Oral Health initiative – is seeking to move routine oral health and caries care to a more preventive model. This is also being reinforced by environmental pressures from government treaties written in response to the United Nations Environmental Programme (UNEP) decision, in response to mercury related concerns, to phase down restorative treatments and to phase up preventive care.

Primary prevention of caries

This is the essential and desirable backdrop to the prevention of caries, with upstream interventions employing the common risk factor approach to overall health and use of optimal fluoride strategies [5] being targeted so as to achieve proportionate universalism to reduce inequalities while improving the health gradient for all.

Secondary prevention of caries

Secondary prevention has become an increasingly attractive proposition, particularly when used in concert with population level primary prevention. For caries, international frameworks to facilitate this have been put in place over many years. From underpinning research in the late 1990s, the International Caries Detection and Assessment System (ICDAS) has been built and tested in the early 2000s[6] and this work has now spawned the International Caries Classification and Management System (ICCMS™)[7] developed in recent years. This framework has been supported recently by the FDI World Dental Federation and its caries matrix.

However, despite the emergence of minimally invasive or tooth preserving operative care,[8] there is an urgent unmet need for new innovations to extend the reach of secondary prevention and avoid the need for caries cavities to ever occur.[9] This unmet need has been documented at international conferences on novel methods for remineralisation and is also consistent with the type of caries care now recommended to be taught to dentists across Europe, in terms of their competencies in caries management and decision-making.[10] The need for better methods of caries activity assessment has also been articulated.[11]

Dentists currently have a range of clinically proven fluoride treatments and occlusal surface sealants to use for prevention of caries on their patients, but there is scope for innovation for better caries control and remineralisation methods to avoid any operative/surgical intervention – particularly for the approximal surfaces, where adjacent teeth touch.

We have seen the development of approximal sealants and new infiltration methods,[12] although these have been said not to be truly minimally invasive, as strong acids remove much of the enamel

The need to prevent and control the so-called silent epidemic of caries has been reinforced recently by changes in ways in which the dental profession is seeking to move routine oral health and caries care to a more preventive model

surface layer. The use of biomimetic self-assembling peptides is a novel approach that may or may not soon help clinicians, as clinical testing of this technology is just begining.[13]

There is then an urgent and continuing need for innovation and smart technologies to improve secondary caries prevention and control in order to improve patient care, quality, outcomes and cost effectiveness – particularly with respect to avoiding repeat restorative care with conventional restorations.

In the dental market, there is currently a gap in innovations and strategic support between the 'classic' toothpaste route for caries prevention and those developing dental filling materials – but such gaps always provide an opportunity for innovation.

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Generation gains

Secretary General Anne-Sophie Parent speaks to *Science Omega Review* about AGE Platform Europe's vision to create a supportive intergenerational society…

Population ageing is a long-term trend in Europe and due to lower birth rates and increased life expectancy, one that is set to increase significantly in coming decades. This demographic skew has repercussions throughout society, and here, Secretary General of AGE Platform Europe Anne-Sophie Parent tells *Science Omega Review* about the priorities for ageing research, the importance of improving elder care provision and the need to maximise on intergenerational solidarity.

It is important in the first instance for Europe to maintain a focus on healthy ageing research. "Because of the rapidly ageing population, we are facing huge challenges to safeguard our social protection systems, but most of all to protect our economy," Parent says. "We need to keep a strong focus on healthy ageing research because we need to find ways to improve the Healthy Life Years indicator – helping people to live longer, healthier lives. At the moment we do live longer but, unfortunately, we are not in good health until the end of our lives and that's part of the reason why people retire too early. We need people to be able to keep fit for work longer and to enable greater independence after retirement."

Governments and health authorities must ensure that this research then translates directly into better care for older people. "We need to find new ways of providing support for healthy ageing, healthcare and peer care," she explains. "We need to help people age in better health and create better quality care, instead of just reducing the cost of care. That means finding innovative ways to proceed, with perhaps greater participation of the care recipient to make it more user focused. We need to find other ways of providing care, aside from the traditional and sometimes expensive provisions, where we could provide improved care in lighter, less intrusive and better quality ways."

There are serious challenges in tackling discrimination and abuse in long-term care for the elderly that remain to be addressed. "The problem comes

from under-reporting, but more widely from a lack of understanding about what elder abuse or poor care actually is," Parent outlines. "It seems that there is a taboo about elder abuse that prevents improvements being made in the services that are provided. We see drastic cuts in some areas, putting the burden back onto already overloaded informal, or even professional, carers."

A primary target, she suggests, is to ensure that everyone will have access to quality care when they need it, rather than when they can afford it. Financing care in later life is becoming an increasing problem for many people across Europe and tackling this can help to protect individuals and empower them to voice any issues.

"We have developed a European quality framework for long-term care as a tool to prevent elder abuse," Parent explains, "because the vast majority of abuse or neglect is actually due to a lack of understanding, a lack of support for the carers and inadequate care provision. This can be solved by introducing more quality control in long-term care provision. There are, of course, some cases of intentional abuse and neglect, but the vast majority are not."

Improving inter-professional communication and collaboration across this sector presents a further opportunity, particularly in light of the way services are currently provided, for change.

"Although provision varies from country to country, we are calling for more integrated care," she outlines. "Care managers, for example, would help to give choice to individuals and their families on the various options that are available, depending on their needs and desires. We often face a lack of coordination, which may be caused by the way the system is organised competitively, or due to different levels of competencies at regional and national levels."

There has been considerable attention from the European Union on upgrading this sector, and Parent believes improved cohesion of care must be a priority, utilising the most successful examples of best practice from across the region.

"Integrated care is the best way to achieve quality care in a more efficient way and of ensuring good working conditions for the carers, as well as diminishing the cost," she says. "We already spend a lot on care provision and it is not always in the most efficient way. We can no longer afford to waste money, so providing cohesion in care, through a care manager, for example, is a way to ensure that the person receives the care that they need in the best condition and with the best choice possible."

One particularly positive result of societal difficulties in recent years has been a noted improvement in intergenerational solidarity.

"Due to democratic pressure, and even more so due to the crisis that started a few years ago, we have seen both a demand and willingness to improve intergenerational solidarity in all aspects of long-term care," Parent highlights.

This covers areas such as making sure that the burden of care needs is not placed only on one generation but generates benefits for future generations, creating more balance in the way the system is structured, along with introducing more solidarity between generations in more novel, and often very simple, ways.

"We see intergenerational housing being deployed more and more," she says, "with neighbourhood support across different generations – where older people are helped by neighbours, but can also provide some support to their younger neighbours. We have now seen quite a demand, due to the deteriorating situation everywhere, from people who want to rebuild the social fabric in their communities, not only in cities but in rural areas too."

Increasingly, initiatives are based on collaborative networks of supporters – incorporating relatives, carers and members of the community – to engage with older people and check they are coping well on a regular basis. As solidarity between generations improves, it offers opportunities to build on this further. This ensures ongoing engagement for all generations to feel the benefit, whilst promoting a better image of older people who can contribute to their community and the economy.

Under the European Innovation Partnership on Active and Healthy Ageing, local, national and regional authorities are coming together along with the research community, NGOs and other organisations, to combine expertise and foster change.[1] Working with the World Health Organization, Parent – who has been involved in this process for several years already – explains that it is now gaining a lot of interest, both from public authorities who are looking for solutions that will help them to provide better care in a more cost-efficient way, and from the research community. There are to be even greater research opportunities under the new EU programmes from 2014 across healthy ageing, active ageing and related areas.

As Parent concludes, "Our vision is to create a society where all generations can live together, support each other and enjoy life together in a fair way."

[1] http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing&pg=about

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Mobilising minds

Lynn McDonald, Director of the Institute for Life Course and Aging at the University of Toronto, considers the trouble with knowledge transfer and exchange…

Herbert Spencer said: "The great aim of education is not knowledge but action." How prescient his words were a few centuries ago. He was on to the latest fad in government, industry and academia well before its time – knowledge mobilisation, the bridge across the 'know-do' gap. Knowledge mobilisation, which emerged in the early 1990s, has become shorthand for a wide variety of activities linking the production of academic research to the potential use of such knowledge in non-academic settings.

Many definitions of knowledge mobilisation abound that are not always viewed as equivalent, e.g. knowledge transfer, knowledge translation, diffusion of innovation, research utilisation, implementation science and dissemination. The targets of knowledge mobilisation vary according to whether an individual, organisation or a whole system is targeted, and it occurs in almost every field imaginable from engineering through technology, medicine, education and agriculture. Lately, knowledge transfer and exchange (KTE) has emerged as a result of growing evidence that successful knowledge transfer actually involves two-way communication requiring genuine interaction among all stakeholders, especially in the social sciences, because of the complex and contested nature of applied research.

What's the trouble?

It comes as no surprise that most industrialised nations have latched onto knowledge mobilisation with fervour. KTE makes sense because it is likely to be cost-efficient, makes use of existing research and can happen at a faster pace than waiting to change the knowledge and behaviours of whole generations of citizens, students, employees, practitioners and policymakers. So what is the trouble with knowledge mobilisation? The KTE industry merrily buzzes onward, but not necessarily upward. The trouble with KTE can be distilled down to what is seriously missing when we examine the 'new' field in its latest manifestation.

Conceptual problems

At the outset, there are many conceptual frameworks for knowledge mobilisation: recent reviews have recognised as many as 63 theories and models, although the main focus is usually on health. This wealth of conceptual frameworks would be considered a strength in most contexts, were it not for the problem that there is very little ongoing research to

substantiate or develop the theory of KTE. Indeed, the more ironic side of this issue is that the granting agencies in many countries, Canada included, have developed theoretical frameworks and models with accompanying definitions for KTE that have remained unrefined and untested in practice. The upshot is that any researcher of intelligence is going to use the granting agencies' frameworks if they want a grant. Under the impression that the theoretical KTE problem is solved, with no funding competitions in sight to stimulate theoretical thought, it is little wonder there have been few investigations of the process-product model of KTE.

Lack of research

Perhaps more startling is the dearth of basic data as to whether KTE is actually effective. We do not know if evidence-based research is really used, how it is applied, under what conditions, for and with whom, and with what outcomes. Nevertheless, millions of dollars for KTE are a compulsory part of requests for proposals to ensure researchers engage in some type of knowledge transfer, as are millions of dollars spent on website after website and social media sites for KTE by the health, social and private sectors. Every major review of the effectiveness of KTE has concluded that the evidence is very slim because there are too few studies and what does exist is unconvincing due to weak methodologies.

When funding is directly provided for KTE, it is usually targeted at scoping reviews, and systematic reviews of existing data, functions already carried out with expertise by the Cochran and Campbell Collaborations. In other instances, funding has been available to develop networks for knowledge KTE, but their effectiveness has been rarely evaluated. More recently, research chairs in KTE have been established in several countries, which may move the research forward. The problem with some of the chairs, however, is that the focus is narrow – one disease, one type of KTE, one segment of KTE and so on, raising the question of accumulation and integration of knowledge.

Funding formulas

Related to this issue is the government formula for KTE of grant by grant knowledge transfer. Essentially, one problem is to be researched with the mandatory requirement of knowledge transfer at the end of the grant. This seems like a matter of new wine in old bottles, where KTE has been imposed on the established order for research grants. Notwithstanding the draconian measures of adjudication committees, what if the research is poorly conducted with dubious outcomes? What happens when stakeholders apply questionable knowledge, even when they have KTE directors/knowledge brokers (trained where?) or when the stakeholders supposedly participated in the formulation of the grant but know little about quality research? What if the research is 10 studies behind having any utility in practice? In light of the narrowness of this tactic to encourage KTE, how do findings get translated into the interdisciplinary environment of most stakeholders when created by one major discipline like medicine or business management? More importantly, what happens to existing knowledge already created and languishing in journals and reports on library shelves or the internet?

Academia and stakeholder problems

This is not to say that academia and stakeholders are hapless bystanders captive to funding policies for KTE. In the case of universities, researchers are not rewarded if they engage solely in KTE; they are rewarded if they attract research funding, produce publications in high-quality journals and present to the converted at disciplinary meetings. As a result, few spend time thinking about or studying KTE. Giving a public lecture/seminar/webinar about their research, hiring graduate students to work on their KTE projects or linking researchers and stakeholders is about as far as KTE ventures.

Sometimes students are requested to do the KTE with little direction about the process, since there are few research methodology courses in any of the sciences or social sciences that teach about KTE at the graduate or undergraduate levels. This is not to say universities haven't reframed what they do as KTE, to the extent it appears most are on the bandwagon. However, a closer look at the hundreds of websites suggests KTE is indeed old wine in a new bottle, where usual university activities are offered as if they were KTE.

Stakeholders are engaged in the very same activities, primarily because they do not have the time, capacity and organisational support to be involved in KTE unless it is outside their routine work. Few can escape work to help develop research proposals or peruse firm sponsored reports etc., online, after hours. Assuming stakeholders wanted to create, use and share new knowledge with research partners, there are few structures permanently embedded in their organisations for KTE and few stakeholders are rewarded for these activities.

Because KTE is so obviously useful, it is sensible that everyone wants to benefit. The value of KTE, though, can only be genuinely realised when the missing research is done, namely research about how research is used.

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A life course perspective

A perspective that more closely resembles the processes of ageing and improves care…

Since its beginning over 30 years ago, the Institute for the Life Course and Aging has provided the University of Toronto with its only interdisciplinary venue for the study of ageing. The Institute has three aims:

- To conduct applied interdisciplinary research on ageing from a life course perspective, setting the Institute apart from most existing centres and institutes on ageing. Using a bio-psycho-social approach, the Institute focuses on the processes of ageing and population ageing. All of the research is competitive and funded by national bodies in Canada: CIHR, SSHRC, NCE, HRSDC;

- To provide graduate education in ageing and the life course through two interrelated, collaborative programme options: ageing and palliative care. The programme is open to students in all faculties who graduate in their own departments with a specialty in ageing. Postdoctoral training of students from around the world and national and international visiting professors complete this programme;

- To transfer knowledge, achieved through research seminars that are open to the public, through online mini-series on ageing for local and national professional communities in Canada and through the National Initiative for the Care of the Elderly, a national centre of excellence and knowledge transfer network with over 2,000 Canadian members and 10 member countries.

The Institute is administratively housed in the Faculty of Medicine at the University of Toronto and operates through an executive committee, advisory committee, awards committee, research/management committee, programme committee, and a general assembly of faculty, including 18 degree programmes and 13 faculties, 27 departments and 60 cross-appointed emeritus and associate faculty members. The faculties represent a wide range of all of the health faculties, from music, law, education and social work to divinity. The Institute has educational and research partnerships with many universities in Canada and abroad, federal, provincial and municipal governments, a host of health and social care agencies, national agencies devoted to ageing and businesses.

A different approach

Over time, our education and research focus have evolved according to three principles that sustain our work: the importance of a life course perspective, the need to rethink ageing within a less ageist framework and the futility of research and education, unless it reaches the hands of those who can improve the care of older adults, including older people themselves.

The life course

The life course perspective links the individual and the social structure and captures accumulative advantage/disadvantage over time. The versatility of the life course perspective is its hallmark, since it can either be incorporated into existing theories like caregiver stress models or, conversely, utilised as a shell-like framework that can host other theories and concepts at macro, meso and micro levels of analysis. The life course perspective is a framework that more closely resembles human ageing and leaves policymakers, researchers and practitioners free to choose an approach at each level of analysis, depending on the question of interest and the researcher's predilection. This perspective enhances collaboration for research and teaching teams.

Rethinking ageing

Ageism, the stereotyping and discrimination against older adults simply because they are old, must be curtailed in education and research. Older adults are generally viewed as frail, sick, poverty stricken, dependent persons with dementia who are a burden on society. At the Institute ageing is not just about 'pathology', it is a vibrant and positive part of the life course. The research and education at the Institute incorporates the idea that older adults are contributing citizens in society like everyone else and can, in many instances, care for themselves with knowledge of appropriate resources and supports. That older adults participate in the Institute like others makes it difficult to maintain stereotypes.

Knowledge transfer

Based on the assumption that knowledge of the core issues of ageing can help prevent and solve problems if the information is easy to understand and access, the Institute places evidence-based knowledge in the form of 'pocket tools', both paper and digital, in the hands of users – older adults and their families, professionals, policymakers and students. Knowledge mobilisation makes sense because it is

likely to be cost efficient, make use of existing research and can happen at a faster pace than waiting to change the behaviours of whole generations of citizens, students, practitioners and policymakers.

Research

In keeping with the three main principles, the research of the Institute focuses on transitions in a number of areas: transition from work to retirement and back, family trajectories (e.g. grandparenting, widowhood), the life course of marginalised populations (e.g. older homeless and immigrants), health trajectories (e.g. abuse, chronic diseases) and trajectories in and out of poverty (e.g. Canadian women). Research can be either qualitative or quantitative, or both, is always interdisciplinary, looks at prevention and ends with knowledge transfer.

Some examples from these research clusters are:

Work and retirement transitions

The latest study in this area investigated the relationships between two transitions – caregiving and retirement – and the implications for income after the caregiving was over. The study employed a multi-method approach using national data files (General Social Surveys) to investigate patterns of involuntary retirement to caregive and in-depth interviews with persons who self-reported that they were forced to retire to caregive. The results indicated that penalties inherent in restructuring a life to solve the immediate crisis of caregiving have long-term consequences. To retire to caregive comes at the expense of income stability in retirement, mainly for women who are the least likely to be able to afford early retirement.

Family transitions

Kinship care is an arrangement in which children, who can no longer be cared for by their parents, are raised by grandparents instead of entering foster care or adoption. Working with a national organisation of kin care grandparents, a needs study of the transition into grandparenting was carried out, finding that financial literacy related to raising children was an overwhelming need since child welfare agencies provide no support for these new older parents. The research team, including the grandparents, is in the process of developing paper and digital pocket financial tools to help ease their burden. The tools will be evaluated according to the degree of uptake, utilisation and outcomes by the grandparents.

Health transitions

A large pilot study to define and measure elder mistreatment, a precursor to a national prevalence study to be conducted in Canada, examined the prevalence of perceptions of abuse at each life stage, the importance of early life stage abuse in predicting types of elder abuse, and early life stage abuse as a risk factor for elder abuse. The conclusions indicate that a childhood history of abuse in this sample had a deciding influence on later mistreatment, over and above what happens in later life.

Homelessness and transitions

The purpose of this research was to examine the individual and structural circumstances that contributed to eviction transitions in housing across the life course; to examine housing trajectories and how they spiralled into homelessness and to examine the confluence of social polices operative during these transitions. Qualitative interviews and secondary data analysis indicated that the transitions from stable housing to unstable housing and back again, from threats of eviction to eviction orders, and from poorer housing to homelessness were different at various stages in the life course and stretched across generations. The study shows how the mismatch between housing policies and life course stages produce negative and costly effects for the precariously housed and the state.

Education

Education at graduate level follows the same principles guiding the Institute. Required and elective courses encompass theory, longitudinal research methods and analysis, how to work in an interdisciplinary framework and to engage in knowledge transfer. The Institute hosts live webcast seminars on emerging topics in gerontology/geriatrics for the university, students and the public. These are archived, as are our mini-series on ageing that we encourage our students to attend. The series is for practitioners on specific topics they have requested (e.g. technology, law, driving, counselling, ethnicity, pharmacology, dementia). Our graduates are in the top tier of researchers, policymakers and practitioners in Canada.

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Strengthening health with strategy

CIHR President Dr Alain Beaudet talks to Editor Lauren Smith about the quality of Canada's health research and the areas in which it must improve…

Healthcare in Canada costs in the region of $200bn per year, a figure that dwarfs the amount spent on health research and development in the same period. Whilst this is typical, putting processes in place to ensure that the proportion spent on health research translates to better patient outcomes will not only improve the lives of individuals, but further support the economy and reduce the financial burden of healthcare on the country. Created in 2000, the Canadian Institutes of Health Research (CIHR) drives forward this aim. Here, President Dr Alain Beaudet discusses with Editor Lauren Smith the priorities of his organisation and his hopes for maximising the impact of high-quality research in this sector.

CIHR's priorities are defined firstly through a governing council, and then refined by a scientific council comprised of the scientific directors of its 13 institutes and other senior members of the organisation.

"The resulting priorities are meant to respond to the needs of the country," Beaudet outlines. "They are based on the research needs and gaps identified by the scientists sitting on the science council, Canada's Science and Technology Strategy, along with the priorities of the Minister of Health, creating a wide mix."

This is formulated under the CIHR's five year strategic plan, the current iteration of which runs until the end of 2013. For the next strategic block, Beaudet foresees a refreshed version of the current approach, rather than completely new targets, given the progress that has been made in recent years. With an annual budget (currently standing at $472m) weighted towards investigator-driven research, in order to drive discovery and the creation of new knowledge, achieving more specifically directed targets can be a challenge.

"It can be difficult to deliver on dedicated areas when the bulk of our budget is put towards investigator-driven research," says Beaudet. "In fact, our strategic budget, which allows us to directly deliver on our strategic priorities, is about a quarter of our overall allowance. It's through this section that we fund the top-down research. This budget is, thankfully, largely complemented through a variety of partnerships: with the charities sector, with other governmental agencies, and with the private sector, depending on the topic."

A major component of Canada's strategic funding envelope is the Strategy for Patient-Oriented Research (SPOR). This strategy, launched in 2011, aims to ensure that each patient receives the right intervention at the right time, by fostering evidence-informed healthcare. Utilising innovative diagnostic and therapeutic approaches, the idea is to enable greater quality, accountability and accessibility of care. In turn, this must encompass vital elements of translation research and implementation research. Beaudet is clear on the importance of ensuring that research evidence successfully results in improvements to procedure and practice, through both preventative approaches and treatment regimes.

"Patient-oriented research is of vital importance because it addresses a big part of our mandate, as defined in the act that created the CIHR 13 years ago,

Placing patients at the centre of decision-making, alongside the health authority, ministry and hospital is essential, says Beaudet

which we feel that we haven't delivered as well on previously as we perhaps should have," he explains.

"It's essential to place the patients at the centre of decision-making, alongside the health authority, ministry and hospital. Now, not only are the users part and parcel of defining the research project, but the decision-makers are at the table from the beginning, being committed to scaling up and implementing any outcomes from the research."

There are considerable complexities to this approach in the context of the Canadian healthcare system. For example, research is constitutionally a mixed federal-provincial responsibility, whereas healthcare comes under provincial and territorial jurisdiction.

"To ensure that you have integration of research so that it actually translates into better care, you have to work in close collaboration with the provinces and territories," says Beaudet. "You come to realise that areas are different – you're not dealing with one healthcare system, but 13 individual ones – and we have to adapt the strategy and the research structure to reflect healthcare needs towards extremely different requirements. Our hope is to ensure that all Canadians can benefit from the excellent research that is being performed in this country according to their needs."

Canada is amongst the top countries for medical research and technologies globally, with an excellent track record in high-calibre investigation, but this is perhaps not as well recognised as it could be. Beaudet feels that more can be done to address this.

"Very often, to my dismay, the strength of our medical research is not particularly acknowledged in Canada," he laments. "It is very well recognised, however, by the international scientific community. Last year, a report by the Council of Canadian Academies looked at the state of research in Canada, across all areas.

"One of the things that they did, which was very unusual, was to poll scientists around the world who were authors on the 1% most highly cited papers. They asked these people about their perception of Canada's position in their own field and it was, to me, quite amazing how Canada's contribution in various fields, including health research, was highly recognised. In fact, their ratings closely correlated with the citation indexes."

One focus area that the CIHR is pressing is greater interdisciplinarity, both across the health

research sectors and with other scientific and engineering fields.

"We have now set into place greater traction through the science council of the different institutes at CIHR, to ensure that we don't segregate their themes. Collaboration and co-funding of multidisciplinary projects has increased exponentially," Beaudet reveals.

"CIHR funds all elements of health research, from the social determinants of health to the molecular bases of diseases. We have four major pillars – biomedical, clinical research, population and public health, and health services and policy research. We fund sociologists, molecular biologists, engineers and so on – the best across all disciplines. But we are talking about centuries of tradition, where there has been a tendency to silo off disciplines. We need to make a real effort to bridge across the various disciplines to bring researchers together.

"We're investing increasingly in joint research, not only across the traditional spectrum of the health sciences, but to bring in mathematics, engineering and physics. That's proving extremely successful so we are moving in this direction even further. There are a number of shared tri-council programmes, which are administered by CIHR, the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC), programmes such as the Canada Research Chairs, Banting and Vanier studentships, and networks of centres of excellence, that are meant to bridge the gaps between the three councils and ensure coherence of their actions."

Beaudet acknowledges that one area in which Canada is not doing particularly well is transforming the knowledge base into commercial and industrial elements. There are two distinct aspects to this: the development of the biotechnology and medical devices industries, and maximising on the potential offered by the pharmaceuticals industry.

"Biotech and medical devices have been going through rough times in the recent economic downturn," he outlines. "They are typically smaller enterprises with less money to invest in R&D. But we've been making progress in encouraging partnerships between the biotech sector and academic health researchers, particularly through a programme jointly with the NSERC, which actually supports research at the interface of our two mandates.

"Part of that is to bring in engineers, physicists, etc. to work together with health scientists or physicians. This has proven very successful in the medical devices sector (such as for medical imaging) where such complementarity is a must. End-users must be involved in the proposals and bringing industry to the table is, in my mind, the best way to foster commercialisation."

The CIHR has been making progress in encouraging partnerships between the biotech sector and academic health researchers, particularly through a programme jointly with the NSERC, which supports research at the interface of its two mandates

Tackling the challenges Canada faces in the pharmaceutical sector is an altogether different beast. "There's a very specific issue," Beaudet comments, "as not a single pharma has its head office in Canada, so we are essentially dealing with branches. Branches don't make decisions on major research investments, which are done at head offices in the UK, Switzerland, the US, and so on. This is a particular challenge for us.

We have now set into place greater traction through the science council of the different institutes at CIHR, to ensure that we don't segregate their themes. Collaboration and co-funding of multidisciplinary projects has increased exponentially.

"It is not that they are disinterested in investing in Canada, but, very often, they are not aware of the quality of science here, or where and by whom the excellent science is undertaken. This is an area that we have to do better in and one that we've started seriously working on, to take advantage of the changing business models of the pharmas. Many of them are intending to devolve more of their upstream research to academia, or to do it in collaboration. Making the decision-makers more aware of what is happening in Canada could bring real benefits."

Another avenue for the country is its strong foundation in clinical research, for which its publications rate highly in terms of both citation and impact.

"There is no question that we have that expertise here, but it's an expensive proposal to have a lot of investment in clinical trials by multinationals. Because of the cost, they've been slowly pulling out to move into Southeast Asia and Eastern Europe. Our idea is to develop the right niches of quality that will maintain our capacity to attract particular clinical trials," he explains.

However, above all of these complex considerations, the most important economic and societal benefit of health research must be kept at the forefront. "The main economic benefit of health research is a healthy population," he emphasises. "The major economic driver of a country is productivity, which is certainly something that Canada could improve.

"Ensuring that we are providing the best possible care, and the best evidence-based practice of care, is to ensure better productivity. The economic advantages of a healthy population are huge, probably greater than all of the other things that health research can bring together."

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Keeping sight of vision loss

The Canadian Ophthalmological Society's Dr Martin J Steinbach, of the University of Toronto, heralds the importance of research to further develop vision loss therapies…

People value their sight to a remarkable degree. A 2003 Environics poll of Canadians discovered that 37% would sell everything they own to keep their vision. The fear of diminished independence and difficulty with daily life that comes with the loss of sight is borne out by statistics showing that, compared to the sighted, the blind have:

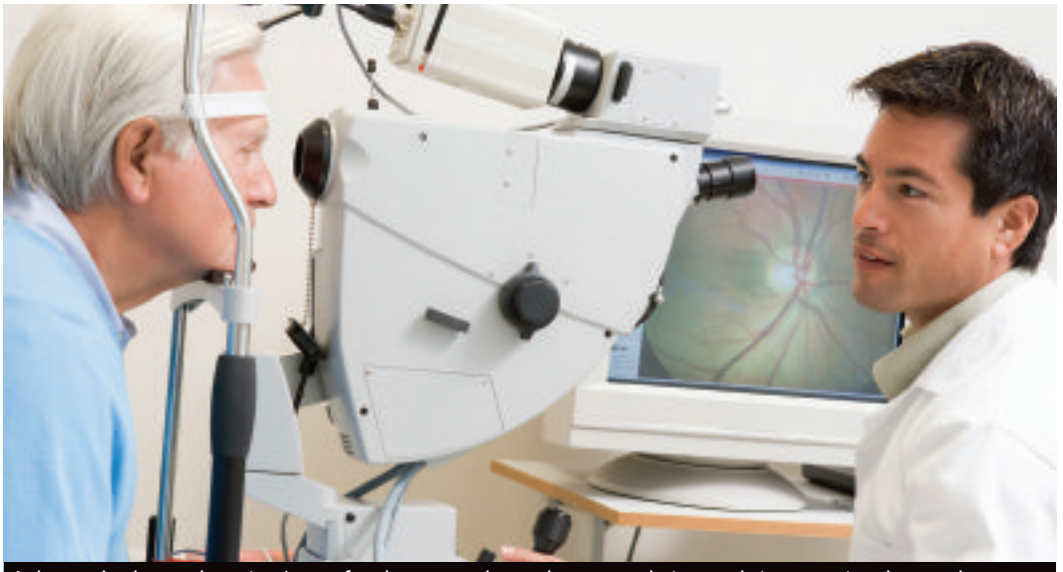
- Three times the amount of clinical depression;
- Twice the risk of falls and premature death;
- Four times the risk of hip fracture; and
- A three year earlier admission to nursing homes.[1]

In addition, low vision and blindness create, for the individual and for society, a very large economic burden. A recent study put the combined direct and indirect per annum costs for vision loss in Canada at $15.8bn.[2]

When you examine the reasons people in Canada are losing their vision, the result is a list that includes age related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR). All these conditions increase in incidence and prevalence with the greying of the population. They also all have treatments – but no cures. We could include cataracts in this list, but the surgical treatment of this condition is a success story in developed countries. However, people still go blind from AMD, DR and glaucoma, and this means that research into the underlying causes, possible prevention and restorative treatment is crucial.

Science is a collaborative effort with teams of researchers from around the world combining their skills and knowledge. Canada, despite its small population and limited funding, has punched above its weight in contributing to basic and clinical research in the areas that will lead to reducing vision loss. Advances from Canada and elsewhere include:

- Implanting stem cells to replace or rescue damaged photoreceptors;[3]
- Replacing defective genes where the genetic defect is known; [4]
- Developing ways to protect or regrow the damaged neurons that characterise glaucoma;[5]
- Implanting prostheses that electrically stimulate retinal neurons to provide visual sensations;[6] and



A doctor checks a male patient's eyes for glaucoma, where advances are being made in protecting damaged neurons

- Turning neural cells in the retina into light-sensitive replacements for damaged photoreceptors (optogenetics).[7]

A few of these techniques have reached the stage of early human trials, but many are still at the proof of concept stage where they have been shown to work in animal models. The science continues, with breakthroughs accumulating, giving hope to those suffering vision loss.

Challenges facing ophthalmology research

Scientists in all fields will always complain that there is not enough funding. However, in Canada, there is some justification for this complaint regarding the funding of vision health research. The burden of vision loss, in direct healthcare costs, is greater than diabetes, all cancers or cardiovascular disease.[8] But eye and vision research receives only a fraction of what is given for research into these other diseases. Clearly, we must do a better job of convincing our policymakers and research funders of the need to improve support for vision science.

Raising awareness of ophthalmic conditions

Raising awareness has to be a priority because education of the population, including caregivers, can reduce the incidence and morbidity associated with vision loss. A sterling example of this is that of DR. Controlling blood glucose in at-risk populations (especially aboriginal peoples in remote locations) could virtually eliminate vision loss from diabetes. Vision loss from glaucoma could be delayed by early diagnosis and treatment. But healthcare in Canada, despite single-payer provincial Medicare, has produced some short-sighted efforts at controlling costs. In Ontario, for example, eye examinations are only covered for people younger than 18 and older than 65. Given that glaucoma affects many working age people, this lack of coverage has been shown to inhibit the identification of patients at risk for vision loss, especially amongst the economically disadvantaged.[9, 10]

To summarise: the costs of vision loss to the individual and to society are enormous. Research must continue, because the development of innovative therapies for blinding eye diseases can only occur when we understand the underlying basic processes.

Spotlight on: International Council of Ophthalmology

On a global platform, the International Council of Ophthalmology (ICO) works to promote the field and regulate ophthalmology standards. The society consists of around 120 member organisations from around the world, including the Canadian Ophthalmological Society.

One role of the ICO is to advise on best practice whilst educating clinicians to ensure a high standard of ophthalmology care. In order to achieve this, the ICO created an 'Ethical Code for Ophthalmologists', based on a set of guidelines laid down by the American Academy of Ophthalmology and expanded by the ICO ethics committee.

These guidelines set the standards and ethical principles that are expected from the professionals within the ophthalmological field, and include how patients should be treated; ensuring high-quality care in practice; maintaining good conduct within the professional community; observing ethical practices for research; communicating efficiently with the public without misleading or providing deceptive information or credentials; and refraining from exploiting patients who pay for services or preventing care based upon economic problems.[1]

Ethics and professional standards are vital for the field and guarantee that high-quality ophthalmology care continues worldwide. International organisations such as the ICO have a role to play in shaping national aims and policies.

[1] www.icoph.org/downloads/icoethicalcode.pdf

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Seeing the way forward

Professor Ian M MacDonald, of the University of Alberta's Department of Ophthalmology and Visual Sciences, calls for a national agenda on vision in Canada…

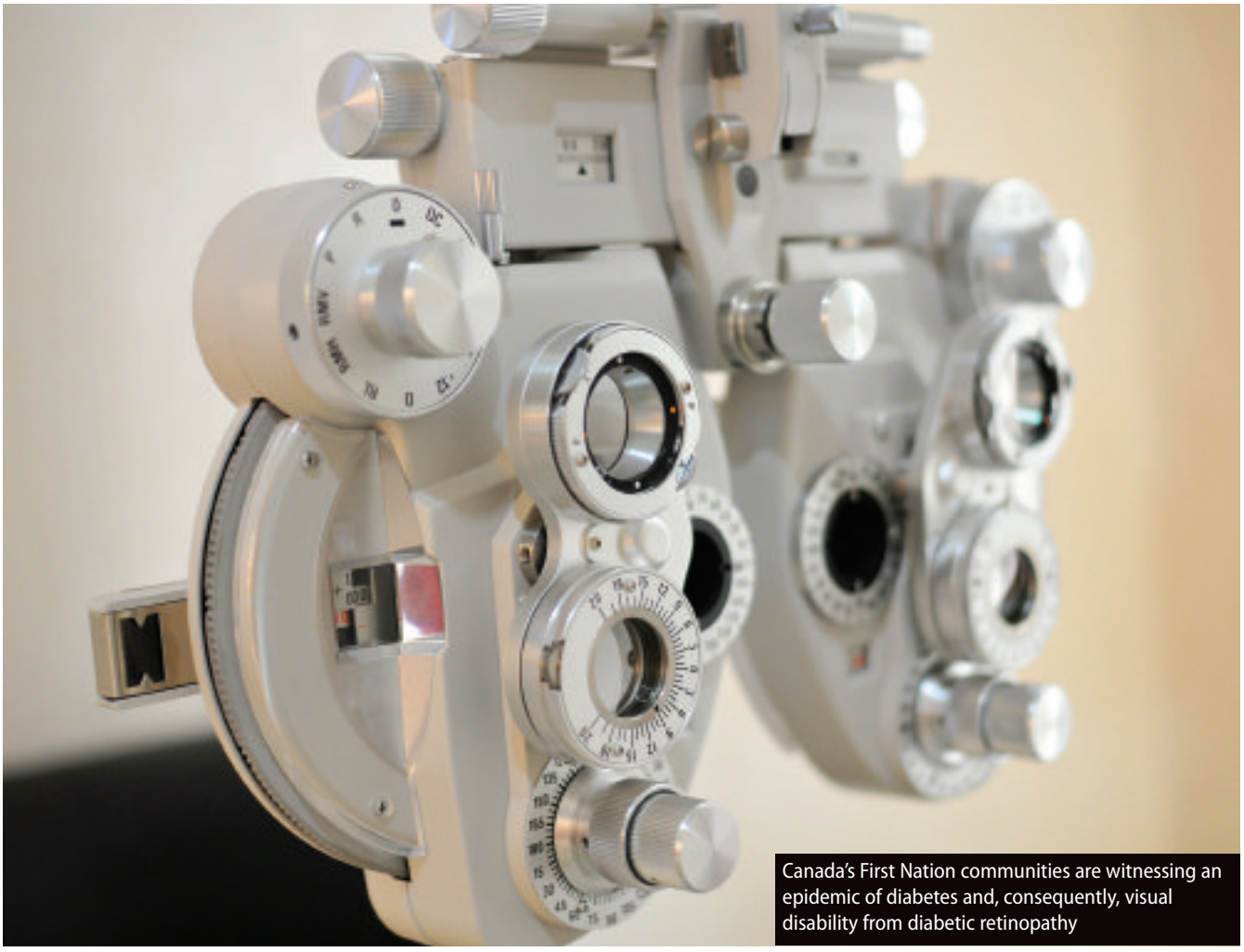
Canada's agenda for health and social research mirrors in many ways the essence of its peoples. A largely immigrant population, with its own prevalent diseases, imposed its society on distinct Inuit and First Nation peoples; admixture with First Nations creating the Métis in the provinces of Manitoba and Saskatchewan. French immigrants came to Nouveau France, English and Irish to Newfoundland, Scots to Nova Scotia and Prince Edward Island, United Empire Loyalists fled the American Revolution to New Brunswick and Ontario. Religious groups (Hutterite and Mennonite), Ukrainians, Poles, Germans and others emigrated to Western Canada; Japanese and Chinese to British Columbia. They had large families and developed the rich multicultural heritage of Canada. Unknown to them, some carried genetic traits and mutations that would lead to human disease. The study of these diseases in research centres and hospitals across Canada has created some of the foundational pillars of the country's vision research.

Our First Nation communities are witnessing an epidemic of diabetes and, by consequence, visual disability from diabetic retinopathy. Monitoring of diabetics in remote communities has been greatly improved through digital retinal imaging by trained photographers and web-based file transfer to servers in reading centres. Experienced clinicians review the images and decided on early referral for specific interventions, such as laser therapy or continued monitoring, reducing the costs of patient transfers. The same technologies and applications are possible for other sight-threatening diseases, such as cataract and glaucoma in Aboriginal and non-Aboriginal communities.

Canada's national peer reviewed research funding for investigator-driven and programme grants comes from three major sources: the Canadian Institutes of Health Research (CIHR, biomedical), Natural Sciences and Engineering Research Council of Canada (NSERC), and the Social Sciences and Humanities Research Council (with a strong Aboriginal research agenda). Further, a programme of infrastructure grants is available through the federally funded Canadian Foundation for Innovation (CFI), which is designed to recruit leading researchers and support teams of researchers or national research enterprises by providing funding for research infrastructure. CFI funds require partnering, generally with provincial or regional research agencies, and privately raised funding. The CFI maintains a database of funded laboratories and projects that is accessible to query by industry, with the intention of forging partnerships.

The CIHR replaced the Medical Research Council (MRC) of Canada, which had supported a largely medical model of clinical research. The grant panel model of MRC Canada for funding decisions curiously grouped vision science into a clinical panel with Women's Health and Perinatal Medicine. Despite vigorous lobby to create a separate panel for vision research, none emerged during the days of MRC Canada. In the changed mandate of the CIHR, vision research was incorporated into the Institute of Neurosciences, Mental Health and Addiction. The CIHR recognises four pillars of research endeavour: basic, clinical, health outcomes and finally social research. The first two categories have traditionally been strong in Canada. The third pillar is strengthened by the distinct public-funded Canadian healthcare system that generates a wealth of population-based information on health outcomes. Vision research is still largely in its infancy within this pillar, when looking at the outcome of health interventions to preserve sight and evaluate the effectiveness of these interventions. The last category, social research, has been historically supported by the Canadian National Institute for the Blind (CNIB). The CNIB has fostered for many years a programme of social research looking at aspects of social isolation and unemployment as a result of vision loss, and the evaluation of services provided to clients to improve their wellbeing.

Canada is a suitable environment for vision research, likely due to the collaborative nature of



Canada's First Nation communities are witnessing an epidemic of diabetes and, consequently, visual disability from diabetic retinopathy

vision researchers in the country and strong linkages to industry and not-for-profit patient groups. The longest and most active of these groups is the Foundation Fighting Blindness, which has a tradition of public advocacy and support for vision research grants. The foundation maintains a registry of patients' de-identified files with genotypes and phenotypes of inherited eye disease, with the intention of linking researchers and patients to approved clinical trials. While professional organisations in opticianry, optometry and ophthalmology do not maintain distinct programmes to foster vision research, some sub-specialty organisations have taken on this important activity. For example, the newly formed Canadian Retina Society and the Canadian Glaucoma Society both have active research mandates with grant programmes to foster studies to improve the care of patients suffering from retinal and glaucomatous eye conditions.

In 2007, a leading document, 'Foundations for a Canadian Vision Health Strategy: Towards Preventing Avoidable Blindness and Promoting Vision Health' was published to guide the development of a health and research agenda on vision in Canada. The document was created by the National Coalition for Vision Health, a multidisciplinary, pan-Canadian initiative that intended to lead to discussion at the highest levels of Canadian healthcare and research. John Rafferty, the CEO of CNIB, emphasised in 2012 that despite warning that vision loss costs the Canadian economy almost $16bn annually, a national agenda to address this societal burden has not developed. Healthcare remains compartmentalised into a provincial model of 10 provinces and two territories. Health Canada has governance over the provision of healthcare to First Nations and some Métis settlements. Sadly, despite these efforts, a Canadian framework to address the WHO initiative, VISION 2020, and the elimination of preventable blindness, does not yet exist. Our challenge, as Canadian vision scientists, is then to continue to educate the public and political leaders on the importance of developing a national agenda for the prevention of blindness and the investment of resources in vision research.

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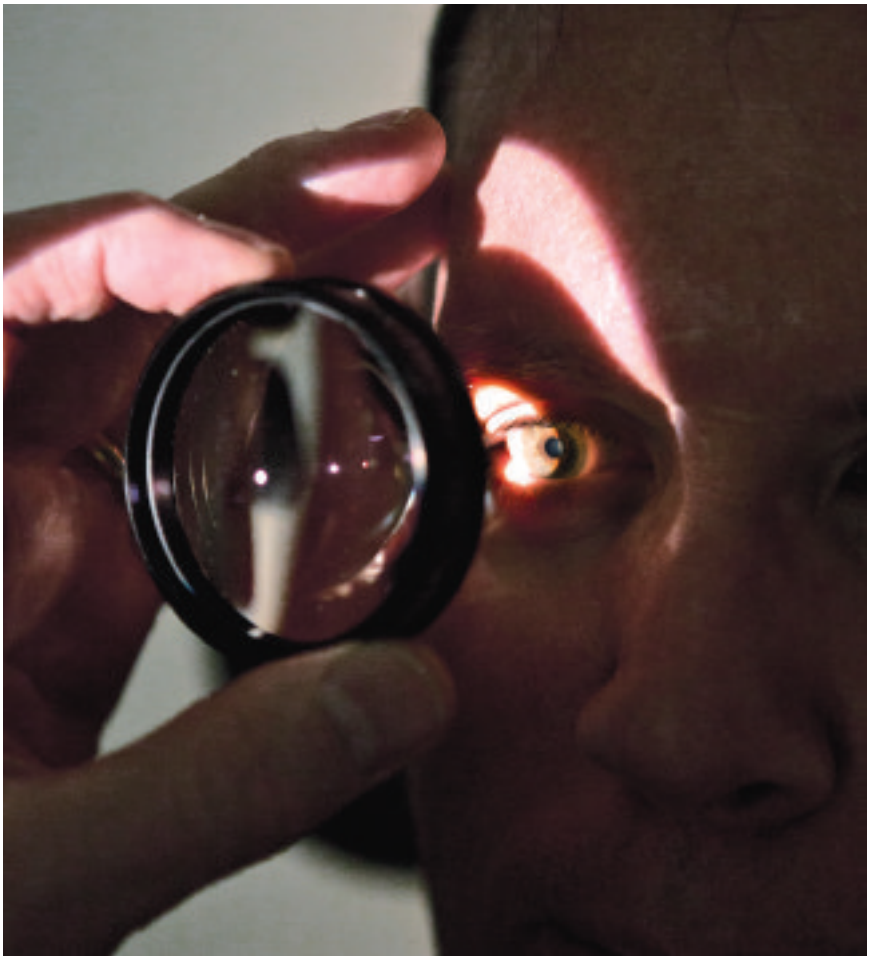
The first ocular gene therapy trial in Canada

Furthering understanding of the process of retinal degeneration and its prevention through gene therapy…

Some 30 years ago, a secretary at the Ottawa Citizen, a local newspaper, contacted our Medical Genetics group at the Children's Hospital of Eastern Ontario to ask if anyone was doing research on choroideremia. This heritable form of blindness, sometimes confused with retinitis pigmentosa, affected males in her family. We replied: 'Not to our knowledge, but would you like us to start a project?' So began a long association with this Irish immigrant family from the Upper Ottawa Valley, and many other families affected by this sex-linked disorder.

The early 1980s were a time of transformation in how genetic research was conducted; the era of molecular genetics had arrived. Before that, chromosomal mapping with cytogenetic breakpoints as determined by Giemsa banding of chromosomes was the limit of resolution of the map location of human traits. With the cloning of DNA fragments, labelling them as probes and the use of restriction enzyme digestion of DNA, researchers in North America and Europe, including our group, then in Ottawa, were able to map the gene location of choroideremia to an area of the X-chromosome.

The Ottawa family was very large; women carriers in older generations had as many as 10 or 12 children, creating an ideal opportunity to do linkage analysis of the choroideremia gene to restriction fragment length DNA polymorphisms (one called DXYS1 was particularly interesting as it mapped to a certain area of both the X and Y chromosomes).



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The choroideremia gene was then cloned, subsequently revealing the important function of the gene product, Rab escort protein-1 (REP-1), in the lipid modification of Rab proteins that are involved in cellular pathways of secretion, phagocytosis and intracellular trafficking. Further, the successful correction of these pathways by gene transfer in fibroblasts from CHM patients generated significant enthusiasm about the possibility of considering ocular gene therapy in human subjects affected by choroideremia. The compelling arguments for such a research initiative are two-fold: the significant burden of visual disability of males with this condition and lack of any treatment for choroideremia that will prevent blindness.

Five years ago there was a major breakthrough for the application of ocular gene therapy in humans. Gene transfer of an

adeno-associated viral vector carrying the RPE65 gene was shown to be safe in small trials of patients with a retinopathy called Leber congenital amaurosis. Since then, more patients have been treated and, in doing so, efficacy of gene transfer in improving vision has been convincingly demonstrated. Using a similar approach, our colleagues in Oxford, led by Robert MacLaren and Miguel Seabra, have treated some patients in a Phase I (safety) trial of subretinal gene therapy with an adeno-associated viral vector containing the normal choroideremia gene. The effectiveness of this approach will be determined over time as we follow the function of the treated eye, especially the central macula, and compare that to the untreated eye.

Our group has partnered with Oxford to build capacity for ocular gene therapy in Canada using the example of choroideremia and based on our considerable research investment in studying this condition over the past 30 years. Successful funding applications over the past two years to patient advocacy groups (Foundation Fighting Blindness Canada and the Choroideremia Research Foundation Canada, Inc.) and provincial and national peer review national research agencies (Canadian Institutes for Health Research, Canadian Foundation for Innovation, Alberta Enterprise and Advanced Education, Alberta Innovates-Health Solutions) have been key to bringing this project to its inception. This research will further our understanding of the process of retinal degeneration and its prevention through gene therapy, as well as inform us how best to undertake such research studies for other rare eye disorders that affect Canadians.

While there has been considerable investment of time, human capacity and resources in the construction of the ocular gene therapy clinical trial, we have not ignored the social aspects of this research endeavour. Our research on patient perspectives of gene therapy show that clear communication is necessary to allow potential participants to appreciate that gene therapy is a research endeavour at present, and is not a cure or a treatment. We have developed a website to better communicate up-to-date information to our patients and families about the trial (www.CHMgenetherapy.ca).

Further, clinicians need to effectively communicate with patients about the timeframes surrounding these trials. Patients typically underestimate the time required to prepare for a clinical trial. We have been helped in designing the ocular gene therapy trial by: a patient consultative committee, an expert panel of retinal specialists and finally a human ethicist. The retinal specialists will advise the trial on patient selection after reviewing the clinical data on visual function of prospective patients to provide a degree of independent unbiased selection of participants.

The regulatory pathway to gain permission for a gene therapy experiment is assiduous, yet worthwhile. In Canada, Health Canada must provide a 'no objection letter' to the investigators before they can undertake the trial, and this is only provided after many steps have already been successfully completed. The vector facility will be audited and details of vector production will be reviewed. Local Health Research Ethics Board approval must be sought along with separate operational approval in the hospital where the vitreoretinal surgery will take place. The vitreoretinal surgeons must be trained in surgical techniques and safety considerations in gene delivery. A genotype/phenotype correlative study of patients may be required to understand which patients might benefit greatest, especially in such small trials. A natural history study should be completed to guide patient selection, especially to understand how the eye health may change in the treated eye as against the untreated eye. Outcome measures of a gene therapy experiment including imaging and electrophysiology modalities will need to be trialled in prospective patients. Personnel will have to become experts in recording and interpreting these measures.

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Tania Bubela, Mark Huyser-Wierenga and Ian MacDonald of the Department of Ophthalmology and Visual Sciences at the University of Alberta

Our Alberta Ocular Gene Therapy Team has undertaken all these steps within the consultative framework that exists in Canada. With some careful coaching from our partners at TEC Edmonton and the Northern Alberta Clinical Trials and Research Centre (NACTRC), we are poised to commence what will be the first ocular gene therapy trial in Canada.

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The VISION in sight

Science Omega Review explores the work of the International Association for the Prevention of Blindness in eliminating the causes of avoidable blindness by 2020…

According to figures from the World Health Organization (WHO) Prevention of Blindness and Deafness programme, approximately 285 million people worldwide suffer from visual impairment, whilst 39 million are blind. Around 90% of people who suffer from poor vision are in developing countries.[1]

Blindness and associated disorders are a major challenge for people who suffer them. In the developing world in particular, it can lead to poor socio-economic outcomes for the individual due to an inability to work or live without assistance.

Cataracts and uncorrected refraction are the main causes of blindness and visual impairment globally.[2] In the developed world, cataracts can be corrected easily with a procedure done as an outpatient. In developing countries, where resources are scarce, this preventable condition blights patients.

Whilst the number of people suffering visual impairment or blindness has reduced over the last 20 years, the figures remain high. Ensuring preventable eye conditions do not occur is imperative to guarantee people from all backgrounds have a good quality of life, free from disease and socio-economic strife.

The International Association for the Prevention of Blindness (IAPB) is working to tackle the fight against avoidable blindness and visual impairment worldwide. Founded in the mid-1970s, the IAPB describes itself as a 'coordinating, umbrella organisation to lead an international effort in mobilising resources for blindness prevention activities.'[3] The IAPB does this by bringing together governments and other relevant agencies to assist with the development of national eye care programmes.

One of the IAPB's main projects is 'VISION 2020: the Right to Sight'. This global initiative is a joint venture with WHO 'to eliminate the main causes of avoidable blindness by the year 2020 by facilitating the planning, development and implementation of sustainable national eye care programmes based on the three core strategies of disease control, human resource development and infrastructure and technology, incorporating the principles of primary healthcare. This will be achieved by mobilising the will and passion for action through advocacy and by mobilising resources.'[4]

Speaking at the IAPB's 9th General Assembly last year, President Bob McMullan stated: "Eye health affects every individual and the economy of every country. Avoidable blindness and vision impairment is a massive problem, but it's a problem that we can do something about through cost-effective solutions."[5]

VISION 2020 aims to prevent approximately 100 million people globally from becoming blind by 2020 by creating cost-effective disease control interventions through training and ensuring the development of infrastructure. VISION 2020 follows four principles:

- Integration with existing healthcare systems;
- Sustainability of finance and resources;
- Equitable care to be received by all;
- Excellence in care standards.

With the technology and medical care available in the 21st Century, there is no reason for preventable blindness or visual impairment to exist anywhere in the world, but while it does, programmes like VISION 2020 are vital to ensure progress is made and the number of sufferers reduced.

[1] www.who.int/blindness/GLOBALDATAFINALforweb.pdf

[2] Ibid

[3] www.iapb.org/about-iapb/iapb-history

[4] www.iapb.org/vision-2020-right-sight

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Diabetic retinopathy: eyes on the prize

DR is a rising global health problem requiring cost-effective and accessible prevention and treatment, writes the Casey Eye Institute's Dr Andreas Katsuya Lauer…

Vision loss from diabetic retinopathy (DR) is more likely to be irreversible compared to other major causes of blindness, such as cataract and refractive error, where vision loss is reversible in many cases and for which cost-effective treatment and delivery systems exist. Vision loss from DR carries very severe physical, psychological, social and economic impacts on individuals and their communities worldwide. Although research and treatment refinements in DR have resulted in better visual outcomes for patients in industrialised nations, it remains a significant public health problem in working age and senior adults in these countries. It has also been recognised that as nations become more industrialised and prosperous, the prevalence and impact of DR rises concurrently. This has been particularly the case with adult onset diabetes.

In the 1990s, the estimate for the 2010 diabetic population worldwide was 221 million. This proved to be an underestimation, since in 2012, the worldwide diabetic population estimate stood at 347 million. Between 2002 and 2012, the World Health Organization estimate for individuals with DR doubled from 7.7 million to 14 million. As the world population increases, life expectancy increases and the incidence of diabetes increases, the consequences of visual impairment and blindness from DR are on a juggernaut trajectory to eclipse the other causes of blindness. DR is poised to be an overwhelming global public health problem.

When caring for diabetic patients, it is widely recognised that prevention of DR or detection and early treatment are the most cost-effective means of minimising the impact of this blinding disease. When systems are not in place to prevent or detect and treat retinopathy at early stages, irreversible vision loss and blindness occur more frequently.

Visually impaired diabetics increasingly require time off from work to visit the doctor's office and often lose their jobs altogether as their vision worsens irreversibly. Visual impairment reduces the individual's capacity to remain actively engaged in their communities. They have difficulty seeing their medication instructions to manage their disease and they rely increasingly on two or more adults to care for them. Vision loss associated with DR results in reduced productivity, reduced economic livelihood and in numerous instances family discord, as working diabetic individuals lose their independence and autonomy.

As the world population increases, life expectancy increases and the incidence of diabetes increases, the consequences of visual impairment and blindness from DR are on a juggernaut trajectory to eclipse the other causes of blindness.

Any hope of quelling the surging global tide of DR in a cost-effective manner will require prioritising individual and societal incentives toward prevention and primary intervention. Increasing physical activity, maintaining a healthy diet, and controlling blood sugar, blood pressure and blood lipids all reduce the incidence and severity of DR.

When sight-threatening DR develops, in addition to the interventions above, primary and secondary interventions include eye care at specified intervals and treatment with retinal laser or intraocular medications injections. Treatments can stabilise or reduce retinopathy and, in many instances, improve the retinopathy and vision. Vitrectomy surgery is of benefit in more advanced cases.

While patients in certain industrialised countries may be able to access sophisticated diabetic eye care, for many health systems, the delivery of these treatments is not economically feasible or sustainable and has limited applicability. Cost-effective screening and treatment systems are much in need for the global stage. In facing this global health problem, it will be incumbent on us to implement diabetic eye care systems that are simple, safe, efficient, affordable, generalisable and portable. Are we up to the challenge?

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Diabetic retinopathy

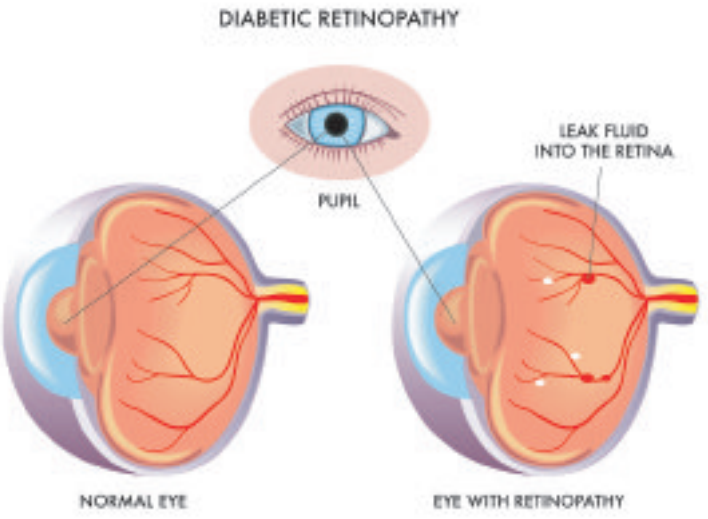
Evidence-based practice and refinement meet the global challenge…

Diabetic retinopathy (DR) is the leading cause of vision loss in working age people in industrialised societies. As population growth and life expectancy increases, and more countries become industrialised, the increasing rate of diabetes mellitus impels societies to face the growing challenge of treating DR. Clinical trials conducted in DR have been essential in guiding treatment and drastically reducing the rate of blindness.

Natural history of DR

The most common cause of visual impairment in patients with DR is diabetic macular edema (DME) where porous retinal vessels leak fluid into the central retina and reduce central vision. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that patients with DME were more likely to develop moderate vision loss.[1] Initially, DME may wax and wane without much permanent visual loss, but if persistent, significant and permanent vision loss occurs.[2]

As DR progresses, further oxygen deprivation (ischemia) induces new abnormal blood vessel growth (retinal neovascularization (NV)). NV defines the development proliferative diabetic retinopathy (PDR) from non-proliferative diabetic retinopathy (NPDR) previously. In PDR, hemorrhaging from retinal NV into the central vitreous cavity of the eye results in obscured vision. 60% of untreated diabetics will eventually develop PDR, resulting in profound visual loss in nearly half.[3] In advanced stages of PDR, retinal NV is accompanied by fibrous scar tissue that may detach the retina. Vitreous hemorrhage or retinal detachment



from this advanced form of PDR is a leading cause of new onset blindness in developed countries worldwide.

Prevention and primary treatment

Large controlled clinical trials have clearly demonstrated that tight blood sugar, blood pressure and serum lipids control are essential to the maintenance of vision in diabetics and is the most cost-effective and most successful means of preventing vision loss due to diabetes.[4-6]

Retinal laser treatment

The Diabetic Retinopathy Study (DRS) and the ETDRS were pivotal trials in the treatment of DR, by elucidating the natural history of DR and establishing that retinal laser treatment is effective intervention.[7-9] For three decades, retinal laser treatment has been the mainstay therapy to prevent or reduce the frequency of further vision loss from PDR and DME.[10, 11]

Vitrectomy surgery

Vitrectomy surgery, a specialised microsurgical technique designed to treat various retinal diseases, was evaluated in the Diabetic Retinopathy Vitrectomy Study (DRVS). The DRVS showed that vitrectomy within one to six months was a beneficial treatment in eyes with severe vitreous hemorrhage or advanced PDR.[12] In recent years, technological advances in surgical instrumentation have changed allowed for earlier and safer intervention.

Intraocular pharmacotherapy

In the last decade, a better understanding of the pathophysiologic mechanisms of DR have translated to standard of care treatment in DME and adjunct in the treatment of PDR.[13] Although, the intraocular administration of corticosteroids is effective in the treatment of DME, the high rate of cataract and intraocular pressure elevation[14-16] has instead favoured the administration of intraocular anti-vascular endothelial growth

factor (VEGF) agents, which offer fewer side effects. Intraocular administration of anti-VEGF agents, such as bevacizumab and ranibizumab, reduce vascular permeability and inhibit NV. Their use is the standard of care for the treatment of DME when the centre of the macula is affected and used as an adjunct for treatment of PDR.[17-21] Other anti-VEGF compounds, such as aflibercept, are completing clinical trials.[22] Whereas laser treatment for DME allowed for stabilisation of vision previously, anti-VEGF therapy has allowed for substantial vision improvement when treatment is given following a specific algorithm as defined by clinical trials.

Conclusion

Large clinical studies were pivotal in our understanding of DR. They established the natural history of DR and incontrovertibly determined that tight glycemic control, blood pressure control, serum lipid control, retinal laser, vitrectomy surgery, and intraocular anti-VEGF are effective interventions. With continued clinical research, novel therapeutics, intraocular delivery systems and sustained improved visual outcomes for patients are very near to the horizon for the growing global problem of DR.

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Proprietary interest

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Breathing easier

Professor Dean Schraufnagel, Past President of the American Thoracic Society, underlines the value of research in battling respiratory diseases in the US…

Respiratory issues affect millions of Americans, robbing them of their health, happiness, and even of life itself. Asthma, COPD, lung cancer, and sleep apnoea are just a few of the important respiratory conditions that pose major threats to citizens. Just as importantly, airborne threats such as influenza, air pollution and bioterrorism can spread rapidly through the air, affecting enormous numbers of people in a very short period of time. Moreover, tobacco smoke kills more Americans in one year than all the wars the US fought during the last century.

Together, respiratory diseases kill more than 400,000 Americans each year, making them the third leading cause of death in the United States.[1] For millions more, respiratory diseases significantly reduce quality of life. Being unable to breathe can be a terrifying experience, yet it is one that many face every day.

Biomedical research has value to society far beyond products. It can increase employment, build infrastructure, and produce financial gain.

The US Congress has recognised the importance of respiratory health and has embarked on programmes to make a difference. From 1998-2003, Congress doubled the budget of the National Institutes of Health. It has strengthened the Centers for Disease Control and Prevention, granted the Food and Drug Administration the ability to regulate tobacco, improved pollution control through the Environmental Protection Agency, and funded tuberculosis programmes throughout the world, realising that in order to control tuberculosis at home, it must be controlled worldwide.

The money invested in research has been money well spent. Americans are living longer and healthier and, for the most part, breathing easier. Some previously untreatable diseases, such as respiratory distress of the newborn, now have treatments; others have cures within their grasp. More progress must be made, both in understanding disease processes in order to develop cures and in bringing these advances to everyone.

The economic cost of lung disease, both to individuals and to society, is vast. The annual cost of asthma exceeds $19bn per year in the United States.[2,3] The estimated annual cost of providing COPD related medical services was even higher, ranging in 2005 from $2,700 to $5,900 per person.[4] In 2009, the estimated annual cost of providing healthcare related to all respiratory conditions, excluding lung cancer, was $113bn and the cost to American society in terms of lost productivity as a result of disability and early death due to respiratory disease amounted to an additional $67bn.[5]

The challenge of curing or eliminating lung diseases is best met through research and application of its findings. The ability today to study complex molecules holds even greater promise than the golden age of bacteriology of the late 1800s. In today's science, the emphasis is on the precise understanding of what leads to the failure of a molecule, cell or system. Understanding of the molecular mechanisms is even more significant than the discovery of disease-causing bacteria was in the 19th Century. Cellular and molecular systems are far more complicated, but the potential payoffs are vastly greater.

Today, most researchers believe that there is a genetic tendency that renders someone more susceptible to a disease. Coupling this genetic defect with an environmental or chance health risk can lead to a functional breakdown and subsequent illness. Linking genetic abnormalities and environmental stimuli to specific diseases could explain why certain individuals develop a disease and others do not. An additional benefit of identifying genes predisposing to a certain disease is that the gene products can be studied. Knowing which proteins the gene produces can unravel the underlying

Respiratory diseases kill more than 400,000 Americans each year

mechanism of the disease and help scientists understand the biochemical interactions that lead to it. Replacement or repair of these gene products can lead to new treatments or even cures.

> **...the cost to American society in terms of lost productivity as a result of disability and early death due to respiratory disease amounted to an additional $67bn.**

Research in the last 20 years has brought great progress in understanding most lung diseases, and some appear close to breakthroughs. With others, however, a cure remains distant for several possible reasons: the disease could be poorly defined, the cause may be unknown, or there may be limited genetic and mechanistic information. Occasionally, previous failed attempts to understand the disease may have discouraged investigators.

Even when a treatment becomes available, it may not be fully utilised. Difficulties in applying new treatments are several-fold. New drugs have been tested in clinical trials to assure safety and efficacy, but usually in relatively small numbers of persons in a controlled environment. More experience is usually necessary before the treatment is accepted for patients beyond a clinical trial. Additional experience and study are usually required before the treatment is incorporated into medical guidelines. Even after new therapies are incorporated into guidelines, their high cost may be a barrier to their use. The emerging field of Comparative Effectiveness Research seeks to distinguish which of the competing therapies is better.

Another important part of the path to cure is awareness. Millions of people around the globe are unaware of the hazards of smoking and air pollution and the enormous afflictions they cause.[6, 7] Even in the developed countries, lung disease is often underrecognised and its research is underfunded. Patients, their healthcare providers and advocacy organisations reach out to the research community and funding agencies to increase awareness of their disease and stimulate research initiatives. Aware-

Tackling COPD: The National Heart, Lung and Blood Institute (NHLBI)

Respiratory diseases encompass numerous conditions such as asthma, cystic fibrosis, emphysema and various chronic obstructive pulmonary diseases (COPD). Chronic respiratory diseases are both debilitating for sufferers and costly to health services, and therefore understanding and investing in research into lung diseases is imperative.

In the US, the government agency responsible for supporting research into lung disease is the National Institutes of Health's National Heart, Lung and Blood Institute (NHLBI).

The NHLBI's Division of Lung Diseases (DLD) covers research into airways biology, lung biology and sleep disorders. It 'stimulates basic discoveries about the causes of disease, enables the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians and communicates research advances to the public. It creates and supports a robust, collaborative research infrastructure in partnership with private and public organisations, including academic institutions, industry, and other government agencies'.[1]

In November last year, a survey was carried out to determine the prevalence of COPD, one of the major sets of respiratory conditions in the US. A joint venture between NHLBI and the Centers for Disease Control and Prevention (CDC), the survey found that the number of women with COPD was higher than men and that the condition is more likely to occur in the unemployed or retired.

Discussing the results, Director of the DLD at the NHLBI, Dr James Kiley, stated: "These findings illustrate that we still need improvement in raising awareness about COPD and its diagnosis and management. COPD can be well-controlled, but it's critical to diagnose it early and to follow the appropriate therapeutic strategies."[2]

With respiratory diseases claiming the lives of hundreds of thousands of American each year, ongoing research from government bodies and associations such as the American Thoracic Society is taking on ever-increasing importance.

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ness helps identify the areas of greatest need, ensure that promising scientific leads are followed up and enrol patients in clinical studies.

Biomedical research has value to society far beyond products. It can increase employment, build infrastructure, and produce financial gain. It is no accident that the United States is the leader in biomedical research – 70-80% of the total global biomedical research is sponsored by US governmental agencies, US-based foundations and US headquartered corporations.[8] The United States has benefited most from its research success, but because the benefits of scientific research can be shared by everyone, research gains may be America's greatest gift to the world. Great advances have come from many nations, and these shared advances have fuelled successes in the United States and other countries. Continuation of this rapid pace of acquiring new knowledge requires ongoing international cooperation.

The answers to the far-ranging question of how to protect and improve respiratory health require strengthening and enhancing of the promising research already under way. Research and application of new knowledge are keys to making even greater gains.

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Looking out for lung health

As a new edition of the European Lung White Book is published, ERS President Francesco Blasi charts what has changed in regards to lung disease in a decade…

The White Book calls for the EU to step up efforts to implement the World Health Organization (WHO) guidelines on air quality, to stop Europe falling even further behind levels that are safe for our lungs.

The field of lung health is large and diverse, with the common factor that encompasses all lung conditions being their impact on the way that we breathe. The field includes infections (such as TB and pneumonia), chronic conditions (such as COPD, asthma and CF), malignant conditions (such as lung cancer), interstitial lung diseases, occupational lung conditions, pulmonary vascular disease and sleep disordered breathing. Together, they are a major cause of morbidity and mortality and are a massive health and socioeconomic burden.

In 2003, the European Respiratory Society (ERS), together with the European Lung Foundation (ELF), produced the first edition of the European Lung White Book – a 200-page report with data on the causes, means of prevention and treatment for a wide range of respiratory diseases.[1] It detailed, for the first time, the financial impact of respiratory disease in Europe and highlighted the requirements to improve both research and patient care. The ERS produced the White Book so that doctors, scientists, patients and policymakers could have a comprehensive basis on which to reach decisions and formulate policy about lung health.

10 years on, in 2013, the ERS and ELF are poised to publish the second edition of this publication, and it offers a great opportunity to examine the changes that have taken place in the field of lung health and the new and ongoing challenges, specifically in relation to the major risk factors.

The changing face of lung disease

The economic burden of lung disease remains huge, with the total estimated cost in Europe being at least €380bn.[2] Lung diseases cause disability and premature death, having a huge cost related to primary care, hospital care and treatment, as well as the loss of productivity of those who cannot work and people who die early because of their condition.

The most important point to be highlighted in the new edition is that the impact of lung disease remains as large today as it was at the turn of the century, and is likely to remain so for several decades. However, the types of lung conditions that contribute most to the mortality and morbidity from lung disease are changing. It is predicted that the number of lung infections will reduce, while chronic conditions, such as asthma, COPD and lung cancer, will increase.

Tackling the risk factors

The White Book not only looks at the impact of lung disease in Europe, but also outlines the risk factors related to those diseases. Many of the underlying causes of respiratory disease can be prevented, and this is why it is vital that these issues are addressed.

Air pollution affects 100% of the population, and particularly people who are vulnerable. A large proportion of Europe's population live in areas with unhealthy outdoor air. Some 87% of Europeans think that lung disease related to air pollution is a serious issue in their country[3] and the average loss of life expectancy in Europe due to poor air quality is estimated at 8.6 months.[4]

By 2050, air pollution will be the biggest environmental cause of premature death, according to the Organisation for Economic Co-operation and Development (OECD).[5] The pollutants that cause the most concern include particulate matter, nitrogen dioxide and ground level ozone.

Studies have shown that the short-term impacts of air pollution include a worsening of existing symptoms linked to a lung condition or a commonly occurring cough. In the long term, air pollution can reduce life expectancy, affect lung development, increase the chances of suffering from asthma and lead to other lung and heart diseases.

The White Book calls for the EU to step up efforts to implement the World Health Organization (WHO) guidelines on air quality, [6] to stop Europe falling even further behind levels that are safe for our lungs. European countries need to integrate air quality into their transport, industrial and energy policies.

Although air pollution is a major concern for EU citizens, tobacco consumption continues to be the major single cause of lung disease. This edition of the White Book shows that half of the burden of respiratory disease is attributed to smoking.[7] This is due to the fact that 60% of COPD, 85% of lung cancer and 10% of other lower respiratory disease in the EU are caused by smoking[8] and 700,000 Europeans die every year from tobacco consumption.[9]

In order to continue the fight against tobacco, there needs to be more smoke-free areas in public places, the price of cigarettes needs to be increased further, plain packaging and large pictorial warnings need to be legislated for and all smokers encouraged to quit.

Advances and gaps in respiratory disease research

Since the last White Book, health funding by the EU has increased steadily. The creation of the European Research Council and the new cross-cutting research programme, Horizon 2020, supports the concept of bench-to-bedside research.

Some breakthroughs have occurred in some areas in respiratory health, including:

- The introduction of diagnostic rapid molecular methods in TB (such as GeneXpert);
- Novel treatments for CF (such as Ivacaftor VX-770) that address the basic defect;
- Advances in lung cancer treatment, in its surgical management (VATS), in tailoring chemotherapy to the tumour subtype and newer targeted therapies, such as the tyrosine kinase inhibitors (erlotinib or gefitinib).

However, many gaps still exist and there is a stronger need than ever to adequately fund respiratory research. In 2011, the ERS published its Roadmap on lung health,[10] which aimed to highlight the major areas in which funding for research was required. The below outlines some of those points and others highlighted in the new edition of the European Lung White Book, areas in which more funding for respiratory research is required:

- Repair and regeneration of injured lungs;
- The origins of asthma – so that it can be prevented and better treated;
- Severe asthma – to help develop more personalised medicine in the future;
- Environmental and genetic causes of asthma;
- Prevention, education, medication, treatment and care of COPD – to drive better standards;
- Different variations of COPD and their economic burden;
- Correcting the underlying abnormalities in cystic fibrosis;
- Genetic causes of interstitial lung diseases – to improve prevention and treatment;
- Radiotherapy techniques and markers for lung cancer – to ensure early diagnosis;
- Causes of pulmonary hypertension;
- Markers of TB – to help predict the success of new treatments and vaccines.

The next 10 years

The ERS and ELF are proud to be able to bring together this compendium, but one with more reliable and complete data for respiratory disease in Europe is needed – in particular, covering disability due to chronic conditions. All EU member states must improve and standardise surveillance and data collection relating to respiratory disease.

The White Book aims to be an impetus and tool for change – providing the data and evidence needed to make important policy decisions. It is hoped that this edition will ensure adequate provision and increased funding for basic translational and epidemiological research.

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The European Lung White Book will be launched on the first day of the European Respiratory Society Congress in Barcelona on 8th September. To access the book online, go to: whitebook.ersnet.org or to purchase a copy of the publication, please visit: www.ersbookshop.com

…there needs to be more smoke-free areas in public places, the price of cigarettes needs to be increased further, plain packaging and large pictorial warnings need to be legislated for and all smokers encouraged to quit.

Francesco Blasi
President
European Respiratory Society (ERS)
www.ersnet.org

Dedicated pulmonary research in Munich

The Comprehensive Pneumology Center – a translational research centre…

Chronic lung diseases (CLDs), including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, asthma, lung cancer and neonatal CLD, are leading diseases worldwide with respect to mortality, morbidity, prevalence, incidence and socioeconomic burden. To a large extent, the devastating impact of these diseases on our societies is due to increased environmental challenges in recent years (e.g. cigarette smoke, allergens, air pollution and related particles). A lack of understanding of dominant pathomechanisms of CLD have led to a paucity of efficient therapeutic options, as well as a lack of awareness of these diseases within societies, which further contributes to disease burden. In terms of mortality, CLDs are the second leading cause of death in the world.

The Comprehensive Pneumology Center is a translational research centre dedicated to clinical and experimental lung research

Munich currently represents one of the leading areas for medical research and care for patients with CLD. Dedicated pulmonary research has a long-standing history in the city. In 2009, these fertile grounds led to the formation and establishment of the Comprehensive Pneumology Center (CPC), a collaboration between three renowned partners: the Helmholtz Zentrum München – German Research Center for Environmental Health (HMGU), the Ludwig-Maximilians-Universität München (LMU) with its University Hospital, and the Asklepios Hospital. The CPC is composed of two departments, led by chairmen with a respective Department Chair ('Lehrstuhl'): the Institute of Experimental Pneumology, led by Dr Oliver Eickelberg, and the Institute of Clinical Pneumology, led by Dr Jürgen Behr. The CPC is located at the High Tech Campus in Munich-Grosshadern, directly adjacent to LMU University Hospital. In total, the CPC building comprises 2,500m^2 functional space dedicated exclusively to lung research, including an outpatient unit for clinical studies.

The CPC is a site of the German Center for Lung Research (DZL – www.dzl.de). The DZL is one of six government initiated German Centers for Health Research that unite leading universities and non-university-based research organisations in one coherent structure to fulfil the mission: 'Translational research to combat widespread lung diseases.'

The primary aim of scientists and clinicians at the CPC is to unravel the dominant pathomechanisms of CLD, define novel preventive measures, and ultimately develop new (personalised) therapeutic and/or diagnostic strategies for the therapy of CLD. The close interaction between clinicians, physician scientists and biomedical scientists cultivates a translational atmosphere and aims to shorten the development time of new therapeutic/diagnostic regimens. CPC scientists focus on the following disease areas:

Interstitial lung disease – idiopathic pulmonary fibrosis (IPF)

IPF is characterised by cellular injury and altered homeostasis in the peripheral lung, leading to excessive accumulation of extracellular matrix (ECM), which subsequently leads to distortion of the normal lung architecture and respiratory failure. Different determinants have been suggested as risk factors for IPF, but the origins of the disease remain unclear. Therapeutic options in IPF are scarce, and as such, lung transplantation remains the main therapeutic intervention with a known survival benefit for IPF patients. While several therapeutic targets have entered clinical trials in the past, and one has been granted approval in parts of the EU (pirfenidone), important questions in IPF remain.

CPC scientists conducted pioneering work with regard to the pivotal role of alveolar epithelial cells (AEC) and interstitial fibroblast in IPF, identifying major pathogenic pathways along with novel potential therapeutic targets. Major contributions include the characterisation of lung epithelial cell plasticity and epithelial to mesenchymal transition (EMT) in lung fibrosis. They identified and investigated critical signalling molecules involved in disease pathogenesis (Scotton et al., 2009; Königshoff et al., 2010; Zhang et al., 2011; Mise et al., 2012; Pulamsetti et al. 2012). In international collaborations, they also compiled the miRNA profile of IPF (Pandit et al., 2010). With the investigation of the Wnt signalling pathway and the Wnt target gene, Wnt inducible signalling

protein (WISP) 1, CPC scientists contributed to the current concept that IPF represents a disease characterised by distorted activation of developmentally active signalling pathways (Königshoff et al., 2008, 2009, Pfaff et al., 2010).

COPD

COPD is a devastating disease characterised by irreversible airflow obstruction, airway inflammation, and loss of functional pulmonary tissue. Currently, COPD is the fourth leading cause of death worldwide. While no causal therapy for COPD is available to date, the avoidance of its major risk factor, cigarette smoke exposure, represents one major effective strategy in the quest against COPD (Sullivan et al., 2000).

At the CPC, several research groups aim to shed light onto the pathobiology and pathomechanisms of COPD. For the verification of potential therapeutic targets and characterisation of key mechanistic signalling pathways, they have established relevant and reliable animal models. Concerning the adult onset of COPD, two major animal models of COPD/emphysema are routinely investigated by semi-invasive longitudinal lung function analysis and design-based stereology to assess quantitative morphological chances in the lung.

These parameters provide clinically relevant readouts for therapeutic intervention studies at the CPC (Yildirim et al., 2010, Kneidinger et al., 2011, John et al., 2013). Novel *in vitro* assays at the CPC, analysing the effects of cigarette smoke exposure on lung cells, have identified protein quality control defects via dysregulated proteasome activity as a new pathomechanism in COPD (van Rijt et al., 2012). Wnt signalling activity in IPF and COPD revealed an important role of Wnt/β-catenin signalling in the establishment of the diseases (Kneidinger et al., 2011, Rock and Königshoff, 2012).

Asthma

Asthma is an inflammatory disease of the pulmonary airways. Asthmatics suffer from intermittent airflow limitation and symptoms of wheezing and shortness of breath. Many children with asthma have persistent symptoms throughout life, leading to a significant reduction of quality of life. Asthma also presents itself in later life, often resistant to treatment. Asthma has a high prevalence and a chronic relapsing course.

Childhood asthma is the most common chronic disease of infants/adolescents. Occupational asthma due to workplace exposure to dusts or chemicals is the most prevalent occupational lung disease in the European community. Thus, asthma is a global health problem that imposes a significant burden on family and healthcare systems, resulting in massive social and economic costs in Germany alone. Several groups at the core of the CPC focus on different aspects of asthma pathogenesis, emphasising asthma as one of the CPC's research foci. CPC scientists focus on asthma and COPD genetics and the dynamics of pulmonary inflammation. An important emphasis at the CPC is investigation into the role of lung development at the onset of asthma in children, creating transgeneration models of epigenetic programming in asthma.

Bronchopulmonary dysplasia (BPD)

BPD remains a significant complication of prematurity and neonatal intensive care that affects more than 30% of all pre-term babies below 29 weeks (Jobe et al., 2001). Mechanical ventilation and oxygen therapy offer live saving treatment to patients, however, the therapy itself significantly contributes to the failure in alveolar formation (Coalson et al., 1999).

CPC scientists show the differential impact of important actors of the innate immunity on BPD development in the neonate, thereby enabling an undergoing clinical study determining biomarkers for BPD in this patient cohort (Hilgendorff et al., 2007, 2009). To study the neonatal onset of BPD, CPC scientists have successfully established a unique model of neonatal mouse ventilation, as well as the classical model of hyperoxic lung injury (Hilgendorff et al., 2012, Mokres et al., 2010, Alejandre-Alcázar et al., 2007), where scientists at the CPC further study the role of ECM remodelling in BPD (Hilgendorff et al., 2011, 2012, Kumarasamy et al., 2009).

From bench to bedside

The CPC follows a 'bench-to-bedside-and-back' approach in the investigation of lung diseases. The experimental and clinical research includes patients from all age groups, from premature newborns to adults and the elderly, which are at risk for specific lung diseases. The scientists at the CPC use cellular and molecular approaches to investigate the role of signalling pathways that trigger disease-specific features. The ultimate aim of translational research at the CPC is to employ personalised medicine for the next decade to alleviate the burden of chronic lung disease.



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The lung view

The German Cancer Research Center's Professor Ursula Klingmüller sheds light on how the most clinically relevant questions to lung cancer are being addressed…

One of the deadliest cancers worldwide, lung cancer causes 1.3 million deaths per year – and these numbers are still rising. Around 80% of lung cancer cases are identified as non-small cell lung carcinoma (NSCLC), and one of the main reasons for the deadly outcome is the early metastatic spread observed in the majority of patients. Furthermore, many patients are diagnosed at a rather late stage of the disease and already suffer from metastasis in other regions of the body. Currently available therapeutic options are very limited; only a small fraction of patients is eligible for tumour resection, whereas the majority receives systemic chemotherapy. Some patients harbour an activating mutation in the epidermal growth factor receptor or an EML4-ALK translocation, and can be treated by targeted therapy. However, in each case the success of the therapy is only transient and the five year survival rate is extremely poor.

Reasons for the dismal situation are multifactorial. Cancer genome projects have provided evidence for an extremely high mutation rate in lung cancer and revealed that apparently different combinations of alterations can lead to the same disease. How this is possible remains a major unresolved puzzle. Evidently, it is not sufficient to focus on individual molecules but rather on properties that facilitate information processing, integration and conversion into responses in tumour cells. Furthermore, communication of the tumour with the environment, its vascularisation and the impact of the immune system need to be considered. The complexity of these highly dynamic processes that occur at different spatial levels and timescales requires a novel systems biology approach that combines theoretical and experimental expertise and applies this expertise to clinically relevant questions.

At the heart of this approach is the close collaboration of clinicians, basic researchers and theoreticians that cooperate in large interdisciplinary consortia with a common goal. The German Ministry of Research and Education (BMBF) is funding initiatives that employ systems biology to tackle key questions in lung cancer.

Cancer genome projects have provided evidence for an extremely high mutation rate in lung cancer and revealed that apparently different combinations of alterations can lead to the same disease.

In the first funding period, the LungSys consortium focused on a potential risk of erythropoietin (EPO) treatment in the context of lung cancer, and showed that a functional EPO receptor is present on lung cancer cell lines. This consortium currently addresses mechanisms promoting early metastatic spread, one of the most urgent clinical questions. These efforts are complemented by studies in the disease area by the German Center for Lung Research, which brings together university and non-university institutions dedicated to lung research, seeking to jointly develop new approaches for the prevention, diagnosis and therapy of serious lung diseases in Germany, including lung cancer.

An important basis to address the clinically most relevant questions is the development of an effective communication between different disciplines, standards for data generation and a policy for data sharing. Major investments are required for the establishment of suitable infrastructures for data storage and exchange.

Taken together, this approach capitalises on the wealth of knowledge available in the different disciplines and by joining forces it holds great promise for improved stratification of patients and the development of therapies tailored to the individual patient.

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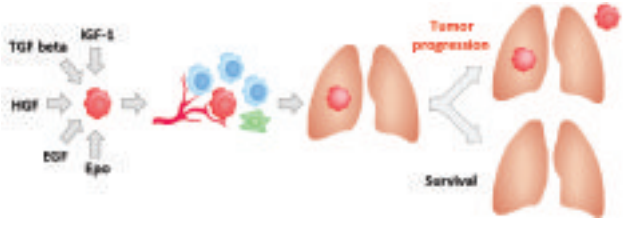
An interdisciplinary approach to lung cancer

Bringing together medicine, biochemistry, cell biology, medical imaging, chemistry, physics, mathematics and industry…

The late diagnosis, early tumour spread and rapid therapy resistance are the main reasons for the deadly outcome of lung cancer. Early metastatic spread involves multiple serial steps such as separation from the primary tumour mass, invasion of the surrounding tissues, entry into the bloodstream and invasion of new organs. One therapeutic option is systemic chemotherapy with cisplatin and taxanes. As a side effect, red blood cell production can be impaired and the resulting anemia is frequently treated by applying the hormone erythropoietin (EPO). However, since the EPO receptor has been uncovered on tumour cells, the safety of the treatment has been called into question. Tumour development and therapy resistance arise through intertwined processes across different scales, ranging from cellular to organ levels. In order to disentangle this complexity and unravel key dynamic properties, a systems biology approach is required that combines extensive generation of quantitative data and different mathematical modelling.

LungSys is an interdisciplinary consortium with members from medicine, biochemistry, cell biology, medical imaging, chemistry, physics, mathematics and industry that uses systems biology to gain insights into lung cancer.

In its first funding period (2009-2012) within the MedSys call of the German Ministry of Education and Research (BMBF), its mission was to identify the effects of EPO treatments in lung cancer. This very focused topic greatly facilitated communication and development of



mutual understanding between researchers from the different disciplines. Standard operating procedures were established to ensure comparability of the experimental data generated by the different groups. The first steps towards the integration of different mathematical models were taken. The developed dynamic pathway model of the interaction of EPO with its receptor promises to permit prediction of strategies to reduce the risk of EPO treatment for patients.

During its second funding period (2012-2015) within the BMBF call CancerSys, its mission is to gain insights into mechanisms that facilitate early metastatic spread and cause therapy resistance in lung cancer. A particular focus is on the impact of the epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), transforming growth factor-beta (TGF-beta) and EPO. The effect of these factors on responses of lung cancer cell lines is determined by biochemical assays and imaging approaches. The studies range from the analysis in 2D monolayer cultures, 3D spheroids, co-cultures with endothelial cells up to xenograft studies and final comparison to patient-derived information. Based on time-resolved quantitative data of the molecular behaviour of signalling pathways, mathematical models are calibrated and subsequently linked to cellular output, such as migration and proliferation or the impact of cell communication. First evidence shows surprising synergism of different factors in enhancing migration of lung cancer cells. The detailed cellular models will be integrated into a multi-scale model that will be utilised to develop model-based strategies to avoid drug resistance and progression of the disease.

Taken together, the complexity of lung cancer requires the joining forces of different disciplines. In order to fully capitalise on the wealth of knowledge available in the different disciplines and to efficiently synergise in tackling key clinical questions, a major challenge is effective communication between experts from different disciplines. The pipelines developed by the LungSys Consortium provide an important basis to advance systems biology towards systems medicine for the benefit of lung cancer patients.

LungSys

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Personalised treatment programmes

Precision medicine for a large cancer centre…

The University of Texas MD Anderson Cancer Center serves approximately 100,000 cancer patients, including over 35,000 new patient registrations, each year. Over 8,000 patients participate in therapeutic clinical trials each year. In 2012 we activated a personalised cancer medicine programme, which aims to grow over the next five years to provide genomic tumour analysis and genomically informed targeted therapy for all of our patients who do not have access to a curative approach with current surgery, radiotherapy and chemotherapy. This brief overview will describe initial barriers and current challenges.

Goals

In its broadest conceptualisation, personalised/precision cancer medicine based on genetic and other molecular information will someday encompass prevention, early detection, prognostication and treatment with the most appropriate therapy. Analysis of tumours will include aberrations in DNA, RNA, functional proteomics and metabolomics. Potential new and important approaches such as immunological competence and tumour-stromal interactions will be addressed as they become clinically actionable. In the future, tumour cells also will be characterised for properties that influence response to therapy, including 'stem-ness' and status along the epithelial-mesenchymal transition continuum.

For our initial efforts, the decision was made to focus upon analysis of genomic aberrations for which experimental or approved therapies are available. This was decided on the likelihood of clinical relevance based on clinical experience during the past decade, the recent availability of multiplex DNA sequencing approaches, and the un-reimbursed expenses that clinical application of many additional assays would incur.

The initial goals were to create the infrastructure and platforms to accomplish targeted genomic analysis of large numbers of tumour specimens, to conduct clinical trials bringing therapies to patients that target the genomic aberrations in their cancers, and to demonstrate the value of this approach so that it will become a standard of practice and reimbursed.[1]

Multidisciplinary efforts

The project required bringing together multidisciplinary teams within our recently restructured Khalifa Institute for Personalized Cancer Therapy to design and integrate the required infrastructure components, including:

- Interventional radiology and endoscopy to obtain tumour biopsies;
- A pathology laboratory to qualify tissue specimens and prepare analytes;
- A clinical Molecular Diagnostics Laboratory with certification for the Clinical Laboratory Improvements Amendments (CLIA) and equipped to sequence DNA with current, rapidly evolving technologies;
- Teams with expertise for selecting among bioinformatics and genomic data analysis platforms and to utilise computational and systems biology to interpret data;
- A multidisciplinary committee to select the clinically actionable genes to be sequenced and address costs and billing;
- Decision support tools for clinicians and their patients;
- A Molecular Tumour Board led by a clinical oncologist and a molecular pathologist to guide treatment planning and to provide education for all faculty members involved in patient care based on genomic analysis of cancers.

The teams providing the expertise to carry out these assignments include molecular pathologists, interventional radiologists, clinical geneticists and genetic counsellors, joined by experienced clinical investigators and translational laboratory scientists who are up to date on current knowledge of potential therapeutic targets involving signal transduction, apoptosis, cell cycle progression, DNA repair and others such as angiogenesis. Ethicists, regulatory compliance personnel and patient advocates must also participate.

Gene analysis and reporting of results

The Molecular Diagnostics Laboratory at MD Anderson had previously initiated analysis of specific loci (hot spots) in selected genes that were relevant for clinical decisions (e.g. EGF receptor and PIK3CA mutations). In 2012, a panel of 72 hot spots in 12 genes was selected for analysis on a Sequenom® instrument. Within a year, based on the needs determined by a multidisciplinary clinical committee, this assay

panel evolved to sequence analysis of 740 hot spots in a panel of 46 genes, using AmpliSeq® and Ion Torrent® technology. This expansion required a parallel scale-up of clinically useful and regulatory compliant bioinformatics and data management.

Amplification continued to be estimated for a subset of actionable genes using FISH analysis. A new Tissue Qualification Laboratory was opened, staffed by pathologists, to provide quality control of specimens and microdissection of select areas in which tumour cells predominate on histopathology and cytopathology slides. To date, more than 4,000 patients' tumours have been analysed through this infrastructure with CLIA compliance for reporting of genomic alterations.

Decisions had to be made about which detected abnormalities were appropriate to report to clinicians as potentially actionable. We instituted a system for grading the level of evidence supporting classification of a genomic aberration as actionable, vetted by the multidisciplinary Molecular Testing Evaluation Committee. Positive clinical results in a phase II or III trial treating cancers with targeted therapy were considered level I, positive reports of single clinical cases were level II, and preclinical data in model systems constituted level III.

The collected data generated a list of more than 30 genes found to have mutations, amplifications, and/or overexpression in at least one tumour sample assessed. In some cases, genomic aberrations were found in sites not previously reported in these genes, raising the question of whether they were actionable targets. Based on analysis of all available data on a specific aberrant genes, often presented for discussion at the Molecular Tumour Board, genotype relevant treatment options were shared with the treating physician. As data continue to accumulate internally, in public databases and in literature, therapeutic decisions will become more precise.

A major future challenge is the need for open sharing of clinical and molecular data that is required for identifying therapeutic efficacy against rarely occurring genetic aberrations, or even more common ones. It is critical that the data are assessed on the basis of the specific mutations, as different mutations in the same gene may alter treatment responsiveness. A consensus has developed that pooling of anonymised clinical and molecular data will enable far more efficient and effective determination of when and for whom a targeted therapy will be effective, or equally important, ineffective.

Optimal data sharing will require agreement on the part of clinical investigators, patients and pharmaceutical companies, and will be greatly enhanced by collection of data in a standardised, interoperable format. The movement towards electronic medical records in the USA is not currently focused on standardisation, but this is being introduced by the National Cancer Institute for reporting data from clinical trials that it sponsors.

Laboratory methods for evaluation of targets and biomarkers continue to evolve rapidly and DNA sequencing technology continues to improve. The Molecular Diagnostics Laboratory will soon introduce full length sequencing of the exomes of 409 genes in a CLIA certified platform using the new Ion Proton® instrument, just 18 months after this personalised cancer medicine project was initiated. Evaluation of copy number variation will shift into sequence-based methods. Again, the required scale-up in application of bioinformatics and analytic tools, as well as the more extensive reports provided to treating physicians and their patients, present challenges. This also will require additional approaches to attempt to separate actionable drivers from passengers.

In the future, we will introduce additional assays to accomplish more complete analysis of mutations, amplifications and rearrangements in DNA and RNA. As assays of other relevant analytes such as gene expression, methylome and non-coding RNAs become ready for application in the clinical therapeutic setting, they also will be introduced in the clinical Molecular Diagnostics Laboratory.

Clinical trials screening for genetic aberrations

The team that developed our initial clinical trials was led by Drs Gordon B Mills (medical oncology, systems biology), Funda Meric-Bernstam (investigational cancer therapeutics, surgery) and Stanley R Hamilton (pathology and laboratory medicine). Beginning in March 2013, the initial protocol, entitled 'Clearinghouse', was introduced into each of our tumour site-specific clinics over the period of eight months. The criteria for enrolling are broad: failure of standard of care to achieve elimination of disease or durable response, and the potential availability of a targeted therapy. Enrollment is, of course, voluntary for the patient and his or her treating physician. To create new habit patterns for considering genetically informed targeted therapy among active clinical investigators, we welcome participation from across the institution.

The Clearinghouse protocol allows sequencing of initial tumour specimens typically obtained from pathology slides of resection specimens, or recent biopsies. The sequencing method is accurate and precise with the use of routine formalin fixed, paraffin embedded tissue. The consent form permits analysis of anonymised, pooled data.

After assaying for genetic aberrations in the CLIA-certified laboratory, residual tumour is transferred to a research laboratory where deep sequencing of 202 targeted exomes is performed, with massively parallel sequencing to screen for other genetic aberrations. These results are reported to

the treating physician, but not in the medical record or to the patient unless they are first confirmed in the CLIA laboratory. Once confirmed, the information may be used to plan treatment for that patient.

During the first year and a half of accrual to the Clearinghouse protocol, cancers from nearly 2,000 patients had next generation sequencing in the CLIA-certified laboratory, and over 600 cancers underwent targeted exome sequencing in the research laboratory, often with parallel sequencing of DNA from non-neoplastic control cells in specimens of blood or saliva.

The goals of the Clearinghouse protocol in transitioning to extensive characterisation of tumour samples (currently in the research laboratory and with the Ion Proton® sequencer in the future) are enhancement of patient care and implementation of novel high-quality genomically informed clinical trials. One of the major opportunities afforded by this approach is the development of trials to determine optimal treatment approaches for rare or uncommon genomic aberrations.

A second clinical protocol, entitled 'Unusual Responders' was introduced for biopsying unexpected responders to targeted therapies, either unusually good or bad. The goal is to identify additional genetic aberrations that explain the unusual response so that these can be used to identify patients likely to benefit (or not) from similar therapies. The findings may suggest the next targeted therapy to administer to these patients, as well as combinations of two or more targeted therapies for future similar patients to attempt to circumvent resistance mechanisms.

In the future, we also would like to obtain pre-treatment and on-treatment biopsies after a few days of treatment with a targeted therapy in order to detect whether an effect on the target has been achieved, to identify early adaptive responses that may be targeted for novel combinatorial therapies, and to determine the way in which the microenvironment responds to the therapy. This approach may involve functional proteomics, analysis of expression arrays and immunohistochemistry. It is hoped that functional imaging technologies will achieve this goal in the future. Overall, the aims are to determine whether doses of the drug adequate to achieve the desired molecular effect are being delivered to the tumour cells, and to use the tumour's response to therapy to identify new combination therapies that are likely to be effective.

Other assays that hold promise for the future involve genetic analysis of circulating tumour nucleic acids, or the molecular alterations in circulating tumour cells isolated from the blood. This 'liquid biopsy' could be used to determine the genomic aberrations present across many different metastatic sites in the body, as well as to monitor the response to therapy.

Therapeutic clinical trials

The utility of the data on genomic aberrations in an individual patient's cancer depends upon access to a therapy targeting the detected genomic abnormality. This has turned out to be the greatest challenge for the new programme. Today, over a dozen therapies that target specific genetic aberrations have received regulatory approval from the US Food and Drug Administration for use in specific types of cancers, based on the results of successful phase II and III clinical trials.

Our most daunting challenge is to obtain access to a targeted therapy when that target has been identified as aberrant in the patients' cancer and the therapy is not approved for that clinical situation. There is past experience in dealing effectively with the issue of treating infrequently observed new genomic aberrations through clinical trials, such as the investigation of crizotinib therapy in the 4% of non-small cell lung cancer patients with an EML4-ALK rearrangement; but here the histologic tumour type was clearly specified and screening was required for only one specific genetic aberration.[2] In the Clearinghouse protocol, all tumour types and many potential targets undergo screening. Identification of a potentially actionable target is the beginning of a process attempting to link up the patient to the relevant targeted therapy. There are a number of possibilities:

- The targeted therapy may be approved for that genomic abnormality in that type of cancer;

- There may be a clinical trial with that targeted therapy sponsored by a pharmaceutical company, usually against one or a few types of cancer in which the genomic aberration is relatively common. However, if the aberration is detected in a different type of cancer, companies generally do not permit 'N of 1' trials to be performed;

- The targeted agent may be approved for clinical use when the genomic aberration is detected in selected types of cancer in which the agent has been tested and proved effective. However, if the aberration is in a different type of cancer, payors may decline to cover the costs of therapy – which could be thousands of dollars per month;

- There may be no therapies available for the particular aberrations or for pathways affected by the genomic aberrations in the patient's cancer. Unfortunately, this is a common problem.

Thus, for addressing genomic aberrations detected in a few cancers or even an individual cancer, with screening protocols such as Clearinghouse, the clinician often faces a protracted negotiation with a pharmaceutical company (for an experimental drug) or a payor (for off-label use of an

approved drug) in order to gain access to the appropriate therapy. A future solution to this dilemma is to form consortia of large cancer centres and pool data on 'N of 1' or 'N of a few' trials with targeted therapies in patients with a variety of cancers. In exchange for gaining access to the results, the pharmaceutical company would sponsor the trial and provide payment for treatment, or at least provide ready access to free drugs. By collecting information from many institutions, a 'go' or 'no-go' decision could be made for each tumour type in which the genomic aberration occurs rarely, and the company could initiate phase II and definitive phase III trials with the types of cancer showing responses. In addition, providers and payors would be able to use evidence of failures with targeted therapies to determine which patients should not receive that agent in the future. Such efforts are being pursued today by the National Cancer Institute in the Molecular Analysis for Therapy Choice (MATCH) trial, and by groups of cancer centres.

Future challenges

With rare exceptions such as imatinib therapy for chronic myeloid leukaemia and patients on the tails of response curves for treatment of solid tumours, the durability of responses to targeted therapies is measured in months rather than years. The need for rational combinations of two or more targeted therapies has been generally acknowledged, both to increase efficacy and to prevent the emergence of resistance. These regimens might include a new targeted therapy combined with conventional chemotherapy or immunotherapy. Preclinical research and clinical studies of responders who develop resistance may provide evidence for effective combinations. However, the accurate identification of the multiple genetic aberrations that are drivers in a particular cancer and the ways that they interact and evolve remain areas of active research that will greatly facilitate selection of combinations of targeted therapies in the future.

The uncertainties in current methodologies used to interpret the primary gene sequencing data and in selecting genetic aberrations that are likely to be responsive to targeted therapies create a major challenge for reporting data. The need for additional fundamental knowledge about the molecular biology of cancer cells in order to improve our predictive abilities is readily apparent.

Another challenge that we must begin to address in the clinic is heterogeneity of genomic aberrations within primary and metastatic tumours in individual patients, and the evolution of changes with time as a result of therapy-driven selection or genetic instability. In order to deal with these problems, a strong case can be made for studying fewer patients and exploring them more intensively with biopsies at multiple sites of metastases, as well as serial biopsies during and after therapy to fully ascertain the consequences of the therapy. This must be complemented with deep analyses using genomics, transcriptomics and proteomics to fully characterise the cancer and help to guide selection of optimal therapeutic options with targeted therapies in combination. This type of trial is extremely expensive, but may teach us far more that will be of use to the patient under study and to other patients.

Conclusion

Precision cancer treatment with therapies that target specific genomic aberrations has been proven to produce responses and prolongation of life in selected situations.[3, 4] However for most cancers, achieving durable responses will require more research, exploration of other biomarkers in addition to genetic aberrations, and the integration of data from clinical trials involving in-depth studies on few patients.

Today, only a few targeted molecular diagnostic tests and genomically targeted therapies have become standards of practice and are reimbursed by public and private payors. Additional clinical trials and translational research studies, as well as collaboration with data sharing among all institutions performing this research, are critical for advancing this promising field. It is hoped that the research efforts outlined above will be supported by pharmaceutical companies, payors and government funding agencies, so that the anticipated benefits can be provided for patients with cancer as efficiently and effectively as possible.

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An emphasis on quality

The EORTC's Efstathios Zikos et al. discuss how measuring the health related quality of life of cancer patients can change clinical practice…

Clinical trials involving cancer have long been dominated by clinically based end-points such as overall survival (OS) and progression-free survival (PFS) to measure the effectiveness of a treatment. A five year OS rate, for example, indicates the percentage of patients alive after five years of treatment or five years after they were diagnosed. PFS indicates the length of time during which a patient's disease does not progress. Neither of these end-points, however, measure a patient's quality of life, and research has shown that health related quality of life (HRQOL) can only be captured accurately by the patients themselves, using patient reported outcomes (PROs).

Patient reported outcomes

The United States Food and Drug Administration defines PROs as the measurement of any aspect of a patient's health status that comes directly from the patient, i.e. the patient's responses are not interpreted by a physician or anyone else. EORTC QLQ-C30 is the most widely cancer-specific HRQOL questionnaire used in the world. Developed in 1991 by the EORTC Quality of Life Group, it is now translated and linguistically validated into more than 60 languages and can be extended with over 40 modules addressing specific symptoms, treatments or cancer types.

At the EORTC, the Patient Reported Outcomes and Behavioural Evidence (PROBE) team is dedicated to the meta-analysis and pooled analysis of HRQOL results from EORTC randomised clinical trials. The unique value of this project is its ability to evaluate quality of life issues across various types and stages of cancer. A large part of the work is standardising the actual data to be able to combine results across different trials, but these efforts are worthwhile and have revealed important results that have informed clinical practice. One of these studies showed, for example, that baseline HRQOL is a prognostic indicator for survival.[1]

Better efficacy does not necessarily mean improved HRQOL

In EORTC trial 18991, 1,256 patients with stage III melanoma were randomly assigned to be observed (629 patients), or to receive (627 patients) pegylated interferon alfa-2b (PEG-IFN-α-2b) following lymphadenectomy. The results showed that adjuvant treatment with PEG-IFN-α-2b had, at 3.8 years median follow-up, a significant, sustained effect on recurrence-free survival (RFS) in these patients.[2]

However, using the EORTC QLQ-C30, it was observed that the HRQOL of the patients in the PEG-IFN-α-2b arm was more impaired.[3] Patients in the PEG-IFN-α-2b arm reported lower scores on two functioning scales (social and role functioning), as well as on three symptom scales (appetite loss, fatigue and dyspnea) than those in the observation arm. These results highlight the importance of considering HRQOL when making treatment decisions.

HRQOL plays role in practice-changing trials

Results of EORTC trial 22952-26001 demonstrated that whole-brain radiotherapy (WBRT) did not improve OS and also adversely affected HRQOL. This trial compared WBRT with observation following either surgery or radiosurgery of a limited number of brain metastases in patients with stable solid tumours. Patients who received WBRT reported lower scores for global health status, physical/cognitive functioning and fatigue. This trial showed that WBRT following surgery or radiosurgery of a limited number of brain metastases may negatively impact HRQOL; observation with close monitoring by Magnetic Resonance Imaging instead of WBRT did not harm HRQOL.[4]

PROs versus proxy assessment: HRQOL research in a novel area

Assessing HRQOL in patients with brain tumours is challenging. As one would imagine, a commonly

The results of one EORTC trial suggested that whole-brain radiotherapy did not improve overall survival and also adversely affected health related quality of life

reported symptom of patients with gliomas is cognitive deficits, and these also hamper adequate reporting of HRQOL by the patient. Exclusion of patients with cognitive deficits from analysis obviously leads to underreporting of such problems as concentration, memory and, reading/writing, etc., in the evaluation of HRQOL during experimental treatment.

In EORTC trial 26091, a currently open trial assessing the significance of bevacizumab in recurrent grade II and grade III gliomas, two EORTC HRQOL instruments are being used to assess patients' quality of life through their caregivers or relatives (proxies). The assessments reported by the patients will then be compared to those reported by their proxies. It would be interesting to find out if the proxies can represent patient views and to what extent the two are in agreement. If proxies have a different perspective, the next question would be which reports the more accurate information.

Future opportunities

The patient's perspective has consistently been considered important in palliative and curative EORTC trials, and recent findings have altered clinical practice and provided data needed to support major recommendations and future improvements. Clinicians, regulatory bodies and industry representatives acknowledge the value of the patient perspective, and the EORTC will continue to include HRQOL endpoints where appropriate. Meta-analysis of HRQOL data has been proven clinically informative and, despite the challenges of funding HRQOL research and the complexities of pooling data together, EORTC supports the development of new methods of electronic assessment of PROs and storage in the central EORTC database. Such efforts increase the volume of HRQOL dataset and stimulate numerous efficiency comparisons, which can inform clinicians, policymakers, healthcare payers, etc.

A further development that EORTC is pursuing is the use of HRQOL data collection via computer systems instead of the classical paper questionnaires. Such an electronic system would have several advantages both for the patient (automatic language selection, adaptive display format) as well as the researchers (automatic data transfer, real-time updates on compliance). In order to have a machine-independent system, EORTC is developing an online version that will run on all common web browsers and would not require any local software installation. Once validated, this can be extended to handheld devices and to introduce the questionnaires that can be adapted according to the clinical status of the patient or tailored to his/her previous answers.

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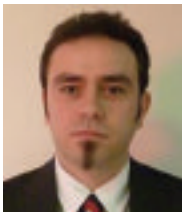

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Keeping treatment on track

Cancer Research UK's Chief Scientist Professor Nic Jones tells Editor Amy Caddick why continued support is needed to translate research into better therapeutic approaches…

In 2010, approximately 325,000 people in the UK were diagnosed with cancer.[1] Despite a number of advances in screening and treatments, cancer remains a disease that has a considerable impact on the people it affects, as well as a significant cost to the health sector.

Cancer research has undoubtedly come a long way in recent decades. Advances in technology and a greater understanding of cell biology have enabled scientists to delve deeper into the progression of tumours and design therapies accordingly. As a result, survival rates for some cancers have noticeably increased. However, in spite of the strides that have been made, cancer is still a major burden – not just in the UK, but globally, therefore tackling this disease requires a long-term approach.

Cancer Research UK (CRUK) has been at the forefront of numerous discoveries in oncology research; Chief Scientist Professor Nic Jones explains why continued research is crucial to effectively tackling cancer and how his organisation is targeting funding.

"Great progress has been made due to the research that has been undertaken," he observes. "More than 80% of patients with breast cancer survive more than five years. That is a huge improvement from 15 to 20 years ago. The vast majority of patients with testicular cancer now survive."

However, whilst some forms of cancer have seen significant boosts to funding and received considerable support, others have not. In 2012-13, CRUK's research budget was £351m. Of this, £128m was spent on research relevant to all types of cancer. The rest was spent on cancer-specific projects in response to applications from researchers around the UK. Research into breast cancer received £41m, but lung cancer only received £13m.[2] Jones recognises that improving support for other cancers is imperative if patients are to receive better outcomes.

"In many cancers progress has not been impressive; in fact, it has been slow. For example, in lung cancer, less than 10% of patients survive more than five years. Equally, statistics for pancreatic cancer and oesophageal cancer are very poor. There is a huge amount that needs to be done in terms of developing better treatments and better ways of diagnosing these cancers earlier. But these cancers have traditionally been hard to research as patients are often diagnosed late, making it hard to run trials to develop new approaches.

"These cancers need a fresh approach, not just more money – we have to look at more innovative ways to tackle the problems and encourage researchers to work with us to do this."

CRUK is one of the largest funders of cancer research globally, second only to the National Cancer Institute in the US. The support for research and researchers from the charity has been invaluable in enabling progression over the years. Jones explains the types of projects that CRUK supports.

"We carry out research across the whole spectrum. From the basic research that helps us understand the disease, through to clinical trials where we test potential new therapeutics. We also carry out research that focuses on all types of tumours. That makes us distinct from other charities that are tumour-specific.

"Cancer Research UK has an impressive track record of success. A number of the drugs that are currently emerging have had input from Cancer Research UK at some point during their development. For example, CRUK scientists helped develop abiraterone, which is a new drug that is used in late stage prostrate cancer."

In the UK, one in three people will develop cancer in some form during their lifetime.[3] Discovering how cancer works and how it can be treated is a vital part of giving those people a better chance of survival, and funding plays a major role in excelerating development. Deciding where to target research funding is, however, a difficult task.

"We spend a lot of time and effort thinking about how to use the funding we get from the public to achieve our mission," says Jones. "We talk to the key leaders in the field, and from that, we develop a strategic framework that guides our funding. In fact, we are currently in the process of renewing our strategy for the next five years. This will be published early next year. Because of this, we are currently doing a lot of thinking about where the opportunities are, where the real clinical needs are, and where we can make a difference. Through that process, we identified certain cancers where the clinical need is highest, such as lung cancer."

Indeed, lung cancer survival rates are currently low and prognosis for patients is poor. In 2010, almost 35,000 people across the UK died from the disease.[4]

"Relative to other tumour types, investment into lung cancer research is low," states Jones. "We're aiming to change this through our strategy. In fact, we have already taken the steps to put initiatives in place that will really advance lung cancer research. For example, we are developing centres of excellence in lung cancer research across the UK. The idea behind this is that in a certain locality, it will concentrate research expertise and focus on the lung cancer problem."

CRUK's newest programme, TracerX, will use the map of the human genome to discover how lung cancer develops and will cost over £10m. By examining the genetic changes in over 850 lung cancer patients, it is hoped that new strides and discoveries will be made.

"This study will help us to identify the changes that occur in lung cancer and help us to identify how those genetic changes have evolved during its progression. That in turn will help us to think about optimum treatments for individual patients."

One of the major challenges facing oncology treatments is resistance – when a cancer stops responding to treatment.

"We can have a particular therapeutic that might initially have a strong effect on a cancer, but if the cancer comes back, usually it is resistant to the same treatments," he says. "That's obviously more difficult to tackle. We need to understand the mechanisms involved in developing that kind of resistance, and then hopefully we can do something about it."

Research is undoubtedly the element that underpins advances in cancer treatments, and understanding the disease pathways is key for these developments. Organisations like Cancer Research UK have a fundamental role to play in facilitating and supporting research.

"We have a huge opportunity – an almost unprecedented era – in terms of our ability to take what researchers understand about cancer and translate that into better therapeutic approaches. In order to really grasp those opportunities, support for research is crucial."

[1] http://publications.cancerresearchuk.org/publicationformat/formatfactsheet/keyfactsall.html

[2] www.cancerresearchuk.org/about-us/how-we-fundraise

[3] http://publications.cancerresearchuk.org/publicationformat/formatfactsheet/keyfactsall.html

[4] www.cancerresearchuk.org/cancer-info/cancerstats/types/lung/mortality

Professor Nic Jones
Chief Scientist
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Provincial partnerships

Treatment and support services across the entire cancer service spectrum…

As the number of new and existing cases of cancer continues to grow, so too does demand for cancer services and new programmes to improve the quality of care and services for patients and their families.

The number of new cancer cases increases each year at a rate of approximately 2%, due to population growth, ageing of the population and risk factor prevalence (the proportion of the population with cancer risk factors). Risk factor prevalence affects Manitoba, Canada, more significantly than other jurisdictions due to the province's far larger proportion of First Nation, Métis and Inuit peoples in its population – 15%, compared to the national Canadian average of 3.8%. This group has two to three times the prevalence of cancer risk factors compared to the general population and is also the fastest growing segment of the population.

If the risk factor prevalence rate in the province remains constant from 2006 to 2026, projections indicate an almost 50% increase in incidence over the 20 years. In numbers, this means that nearly 8,000 new cases of cancer will be diagnosed in 2026, compared to the 5,500 cases that were diagnosed in 2006. Prevalence projections over the next 15 years estimate the number of Manitobans living with cancer in 2025 to be 61,000 (or 5% of the population), significantly increasing the requirement for cancer services and taxing the available resources.

CancerCare Manitoba (CCMB) is the provincially legislated cancer agency in Manitoba and is responsible for delivery of cancer services across the province. CCMB provides care, treatment and support services across the entire cancer service spectrum – from prevention, early diagnosis, treatment and care, to palliation and end of life care.

Partnership between local healthcare providers and tertiary care based coordinating programme.	Agreed minimum standards of local facilities and adequate medical and multi-disciplinary support staff.	Training and Quality Assurance Programme with continuous training and regular evaluation.	Agreed Clinical Practice Guidelines, protocols, standard operating procedures, care pathways.	Risk stratified local care supported by information technology assisted solutions.

Community cancer programmes – key elements

With the support of the government of Manitoba, CCMB works closely with its partners to provide world-class cancer services to Manitobans. Our valued partners include Manitoba's regional health authorities, such as the Winnipeg Regional Health Authority (WRHA), the University of Manitoba's Department of Medicine, Diagnostic Services Manitoba, and volunteer funding agencies; in particular, the CancerCare Manitoba Foundation.

CCMB has two tertiary locations in Winnipeg, with our main site at the Health Sciences Centre (HSC) campus, Manitoba's largest healthcare facility. Services at our main site include medical and radiation oncology, patient and family support through psychosocial services, and combined clinical and research programmes for staff.

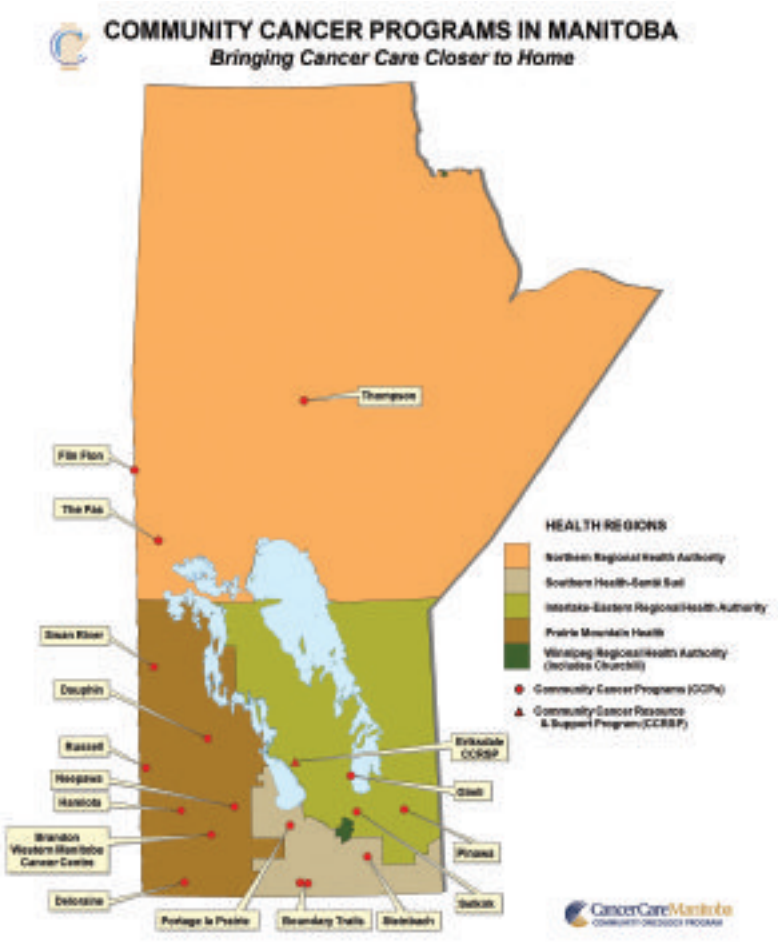
Our second site is located in the eastern part of Winnipeg at the St Boniface Hospital, and provides chemotherapy and support services to patients. Thanks to a collaborative partnership with the WRHA, CCMB specialists also work with healthcare providers at six additional hospitals across the city of Winnipeg, such as through the leukaemia/bone marrow transplant programme at the HSC campus, and chemotherapy and support services at the Grace, Concordia, and Seven Oaks hospitals.

Multiple impacts of poor access to care: - less screening and prevention services - delays in diagnosis and treatment - reduced psychosocial, supportive and palliative care services
Insufficient expert help for follow up and survivorship care.
Travel associated with loss of work and increased financial burden.
Greater isolation at stressful time.
Access to clinical trials restricted.

Challenges Facing Cancer Patients From Rural/Remote Locations

CCMB has also formed strong partnerships with the province's four additional health authorities across Manitoba through the Community Oncology Program.

The programme is a provincial network of cancer services, cancer support services and primary caregivers who have



received specialised training from CCMB. The first in Canada Community Cancer Programs Network was established over three decades ago, initially to answer, in a formal study, the question of whether complex chemotherapy could be safely delivered closer to home, well away from the centralised, academic setting of large urban-based hospitals and ambulatory facilities. The answer was emphatically 'yes', providing certain key conditions were fulfilled. The experience has been replicated numerous times since, both in Canada and elsewhere.

The programme runs at 17 healthcare centres across the province, enabling CCMB to provide cancer services for Manitobans as close to home as possible. It has gradually evolved and matured to now begin transformation into a network that will provide the full spectrum of cancer services.

In terms of the spectrum of treatment options in cancer care, the complexities and infrastructure requirements preclude decentralising radiation treatments and complex low volume cancer surgery, and systemic treatments such as stem cell and bone marrow transplantation, as well as high-risk intensive chemotherapy. This is based on the primacy of the principle that provision of care closer to home cannot compromise the quality of care and patient outcomes.

Through the Manitoba Cancer Patient Journey Initiative, announced in June 2011, a $40m provincial commitment is enabling CCMB and partner healthcare providers to streamline and expedite the time it takes a cancer patient to receive first treatment. An excellent example of expanded partnerships is the Western Manitoba Cancer Centre in Brandon, Manitoba, which opened in June 2011, providing radiation therapy outside of Winnipeg for the first time.

CCMB has over 800 staff, including world-class experts in medical and radiation oncology, top researchers, nursing staff – including those with an expanded role as nurse practitioners – and many other healthcare professionals. CCMB is currently in the planning phase of establishing a second co-located site on the HSC campus with expanded research facilities, multidisciplinary-based medical teams and improved patient services.

CCMB must meet the needs of today, while planning for care and treatment of Manitobans in the future. To do this, a comprehensive and strategic report – the CancerCare Manitoba Cancer Plan – is created every five years. The CCMB Cancer Plan 2011-2015 builds on our previous efforts in prevention, detection, treatment, care and use of resources.

To stay the course and meet the anticipated rise in cancer cases in the future, CCMB must achieve breakthrough objectives in the next five years. Working with our partners, we will build an aligned, integrated cancer service that provides accelerated early diagnosis and rapid delivery of quality care to patients, based on the following goals:

- Enhance our efforts to reduce the incidence of cancer;
- Ensure timely access to cancer services for all Manitobans;
- Incorporate highly safe practices and put patients and their families at the centre of care;
- Improve the cancer system's performance and responsiveness;
- Translate research in improving cancer control and treatment.

An overview of the CCMB Cancer Plan can be viewed at: www.cancercare.mb.ca/home/about_us/tomorrow_starts_today/op/mcp

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A strong position for survival

Science Omega Review highlights the progress the American Association of Cancer Research has made in treating and understanding cancer through research…

Cancer is the second most common cause of death in the United States and accounts for almost a quarter of all deaths. In terms of prevalence, men have approximately a one in two lifetime risk of developing cancer, and women one in three. Whilst great strides have been made in cancer prevention and treatment, the National Institutes of Health (NIH) estimates that the overall cost of cancer is in the region of $200bn per annum – encompassing direct medical costs of approximately $77bn for all health expenditures and the significant remainder owing to costs associated with lost productivity due to premature death.[1]

The American Association of Cancer Research (AACR) looks to prevent and cure cancer primarily through research, alongside education, communication and collaboration initiatives.[2] The organisation has distributed more than $170m in research funding since 2001 and last year, for example, the AACR Foundation for the Prevention and Cure of Cancer provided $6.4m in grants and awards, specifically targeted towards funding and highlighting particularly innovative or meritorious research.

The AACR Foundation's work supports that of the AACR, and its recently appointed Executive Director Mitchell R Stoller – an expert in solving complex strategic challenges and fundraising – has emphasised the need to ensure monetary backing is ongoing: "The mission of the AACR Foundation, to accelerate progress in the conquest of cancer by providing financial support for research, education, and communication, is vitally important at a time when federal funding for cancer research is flat and the number of people receiving a cancer diagnosis is increasing every year," he said.[3]

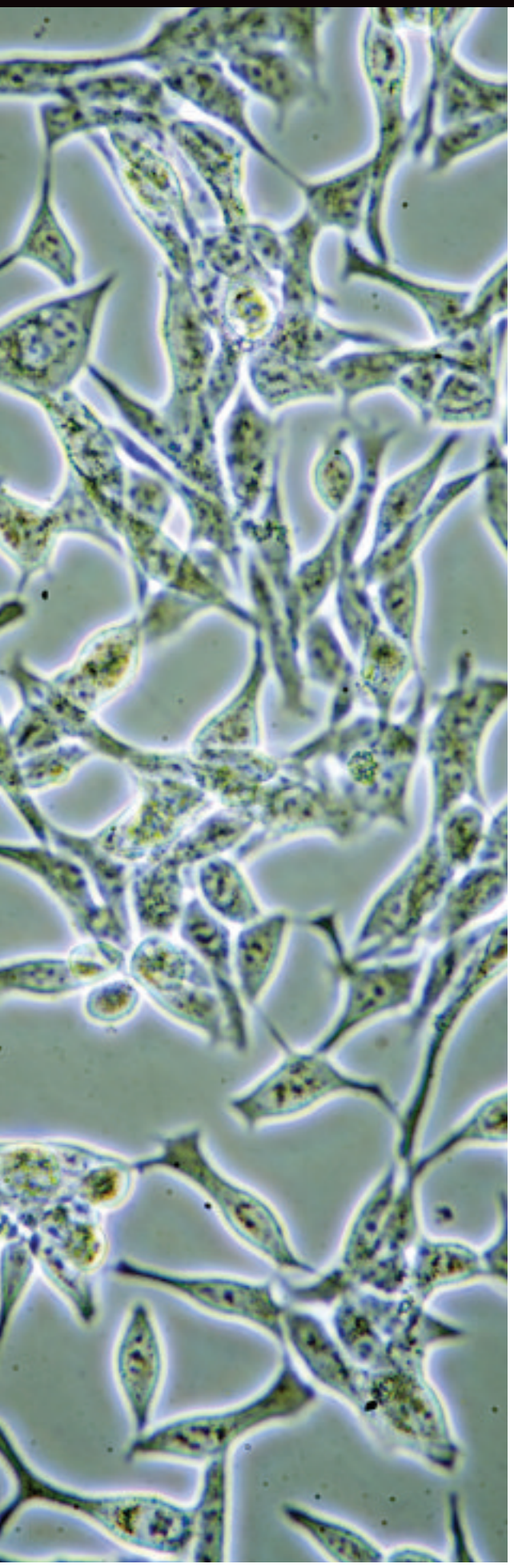
At a congressional briefing in July to underline the vital contribution that federally funded biomedical research is making, the AACR warned that diminished NIH funding could jeopardise the ability to eradicate cancer health disparities. "Even though cancer research has enabled tremendous advances against cancer, more than 1.6 million Americans will be diagnosed with this terrible disease this year, and a disproportionate amount of the suffering and deaths due to cancer will fall on racial and ethnic minorities, the poor and the medically underserved," said AACR CEO Dr Margaret Foti. "The AACR is committed to eliminating cancer health disparities by fostering research into their underlying causes."

There are constant strides being made as the application of research findings lead to improved treatment regimes and outcomes for patients. However, other demographic influences must also be taken into account when considering the statistics for cancer survival.

Earlier this year, the AACR released its second 'Annual Report on Cancer Survivorship in the United States'. The report, originally published in the AACR's journal 'Cancer Epidemiology, Biomarkers & Prevention', shows that as of the beginning of 2012, there were approximately 13.7 million cancer survivors in the US. This number is expected to rise by almost a third, up to 18 million, by 2022.[4]

"The increase in the number of survivors will be due primarily to an ageing of the population. By 2020, we expect that two-thirds of cancer survivors are going to be age 65 or older," said Dr Julia Rowland, Director of the Office of Cancer Survivorship at the National Cancer Institute.

The report further illustrates that survival is not uniform across cancer subtypes – since cancer is not a single disease, but a group of more than 200. For example, patients with prostate cancer have almost a 100% five year survival rate, but in comparison people with lung cancer, the second most common cancer in terms of diagnosis, only represent 3% of total survivors. According to Rowland, the increase in the cancer survivor population will present new issues for the healthcare community about how to ensure that these patients lead not only long, but healthy and productive lives.



Prior to April's AACR annual meeting, past President Frank McCormick commented on the biggest challenges facing the cancer research community at present.[5] "There are two types of challenges," he said. "One, the complexity of cancer itself. As we understand more about the disease we realise how heterogeneous it is and how complicated it is, and this is a real challenge to identify new ways of treating cancer. On the other hand, we have major challenges in funding cancer research, which make it rather difficult to pursue some of the innovations that we've been coming up with and to keep momentum going forward in cancer research."

He went on to say that the AACR's role in addressing these aspects is multifaceted – from the organisation of international and local meetings or workshops, through to training programmes, networking and providing a forum in which scientists can present their data and publish it for the international community. It also has a part to play in engaging more with individuals outside the scientific community.

"Many members of the public, and certainly cancer patients and survivors, recognise the value of research and recognise the value that the AACR contributes to the whole research enterprise," he continued, "but we see a huge opportunity there to increase our educational mission, to help educate people, not only in what progress has been made in treating cancer and understanding cancer, but the value of research in that process."

Passing on the presidency baton for the period 2013-2014 to Dr Charles L Sawyers, it was clear that these priorities will remain at the forefront of the organisation's agenda.

"This is an exciting time in cancer research, as we see so many promising therapies emerging from our work," Sawyers said. "But it is also a time of financial strain, and we must be sure that Washington understands that it is imperative that we continue to invest in medical research.

"As President of the AACR, I will work with the organisation to make sure that this message is heard, because it is imperative that the AACR and its members are in the strongest position to continue to have a positive effect on the lives of those touched by cancer."

[1] www.aacr.org/Uploads/DocumentRepository/PublicandMedia/Facts_About_Cancer_Flier_2013_rev3.pdf

[2] www.aacr.org

[3] www.aacr.org/home/public—media/aacr-in-the-news.aspx?d=3135

[4] www.aacr.org/home/public—media/aacr-press-releases.aspx?d=3038

[5] www.aacr.org/home/scientists/meetings—workshops/aacr-annual-meeting-2014/previous-annual-meetings/annual-meeting-2013/program.aspx

Science Omega Review
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The two faces of bladder cancer

A quick and easy way to diagnose whether bladder cancer is dangerous or not…

Bladder cancer is the sixth most frequent cause of cancer death globally. The main cause of this cancer is smoking. Despite its high frequency, public awareness of bladder cancer is very limited. However, every year more than 380,000 people are diagnosed with bladder cancer worldwide and approximately 30% will die due to this disease.

Due to its high prevalence, bladder cancer is also the most expensive disease for public health systems. Despite this, public funding is in sharp contrast to its prevalence. In both Europe and the US, funding for bladder cancer research is only 5-10% the amount of funding for other important cancers, such as breast, prostate, colorectal or lung cancer.

Bladder cancer, Dr Jekyll and Mr Hyde

Bladder cancer comes in two variants, with large differences in the prognosis for the patients. Professor Margaret Knowles from Leeds compared this few years ago with the famous story of Dr Jekyll and Mr Hyde. In one variant, non-invasive, mostly papillary growing tumours are found. This is the most frequent type of bladder cancer, occurring in 70% of patients. Tumours are removed from the bladder during cystoscopy by an urologist, and investigated in pathology. This type of bladder cancer recurs in two-thirds of the patients. However, it can progress to the invasive and metastasising disease, but this is rare (Dr Jekyll).

Due to the high frequency of recurrence, and the relatively good prognosis, the prevalence of this type of bladder cancer is very high. Patients are closely monitored and during control cystoscopies the frequently recurring tumours are removed, but this can happen many times over many years, leading to high costs for the healthcare system.

The second type of bladder cancer (Mr Hyde) is a highly dangerous disease. Tumours develop through precursor lesions like carcinoma in situ and they progress very quickly to the invasive disease that infiltrates the muscle wall of the bladder. At this stage, more than 50% of the patients will die from the disease. The challenge is to detect this type of bladder cancer very early on to be able to remove the entire tumour and treat the patient with intravesical therapy – this frequently involves cystectomy (removal of the bladder).

This type of bladder cancer illustrates the challenges in the detection, treatment and surveillance of bladder tumours. Due to its aggressive nature, all patients are closely monitored after primary diagnosis. For the majority of patients with the non-invasive papillary tumours, this type of surveillance is an over-treatment. Many of these patients will never develop the invasive, deadly disease. On the other hand, it is important to detect the patients with the dangerous type as early as possible to save their lives.

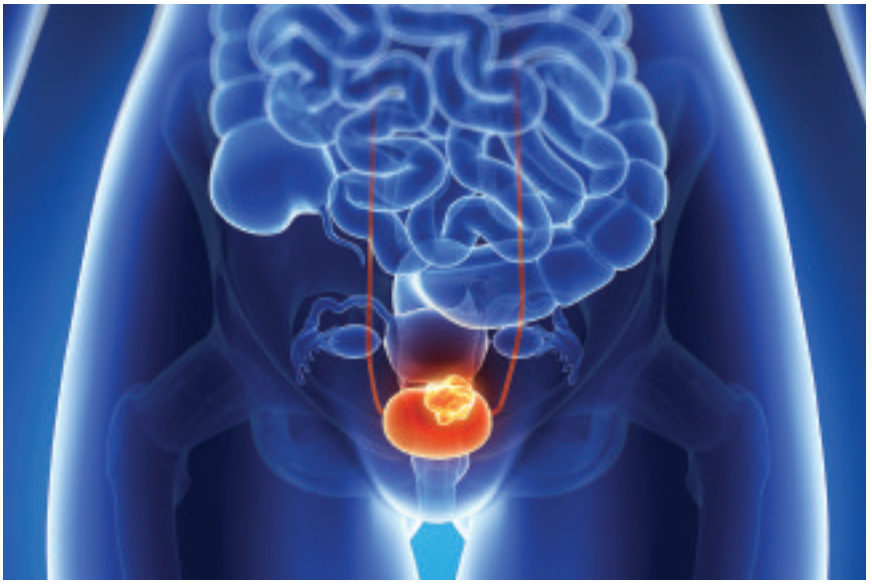
The role of pathology in bladder cancer management

Pathologists play an important role in the management and treatment of bladder cancer patients. It is the pathologist who sees the tumours under the microscope, and who will see which patients present with the dangerous disease. However, even if a tumour looks innocent, a small percentage of the patients will progress to the aggressive disease. Distinction between these two types of tumours is not possible every time in pathology. The differentiation and the growth pattern of the tumour and the extent of invasive growth can help to diagnose the dangerous type, but for the individual patient the course of the disease is still unpredictable.

Molecular pathology of bladder cancer

To overcome the problems in the prediction of the clinical course of bladder cancer, the molecular changes in bladder cancer has been extensively studied over the last 15 years. Interestingly, the two clinical faces of the bladder cancers are mirrored by fundamental differences in the molecular make-up of the tumours. The papillary non-invasive tumour with excellent prognosis shows few genetic alterations, mostly in oncogenes inducing cell proliferation, such as the fibroblast growth factor receptor 3 (FGFR3).

In contrast, the aggressive bladder cancer is characterised by a multitude of genetic alterations and a high degree of genetic instability. Many studies are on the way to use genomics to predict the fate of patients. Especially promising are experiments, where gene expression analysis is investigating the expression of many thousands of genes in the primary tumour tissue to help to distinguish the two variants of bladder cancer. The European Community is funding a large multi-centre



European study (UROMOL) to investigate specific gene expression profiles in a prospective manner.

Bladder cancer screening

Theoretically, bladder cancer is a disease in which early detection can be achieved easier than in nearly any other type of cancer. The tumours shed cells into the urine; therefore, the development of urinary tests to detect the tumour is feasible. In fact, urinary cytology is, up to now, the most sensitive technique to detect the dangerous, high grade bladder cancer, whereas the papillary bladder cancer with few morphological changes is a lot harder to detect. It is important to use the knowledge on molecular changes in bladder cancer to develop urinary tests for early detection.

However, a general test that will detect all types of bladder cancers (all small Dr Jekylls) would lead to a large increase in bladder cancer incidences. Like the PSA test for prostate cancer, an overall bladder cancer urine test would detect a multitude of small, harmless, papillary tumours, which would increase the problem of over-treatment. A sensitive urine test that only detects the serious aggressive bladder cancers would be ideal in the screening for high-risk patients, for instance, heavy smokers who have a 10-fold higher risk of developing bladder cancer.

The first urine tests investigating mutations in FGFR3, the most frequent genetic abnormality in bladder cancer, show very promising results. These tests could, theoretically, also be used to replace cystoscopy in the surveillance of patients with bladder cancer. Only if genetic markers are detected in the urine, pointing to progression of the disease, then cystoscopy would be done. However, no large multi-centre prospective studies are on their way to change the clinical practice of this frequent disease, which is due to heavy underfunding of bladder cancer research.

No advances in bladder cancer treatment

As for other frequent cancers, such as lung, colorectal or breast cancer, new targeted therapies have been developed that directly attack the genetic changes in the cancer cell. Unfortunately, there has been no progress in bladder cancer yet. Treatment options of advanced metastasising disease are still very limited – different highly toxic chemotherapy protocols are in use.

Theoretically, molecular pathology could detect specific genetic alterations in bladder cancer, which could then lead to a specific therapy targeted against these changes. The targets have already potentially been discovered, but again there are no large-scale trials to stratify the patients according to the genetic alterations of their tumour.

Department of Pathology, University of Erlangen, focuses on bladder cancer

Bladder cancer research has been the main focus of our research group for more than 15 years. We aim to detect important molecular alterations in precursor lesions of the two types of bladder cancer, such as hyperplasia and dysplasia, and molecular and histopathological markers to predict prognosis of the patients. The main focus of our current work is in the detection of progression markers of papillary bladder cancer (how can Dr Jekyll turn into Mr Hyde?). Furthermore, we are searching for markers that will allow us to predict the response of the patients to radio- and chemotherapy, and to identify predisposing factors for bladder cancer by investigating patients with early onset disease.

In summary, bladder cancer is a frequent disease with two faces. The challenges for future bladder cancer research are:

- To develop early detection methods for the aggressive disease to diagnose these tumours at the earliest possible point;
- To develop new stratified tests to distinguish the aggressive type of bladder cancer from the more frequent non-aggressive disease to reduce over-treatment;
- To identify specific targets for new drugs to improve the prognosis of bladder cancer patients with advanced and metastasised disease.

To achieve all these goals, a considerable commitment and increased public funding have to be made to allow bladder cancer research to succeed.

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The future of lung cancer screening…

…using low-dose spiral computerised tomography…

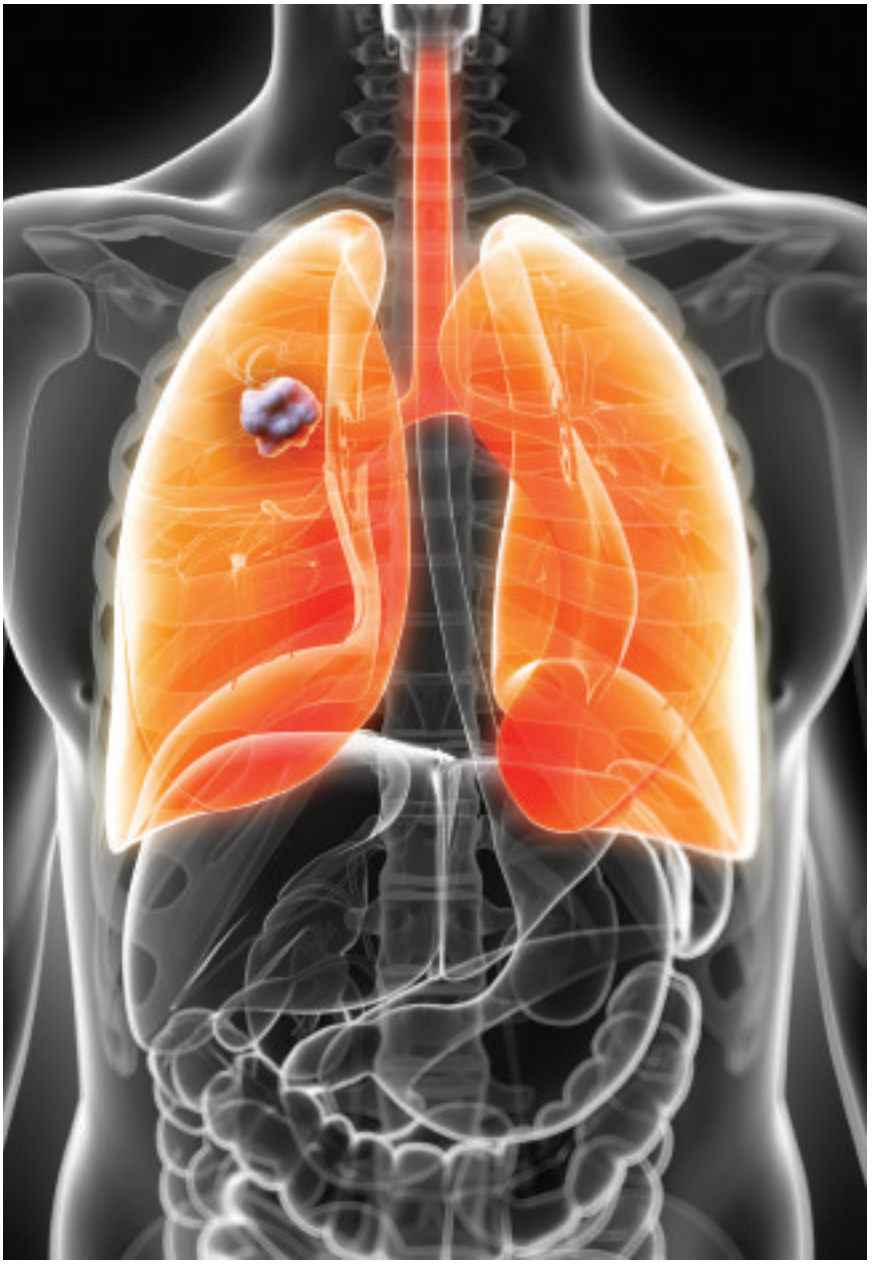
Lung cancer has remained the leading cause of cancer related death in many countries of the world. Unabated for the last two decades, lung cancer mortality imposes a heavy burden in countries where significant portions of the adult population smoke or have smoked tobacco. Based on new evidence and several professional organisations' recommendations, lung cancer screening with low-dose spiral computerised tomography (LDCT) is quickly becoming an option for millions of tobacco-exposed people. This article will briefly summarise the reports and recommendations that have been made for lung cancer screening. In addition, it will address some of the issues that must be considered by healthcare policymakers in the development of lung cancer screening programmes.

In the two years since the publication of the results of the National Lung Screening Trial (NLST),[1] lung cancer screening has taken on a new widespread support. The trial showed that among subjects between the ages of 55 and 74 with at least 30 'pack years' of smoking exposure (calculated as one pack per day for 30 years), there was a 20% reduction in mortality from lung cancer following three annual examinations with LDCT compared to chest X-rays (CXR). It provided evidence for the first time that screening can shift the detection of lung cancer to earlier stages and that treatment of early lung cancers can improve the overall five year survival rate from lung cancer. This concept is a welcome finding for the millions of tobacco-exposed adults that have seen virtually no substantial improvement in the 15% five year survival rate from lung cancer.

Several professional organisations, including the American College of Chest Physicians (ACCP), the National Comprehensive Cancer Network (NCCN), the American Lung Association (ALA), the American Association of Thoracic Surgery (AATS), the American Thoracic Society (ATS), the American Society for Clinical Oncology (ASCO) and the International Association of the Study of Lung Cancer (IASLC), have supported lung cancer screening for people between 55 and 74 with a cumulative smoking exposure of 30 pack years. In addition, two organisations, the NCCN and the AATS, have also recommended screening for 50 year olds with 20 pack year exposures with other co-morbidities related to lung cancer risk, such as a strong family history of lung cancer and chronic obstructive lung diseases.

Recently, there have been two new publications that provide more information and support for lung cancer screening with LDCT. The first, the US Preventive Task Force (USPTF) Report,[2] gives a comprehensive evidence-based summary of the current knowledge of lung cancer screening; summarising the NLST results as well as other smaller studies completed in Europe, and providing a grade B level recommendation supporting LDCT screening for lung cancer.

Implementation of lung cancer screening will require the development of eligibility and treatment criteria that can be tailored to each healthcare system. In the US, approximately 20% of adults are active smokers and there are over 50 million former smokers with substantial smoking exposure that are at some increased risk of lung cancer. Nearly half of all lung cancer patients diagnosed in the US are former



smokers, the results of a slow return to near normal risk levels after years of cessation.

Given these numbers, and the costs associated with monitoring detected nodules and performing invasive testing for a subset of positive exams, full implementation of screening based on the NLST criteria will be very taxing to healthcare systems. With the grade B recommendation by the USPTF, screening must be made available to eligible patients in the US under the new healthcare guidelines. However, it is in the best interest of policymakers to identify those risk groups who will get the greatest benefit from screening, while minimising false positive tests and unnecessary treatment.

The second publication to address some of these issues is Kovalchik et al.[3] In this paper, the subjects in the NLST were divided in quintiles of five year risk of death from lung cancer. Risk level was based on demographic and clinical risk factors, such as smoking history, lung conditions, number of years since quitting smoking and family history of lung cancer. The lowest quintile referenced the lowest risk. Based on these categories of risk of lung cancer death, it was shown that the subjects with multiple risk factors saw the greatest reduction in lung cancer mortality, lower false positive test rates and the smallest number of screening tests to prevent lung cancer deaths.

As an example, the lowest risk quintile saw 1,648 false positive tests to prevent one lung cancer death as opposed to 65 false positives in the highest risk quintile. A total of 5,276 LDCTs were needed in the lowest quintile risk group per lung cancer death prevented, versus 161 in the highest risk quintile. While the NLST has provided us with a great leap forward in the early detection of lung cancer and subsequent prevention of lung cancer death, this analysis shows that as lung cancer screening programmes are implemented, choosing a higher risk group for screening will result in the best use of scarce healthcare dollars.

There are three main areas raised in the recommendations for lung cancer screening that must be addressed in order to control its anticipated burdens: the number of eligible patients and the number of LDCT tests that must be performed; the number of false positive LDCT tests that will require follow-up and intervention procedures; and the number of lung cancers that will be detected that would not pose a risk of developing into a dangerous cancer (otherwise known as overdiagnosis).

In the NLST, 53,000 people were randomised to LDCT versus CXR and over 75,000 LDCT tests were done over the three years of screening. After a median of 6.5 years of follow-up, 645 lung cancers per 100,000 person years (py) of observation were detected in the LDCT group and 247 lung cancer deaths per 100,000 py in the CXR group.

At the Roswell Park Cancer Institute in Buffalo, NY, USA, we have had a standard of care lung cancer screening programme since 2005. As part of the Stacey Scott Lung Cancer Registry, using data from 497

patients undergoing surveillance with LDCT, we performed 3,791 LDCTs. Just over 91% of our patients had at least one LDCT that was positive for a nodule and 2,476 of the LDCTs had a nodule mentioned in the final report. As a free-standing cancer centre with multidisciplinary teams, including interventional radiologists and pulmonologists, the management, follow-up and scheduling for these numbers of positive tests is a significant undertaking. This further supports the view that in busy, resource limited settings, it is appropriate to narrow screening to the highest risk subjects.

Other publications on the use of LDCT for lung cancer screening have raised concern over false positive results. LDCT is superior to CXR in detecting very small lesions. This means that many lesions that are detected are not cancerous. In the NLST of the nodules detected on LDCT that were large enough to be potentially cancerous, more than 96% were found to be benign. This represents a significant cost and potential added risks for the patients. We are, however, limited by our current technologies and biomarkers to distinguish nodules that harbour cancer from those that do not. Again, in Kovalchik et al.,[4] selecting patients with the highest risk of lung cancer dramatically reduced the numbers of false positives.

The potential for a screening test to identify small cancers that would never progress to larger, deadly lung cancer is the definition of overdiagnosis. The problem results in many new cancer diagnoses that are treated, but would not have progressed into clinically important lesions. An example of potential overdiagnosis is PSA screening for prostate cancer. The PSA was highly sensitive and detected many cases of prostate cancer that would never pose a risk to the patient. This led to many indolent prostate cancers detected and treated, imposing unnecessary costs and co-morbidities on the patients.

In the case of lung cancer screening, the risk of overdiagnosis is unknown as, for several reasons, we don't fully understand the natural history of lung cancer. Based on what we know of early lung cancers, which represent only 15% of lung cancers diagnosed, there is a high level recurrence, even when the cancer is detected at stage I. There is some evidence from the ELCAP lung cancer screening studies that early stage cancers that were left untreated eventually progressed and resulted in lung cancer related deaths.[5] Until we have a better understanding of the molecular genetics of early lung cancers and have identified the conditions that drive these cancers to progression, all lung cancers detected, regardless of size and stage, will be treated under established guidelines.

In conclusion, lung cancer screening with LDCT for high-risk lung cancer patients is our future. The researchers and clinicians working on lung cancer screening need to further clarify the patient risk level best served by this testing and the limitations of healthcare systems in implementing tests, managing results and monitoring outcomes of patients with suspicious lesions. Continued efforts are needed to identify biomarkers that will help to distinguish which tobacco-exposed people are at risk of lung cancer and which nodules contain lung cancer. Regardless, we must recognise that detecting lung cancer early will improve survival, and that exposure to tobacco products of any kind must be prevented. The cost effectiveness of preventing tobacco exposure is undeniable and must be part of any strategy to minimise the burden of lung cancer.

As we move into the age of lung cancer screening with LDCT, the international lung cancer community should continue to share information to address the benefits and risks associated with screening. Collaborative screening programmes, biomarker development research, health outcomes and cost effectiveness studies

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across healthcare systems in multiple countries must be a priority to maximise the benefit to the public in controlling this deadly cancer.

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One Health: crossing the animal interface

The world's increasing interconnection has seen new zoonotic diseases emerge, and a cross-sector response is needed, writes Carol Rubin of the CDC…

More than half of the infectious diseases that cause illness in humans originate in animals and the majority of newly discovered human pathogens and re-emerging historic pathogens are zoonotic.[1] Many of these pathogens exist in animal populations without adverse effects, but cause serious morbidity and mortality when they infect humans. Transmission across the human-animal interface appears to be occurring more frequently, likely due to population and environmental changes that are altering the delicate balance between humans and pathogens with animal reservoirs. Addressing the threat of emerging infectious diseases requires public health officials to understand the relationships between human, animal and environmental health and to work collaboratively with other disciplines using a unified 'One Health' approach.

Why are emerging zoonoses more likely now?

Various drivers have changed the relationship between humans and animals and the environment they share, and have thus increased the likelihood that new zoonotic diseases will emerge as human health threats.[2] These drivers include: deforestation; intensive agricultural practices, including concentrated animal feeding operations; the global movement of people, animals and animal products; and an increase in the number of people who are immune-suppressed.[3]

As the Earth's population increases, people are moving into environments with wildlife and vectors that have had little previous contact with humans. The interface between animals and humans is irrevocably redefined as trees are cut down, pristine forests converted into farmland, domestic animals imported and new communities established. As a result, an unexpected exchange of organisms occurs as people are exposed to new animal pathogens and, because people bring their own unique collection of pathogens with them, an additional exchange of organisms may occur from humans to animals.

The potential impact of this redefinition of the human-animal interface is compounded by the ease with which people and animals travel around the globe. Pathogens do not respect political or geographic boundaries. A person can be infected with a new disease in a remote location, board a plane and arrive in a major metropolitan area across the globe before manifesting any signs of illness. Healthcare settings in metropolitan areas may not be prepared to identify new zoonotic diseases and these pathogens can be inadvertently spread before proper precautions are put in place. Animals and animal products also move across the globe by plane and ship. Every day, more than 40,000 cargo ships legally transport animal and food products internationally; an additional unknown quantity is transported illegally, including items such as bush meat and exotic pets. These products, and their pathogens, arrive in major cities with large biologically naive human populations, which can lead to unexpected outbreaks in the population.

Effective response requires an integrated approach

Traditional hospital-based surveillance for human morbidity and mortality may no longer be adequate to detect these emerging pathogens. Integrated surveillance systems that incorporate pathogen detection at the human-animal interface would be more effective. Although a case of human illness is often the sentinel of an emerging infectious disease, rapid identification of an animal source is instrumental in mitigating the impact of a new pathogen.

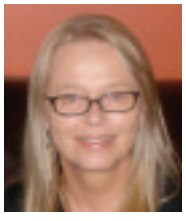
This was recently demonstrated in China when the novel H7N9 influenza virus was detected in a severely ill man. Early recognition that this novel strain originated in poultry led to a series of integrated events and proactive interventions, including live bird market closures and market cleaning recommendations. Careful trace back of human contacts for each case, rapid development of laboratory tests for both humans and animals, and scientific verifica-

Fairs and petting zoos bring children into very close contact with animals: transmission across the human-animal interface appears to be occurring more frequently, likely due to population and environmental changes that are altering the delicate balance between humans and pathogens with animal reservoirs

tion that this was a low pathogenic avian influenza virus (i.e. unlikely to cause clinical illness) in chickens provided insights that informed and enhanced intervention. Cross-sectorial communication occurred within countries as well as among countries and international organisations. Enhanced hospital-based surveillance was implemented in order to rapidly detect H7N9 infection among ill individuals with a travel history to affected regions. The response incorporated a coordinated approach, which included both the human and animal sectors.

Rift Valley fever (RVF) in Africa offers another opportunity to utilise a systems-wide approach for detection and response to zoonotic disease. Although this virus causes severe disease in both humans and animals, interventions have historically been handled separately by each sector. Moreover, traditional outbreak responses are not effective for preventing infections. RVF is transmitted by mosquitoes in a geographic area too extensive for environmental pesticide treatment to be feasible. There is no vaccine to prevent infections in humans. Existing animal vaccines are expensive and associated with reproductive losses. However, a safer animal vaccine was recently developed that could allow for the use of a One Health approach to control the impact of RVF on human, animal and economic health.[4] Environmental forecasting data could be used to predict rainfall and concomitant hatching of infected mosquitoes. This would allow susceptible animal populations to be identified and vaccinated with the safer vaccine, thus preventing human infections. While this approach may seem to be common sense, there are barriers, including: no established lines for timely communication among animal, human and environmental decision-makers; lack of jurisdictional definition for authorising animal vaccination; and a need to clarify funding for animal vaccinations primarily intended to protect human health.

Global factors, ranging from man-made environmental impacts to escalating international relocation of people and products, present increased opportunities for disease emergence as well as innovative opportunities to mitigate risk. Our world is increasingly interconnected; coordinating communication and public health response across human, animal and environmental sectors is vital to effectively respond to emerging zoonotic diseases.



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Blurring the borders of brain science

Professor Gian Luigi Lenzi, Vice President of the European Federation of Neurological Societies, stresses the importance of multidisciplinary approaches in neurology…

The Encyclopaedia Britannica defines neurology as 'the area of science that deals with the nervous system'. The Britannica World Language Dictionary indicates that 'neurology is the science of the nervous system in health and disease'. However, if we move away from these dated references and Google the two words 'neurology' and 'definition', we obtain the same results. It appears that the nervous system is so important that it has originated more scientific disciplines to deal with its functions in health and disease, specifically neurology, psychology and psychiatry. There is no other organ in the human body that commands such wide-ranging attention, and no other single organ whose diseases have been separated into two or three disciplines.

This, in my opinion, is due to the fact that up to a little more than a century ago, ignorance of the subject was so deep that scientists were still debating

if the nervous system was organised through single cells or otherwise. During the last 100 years, the discoveries on the functioning of the nervous system have been so important that scientists and physicians in the field have been overwhelmed by the realisation of how deep their ignorance still was, and have restricted the focus of their studies to one aspect or another of 'the science of the nervous system in health and disease.' Neurology, psychology and psychiatry were born as separate (and often conflicting) entities.

However, in medicine, the last two decades of the 20th Century have been characterised by the impact of imaging, and neuroimaging in particular has brought to physicians data on how the brain works, region by region, in health and disease. Moreover, the borders between neurology, psychiatry and psychology are becoming increasingly indistinct, obliging scientists to rediscover the science of the brain, the diseases of the brain, and to meet together to discuss the mirror neurons, as neurologists, neurophysiologists, psychiatrists, psychologists and psychoanalysts did recently in Erice, Sicily in September 2012.

This is why neurology is so important – as 'the science of the nervous system in health and disease', considered together with psychiatry and psychology. The brain is important, and brain disorders are important, as well as expensive.

In particular, in the present years of economic crisis, political authorities and taxpayers are concerned about health costs in Western countries, which are doubling every 5-6 years, and raising serious problems for national budgets. In 2011, health expenditure in the EU was ±8.9% on PIL (with an increase of 45.2% in the last decade), of which pharmaceutical expenditure accounted for around 20%.

Brain disorders are at the top of this list. In 2010, the total European cost of brain disorders was estimated at approximately €798bn, exceeding the expense of other conditions considered more costly, such as cardio-cerebrovascular diseases, diabetes and cancer. World Health Organization (WHO) data indicates that brain disorders account for one-third of the burden of all diseases in the wealthy part of the world, thus representing 'the most important economic challenge for the European sanitary assistance, now and in the future'.

One of the reasons for this financial burden is the fact that many brain disorders are chronic and lifelong. Brain disorders that affect mood, from anxiety to panic attacks, from manic conditions to mutable depressions, will require therapy for the duration of the lifespan. Brain disorders that affect neuronal excitability (causing epilepsy) will require a lifetime of drugs treatment or sophisticated neurosurgical procedures. 50% of stroke survivors require assistance for the rest of their lives. So far, the brain has been characterised by a modest capability to supplement through other parts the functions of the impaired region, except in the very young. Ongoing research is strongly focused on strategies of by-passing these intrinsic limitations of the nervous tissue, through the utilisation of stem cells. This line of research is so fashionable that unfortunately it has raised unfounded hopes for terminal patients, in experiments quite distant from a scientific approach that are in some cases close to being fraudulent.

Considering requests from patients and the limits of our armamentarium, the medical care for neurological patients – that is, for patients with a disorder of the nervous system – is far from sufficient. Chronic psychotic patients are under the care/burden of families and of peripheral structures. Elderly patients with dementia will be the epidemic of 2020. Thrombolysis for acute ischemic stroke is provided to less than 10% of the potential patients. Panic attacks affect nearly 10% of the population (and probably 20% of my fifth year medical students).

The primary purpose of this article is to explain why a multidisciplinary approach is so fundamentally important for the study of disorders and therapies of the nervous system. Neuroimaging will shortly be able to show the impaired levels of neurotransmitters, not only for Parkinson's disease, a typical 'neurological' disorder, but also for manic depressive psychosis, and obsessive compulsive/phobic patients. I am not convinced, nor do I claim that these last disorders will come back to the neurology 'Grand Duchy'. I only hope that the increasing multidisciplinary approach to the sciences of the brain will help to build a common knowledge of its complexities and disorders.

Neurogenetics will probably play a major role in this, since it is easily foreseen that many 'disorders of the brain' will show an important genetic factor. Genetic factors could play not only a determinant role from inside the newborn, but also an imprinting in the personality and mood of the infant that is so powerfully transmitted by parents totally ignorant of how their attitude, affective relationships and attachment may determine the possibility of their infant becoming a happy person or a brooding, unhappy, anxious individual.

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Neuroscience drug discovery in the open

A new approach to neuroscience drug discovery…

Brain disorders are the epidemic of the near future. There are more than 1,000 diseases and types of injuries affecting the brain and spinal cord, most with no known cause or cure. Therapies exist for some, but, in most cases, there are no medications that slow the progression of these diseases or induce repair. With our ageing population, the incidence of brain diseases will climb to become the leading cause of death and disability worldwide. Unfortunately, the prospect of new treatments is slim; the challenges associated with discovering treatments for these diseases have led many pharmaceutical companies to halt their internal research.

Pioneer medicines – the productivity crisis

Despite increasing annual investment over the past 30 years, the number of pioneer medicines approved by regulators each year has not increased. This declining productivity is now being acutely felt by companies, which are reducing internal research, closing R&D sites and completely abandoning disease areas of highest risk, such as neuroscience. The productivity crisis also poses serious concerns for society, as we rely on industry to discover and develop the new medicines for those neurological diseases of current greatest unmet need, such as amyotrophic lateral sclerosis (ALS), or with impending socio-economic burden, such as Alzheimer's or Parkinson's disease (PD).

The drug discovery ecosystem is in trouble, largely because of the costs associated with the >90% failure rate of pioneer drug discovery programmes – costs that are amplified because most pioneer drug targets are pursued in parallel by many companies, as well as in academia. This duplication of effort, which severely limits pharmaceutical innovation, is a consequence of the academic and industrial reward systems, whose 'invisible hands' force industry and academia to focus their resources on a relatively small number of protein targets and hamper sharing of knowledge.

The economic consequences of these parallel activities can be staggering in their scale. As an example, over the past 20 years, dozens of companies and hundreds of academics have invested many billions of dollars in pursuing β-secretase as an Alzheimer's drug target. Yet after all this effort and multiple failed clinical trials, we still do not understand the therapeutic relevance of β-secretase in Alzheimer's, and dozens of companies and academics continue to pursue β-secretase drug discovery. It is evident that a transformation of the pioneer drug discovery ecosystem is required – but what should be changed, and how?

How to improve the drug discovery ecosystem

Currently, there is a belief that knowledge of a therapeutic target offers a competitive advantage, but the evidence for this is lacking; in fact, the historical evidence is clear – in all diseases, even with increased regulatory hurdles and more cost sensitive payers, there is no validated target that is not the focus of multiple companies. Open access to validated targets would likely stimulate competition, minimise risk, increase productivity and encourage the development of the best-in-class medicine. Thus, we believe that the key to a profitable and productive drug discovery ecosystem is open access to a wide range of well-validated drug targets.

Induced pluripotent stem cells – the future of drug target characterisation?

One important limitation in the search for clearly validated new drug targets or therapeutic mechanisms for brain disorders is the lack of pathogenically and physiologically reliable animal models. In multiple sclerosis (MS), the predominant animal model has been quite unreliable for validating human MS treatments. Indeed, some drugs were beneficial in animal models, such as interferon γ or tumour necrosis factor-α blockade, but made human MS worse. In PD, researchers have relied mainly on injury induced models that mimic dopaminergic neuron deficiency in the substantia nigra. However, these models do not recapitulate the slow, progressive, and degenerative nature of the disease in humans. In ALS, the standard model for therapeutic studies is a mouse with 23 copies of a human SOD1 single point mutation transgene. Firstly, this model may only be valid for patients with SOD1 mutations – about 3% of the patients with ALS. Secondly, the mutant SOD1 protein levels are so high (up to 10% of cellular protein) that no pharmacological intervention outside of the direct inhibition of SOD1 will ever affect ALS related survival.

The challenging situation for drug discovery may now be changing through the

successful generation of induced pluripotent stem (iPS) cells derived from human skin fibroblasts, and their differentiation into relevant cellular subtypes. These tools, enabling disease and patient-specific cell-based assays that can perhaps capture the physiological, cellular and molecular mechanisms underlying the disease process, are the basis of any robust platform for drug target validation.

A proposal for open access target discovery and validation

At the Montreal Neurological Institute and Hospital (the Neuro), we are implementing a transformational model for early stage drug discovery based on open access, where academia, industry and clinical centres carry out drug target characterisation as partners in a pre-competitive environment.

The Neuro, founded by Wielder Penfield in 1934, is an integrated academic medical centre dedicated to neuroscience. Building upon our track record and existing strengths in molecular and cellular neuroscience, as well as clinical and translational research in neuroinflammation and neurodegenerative disorders, our objective is to create a platform of innovative cell-based assays derived from well-characterised and genetically stratified patients with MS, ALS and PD, and to use these assays to profile compounds that explore known mechanisms, potential new pathways revealed by genetics and genomics, and completely novel mechanisms.

For the diseases we are targeting, the relevant tissues, and particularly live CNS cells from affected individuals, are not readily obtainable. For the cell-based assays, we will use skin derived iPS cells collected from each patient being studied, and differentiate these into spinal motor neurons, dopaminergic neurons or microglia. Novel disease relevant assays need to be developed to maximise the likelihood that they will identify disease relevant therapeutic mechanisms.

The initial objective is to focus on neuroinflammation and epigenetics, with the profiling of over 50 novel inhibitors in over 20 disease relevant assays that comprehensively capture disease phenotypes. To ensure that our results have maximal impact and are generated most efficiently and with minimal delay, all data from the project will be made available to the community without restriction on use.

An approach enabled by open access chemical probes

In our partnership, pharmaceutical companies and the Structural Genomics Consortium (SGC) will provide >50 small molecule inhibitors of previously undrugged human proteins. SGC is a public private charitable partnership that supports the discovery of new medicines through open access research at its research hubs in Toronto and Oxford. With support from eight major pharmaceutical companies, the Canadian and Ontario governments and the Wellcome Trust, the SGC generates small molecule inhibitors of key human signalling pathways in order to make them available to all scientists with no strings attached.

The SGC and its industry partners have extensive experience in using small molecule inhibitors to identify new biology and new therapeutic opportunities. The collaboration has already yielded 15 chemical probes, generated significant knowledge both within the collaboration and, by making the chemical probes available to the community, helped to identify a target and mechanism currently tested in clinical trials for cancer. Relevant to the Neuro partnership, the experience with the first 15 chemical probes shows that, although the community has equal access to the freely available probes, the first publications are accelerated by up to two years if they are provided to dedicated and prepared collaborators in a systematic, organised way, such as in the approach we are launching.

Perspective

This model combines human disease relevant tissue assays and the exploration of disease pathways, all in a pre-competitive environment. The accelerated discovery of novel therapeutic targets that are validated in human disease models will allow society to overcome the challenges we are facing from an increasing disease burden and declining pharma industry productivity. Such academic, clinical and industry partnerships are ideal to accelerate the development for much needed novel treatments for brain diseases. The ultimate extension of this concept is to test the therapeutic relevance of some of the potential targets in clinical proof of concept trials within a pre-competitive environment. This is a rather progressive concept, but one that is gaining traction.

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Nursing care back to health

Paul De Raeve, Alessia Clocchiatti and Silvia Gomez Recio, of the European Federation of Nurses Associations, advocate investment in health to boost the economy…

Investing in the delivery of care has proven cost-effective and is key to improving healthcare systems in the EU. The EC Social Investment Package,[1] which sets investing in health as a priority, is, therefore, well-timed to build trust between EU citizens and in the design of EU health policies that impact their daily work and life. The initiative aims to help member states use their social and health budgets more efficiently, by promoting best practice and providing guidance. Focusing on sustainable health systems, people's health and the reduction of health inequalities, this initiative aims to strengthen the link between EU health policies and national health system reforms.

Allocating resources where concrete changes and reforms make a difference for each individual deserves appropriate investment. With around €80bn budget[2] for the EU's new programme for research and innovation between 2014 and 2020, nurses will see many opportunities for investing in health in order to turn the healthcare sector into a key driver of wellbeing, productivity and growth, which is particularly relevant in the context of the ongoing economic and financial crisis and increased societal challenges.

Building on good 'frontline' examples and experiences, policymakers need to embrace the evidence for strengthening the efficiency of the healthcare sector by investing in education, e-health services, nursing and social care innovation for integrated care – including patient empowerment – and the benefit of knowledge sharing to advance clinical, governance and leadership practices where citizens live and work.

Sustainable health systems: a paradigm shift to boost productivity

Europe is faced with a rapidly ageing population and increasing non-communicable and chronic diseases, alongside fewer resources and a decreasing health workforce delivering care. It is clear that it is socially and economically unsustainable to maintain the traditional vision of healthcare delivery, which focused on a curative approach. We need to shift towards preventable and integrated care systems that are supported by efficient e-health services and increased interconnection of all related sectors.

In this context, innovative practices and models are reorganising healthcare in ways that are proving to be more cost effective and that better relate to patient outcome.[3] Despite economic constraints, the nursing community is turning around the difficulties and has started to move towards better management of chronic conditions, an enhanced community and an improved primary care sector.[4]

However, it seems that finance ministers struggle to connect health with growth, despite the initiatives the EC has launched, such as the concept 'Health is Wealth', which raises awareness of the consequences that short-term measures have on worsening health outcomes and increasing costs in the long run, and the related 'Health in All Policies', which focuses on health aspects in other sectors. Therefore, there is still a long way to go to see appropriate investments.

The need for a competent workforce: a new OSH strategy

Investments in health can support economic growth by enabling people to remain in good health and be active and more productive in the workplace for longer. In addition, the healthcare sector has significant potential for job creation (e.g. link nurses, advanced nurse practitioners), employing 10% of the workforce. Healthcare is one of the largest sectors in the EU, and more than one million new jobs are expected in this field between 2010 to 2020.[5]

However, despite these acknowledged needs, the paradox lies in health and education budgets that have been cut, and posts that have been made redundant, especially in nursing.[6] Furthermore, productivity and competitiveness depend not only on a sufficient workforce but also a healthy one. The EU needs to invest in health by expanding the highest labour-intensive workforce. Due to cuts in health budgets,

the remaining health workforce is confronted with increased workloads as more needs to be done with a significant reduction of highly qualified personnel. Closely linked to their ethical commitment to deliver care, nurses are eager and committed to continue delivering the same care to a larger number of patients at the expense of their own health and well-being, leading to stress and burnout. Nurses are the largest occupational group among all healthcare professionals, providing the majority of direct care, and cuts in post and qualification ratio will impact immediately on patient outcomes and quality and safety.[7]

The immediate consequences are a jeopardised quality of care and a decline of attractiveness towards health professions, leading to a major shortage of nurses. This alarming context demands an appropriate workforce strategy with the right forecasting of a balanced mix of skills and competences, anticipating needs based on societal challenges. The continued focus on strengthening the EU health workforce, besides determining and forecasting the nursing workforce, is to sustain the EU Sector Skills Council, ensuring a cost-effective and long-term approach to system redesign in order to consider the impact of policy trends and political decisions by member states on the EU nursing workforce, and specifically on the development of skills and competencies.

One section of the strategy implies establishing recruitment and retention measures, including improved working conditions, career advancements and fostering opportunities for continuous professional development. Investing in health means tailored implementation that can be better achieved with the use of European Social Funds. The framework, at EU level, must support citizens and professionals through concrete actions supported by appropriate tools to implement change for those who stay in the profession and deliver daily frontline care.

Reducing inequalities: integrated primary care and inclusive growth

The lack of investment in health leads to negative economic effects, such as increased inequalities in access to care and treatment.[8] Nurses play a central role in shifting traditional healthcare approaches towards integrated care. Investing in infrastructure such as e-health and ICT solutions that facilitate communication amongst professionals, will foster a transformational change in the health system, and using EU Social and Research Funds will change the current national health models into efficient integrated care systems that will improve access to affordable, sustainable, high-quality healthcare.

Investing in primary care and supporting communities have proved to play a crucial role in promoting citizens' and patients' empowerment towards supported self-management, delivering more targeted interventions that lead to cost-effective systems. Promoting research and collecting of evidence on health system sustainability are other key investments.

The health sector, corresponding to almost 9% of the EU GDP, has the potential to foster employment and growth.[9] Notwithstanding the importance of the widely used GDP measure to assess growth, the evaluation of growth of our societies also necessitates the deployment of inclusive growth.[10] Moving away from standard GDP as a single measure of socioeconomic success implies developing different kinds of indicators that are sensitive to better 'wellbeing', 'successful health policies' and 'growth'.

Inclusive growth combines prosperity and equity, two important EU concepts at a time of economic and financial crisis. Tackling inequalities by investing in health needs to be indexed and benchmarked. Effectively contributing to integrated care, focusing on the health workforce to decrease unemployment and using this investment to better deliver a more targeted, organised, preventive and integrated care will contribute to achieving this inclusive growth.

In a period of austerity and EU criticism, joining and pooling forces to achieve change for the individual citizen will make an overall difference. Nurses remain committed to reinforcing the collaboration with the EU civil society and key EU stakeholders to further orient policymakers and politicians in selecting the right priorities when investing in health.

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Collaborative approach

Academic and practice-based research in nursing…

What makes for a successful research-intensive nursing faculty? For the Lawrence S Bloomberg Faculty of Nursing at the University of Toronto, the answer boils down to one word – partnerships. Our success lies in integrating research and education endeavours across practice partnerships.

University of Toronto nursing researchers are members of hospital research institutes, are cross-appointed to other divisions and university faculties, and are fully engaged in multidisciplinary teams. Our teachers include nurses who are deeply engaged in clinical practice. We support multiple innovative appointments to ensure that policymakers, practice leaders, frontline clinicians, managers and clinical educators are integrally involved in the education of our undergraduate and graduate students. In turn, we support our varied partners as they develop their scholarly interests within our faculty.

These partnerships are underpinned by structures that support our collaborative practice-based approach to research. The prime structure – and the hallmark of the University of Toronto health sciences – is the Toronto Academic Health Science Network. This multidisciplinary academic practice collaboration encompasses 10 fully affiliated teaching hospitals, multiple research institutes, and all 11 of the university's health professional programmes. It's at this education research practice interface that we are developing world-leading initiatives, such as a mandatory interprofessional education curriculum for all health sciences students. Led by the Centre for Interprofessional Education, this partnership between four teaching hospitals is fulfilling its mandate of improving patient care by creating collaborative healthcare practitioners and bridging research into practice innovation.

In addition to partnerships across the Toronto Academic Health Science Network, the Faculty of Nursing also partners with multiple other organisations locally and internationally, from the Institute for Clinical Evaluative Sciences (Ontario), to the Ontario Cancer Institute and Cancer Care Ontario, to the World Health Organization.

Much from little

University of Toronto Nursing recently ranked number one in Canada and in the top five in North America among all public and private nursing schools for the number of publication citations and for having the greatest impact, a measure of how much the research is used. This success is no small achievement given the modest size of our faculty.

In both our teaching and research roles, we number only 50. Yet we educate 700 students in our Bachelor's, Master's and doctoral programmes. To meet our mission of excellence and leadership in education and research, we rely on more than 600 cross-appointed researchers and practitioners. And it is through these collaborative partnerships that University of Toronto nursing researchers rise above the crowd.

Partnerships give our researchers opportunities to develop multidisciplinary and cross-disciplinary approaches and relationships. Partnerships also give them access to populations and research methodologies that strengthen their work. As a result,

the findings of our nurse researchers have led to improved healthcare delivery and funding and, most importantly, bettered the lives of countless individuals.

Our strong partnership across the teaching hospitals has also resulted in the establishment of seven joint named research chairs. Our chairholders are demonstrating global leadership in oncology, paediatrics, women's health, mental health and nursing research. Our diverse teachers and researchers are affiliated with other sectors of the university and major healthcare centres. And these partnerships are generating strong multi and cross-disciplinary engagement that is leading to engaged, relevant and transformative research.

But our partnerships certainly don't end at the city limits. A core aspect of nursing at the University of Toronto is our commitment to global citizenship. We are involved in multiple international partnerships, most notably in Brazil, Ethiopia, India and Spain. Our projects include the development of a specialised course to foster collaborative practices in primary healthcare among frontline providers in two states in Brazil for nurses and multidisciplinary teams. In Ethiopia, we support the development of graduate research in nursing through long-standing multidisciplinary health sciences collaboration with Addis Ababa University. The faculty also has a long-term partnership with the Catholic Health Association of India, which offers student exchange opportunities. Through this collaboration, we are helping address the shortage of nurses in rural India.

Moving forward

To lead the way in the development of an academic health science network, the Faculty of Nursing looked back to move forward. To help lead this trailblazing collaboration, it gathered momentum from its proud heritage of firsts. In 1928, we became the first wholly university-based nursing programme in Canada. Later we became the first in funding for individual nurse investigators in Canada.

Today, the Faculty of Nursing's strong position in the Toronto Academic Health Science Network, along with its relationships with local, national and international healthcare institutions and organisations, provides unparalleled advantages in developing research programmes. University of Toronto Nursing now has three main research areas that are closely aligned with the doctoral programme's fields of study. These research areas are:

- Effective care and health outcomes. Using randomised controlled trials, theory-driven evaluations, interventions and systematic reviews of evidence, our researchers are evaluating conventional and innovative forms of nursing and healthcare;
- Nursing health systems. Our investigators employ mixed method approaches to find answers to questions about nursing and health services workforce issues, as well as the organisation, management, financing and safe delivery of care;
- Critical approaches to health and healthcare. Our researchers are exposing the health disparities that result from interconnected and marginalising social relations; the historical, ethical and political basis of healthcare; and migration, as well as international and global health.

And what have we learned? We've learned that a successful research-intensive faculty of nursing stands on partnerships. We've learned to look beyond our own faculty to seek a diversity of perspectives. We've learned that by integrating research and education endeavours across practice partnerships, we can begin to address the urgent health issues both in Canada and around the world. We've learned that the University of Toronto Nursing's relationships strengthen and deepen our commitment to research and education.

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From classroom to marketplace

Lejf Moos, Theo Wubbels, Maria Pacheco Figueiredo and Marit Honerod Hoveid, of EERA, consider the true meaning of education in the 21st Century…

The description of the aims of education as either personal development or employability is a false dichotomy and oversimplifies educational aims. These aims do not exclude each other and have to interplay continuously.

It seems that over the past two decades we have experienced a detrimental shift of the basic paradigm of education: from personal development toward employability. This shift hasn't been explained explicitly to the public or professionals. Implicitly, however, the conditions and purposes of education have changed. We have almost got used to new thinking and procedures without knowing, really, that a new paradigm has evolved or what it consists of. This may have happened because in its origins, these changes were not part of education, but rather a side effect of restructuring state-market relations and of social and labour market policies, and this restructuring has dramatically changed the aims of education.

In the history of education, discussions on the relative importance for schooling have addressed two paradigmatically different aims of basic education: Should education help children and adolescents develop their full potential as human beings, or is its overall goal to prepare new generations for work and to be able to adapt to changes in the labour market? The emphasis on these two different aims not only varies over time, but also over different classes in society. In the 19th and first half of the 20th Century, for example, we traditionally saw the lower working class go into vocational education, if at all, whereas upper and middle class experienced what Wilhelm von Humboldt called 'Bildung' in general education.

Until 1990

Personal development as an educational aim fully blossomed in a time period in the 20th Century from the Sixties to the Eighties. Everyone was given the opportunity to become who he or she essentially had potential for becoming, and it was in many cases given permission to do and to experiment with identity and behaviour that stood in stark contrast to and opposed many of the norms and values of the society at that time. This led to a reaction that in the years to come put the emphasis of general education on educating the next generation of citizens to take over the prevailing form of democracy, culture and knowledge, and adjust these according to society's needs.

The main purpose of general education was to support all youngsters in getting to know about themselves, about their relations to other people, and also to the natural and constructed world. In vocational and academic institutions, preparation for the labour market in further education was more like an implicit aim. The main purpose of general education, however, was not related to employability.

The millennium change

This worked well when individual states were distinguishable from other states and when we could provide for the necessary labour force by pulling people from rural to urban settings and have women included in the labour force. At the turn of the millennium, however, with global competition for market shares and a demand for educated employees, new European challenges emerged. Competition in the marketplace brought a higher demand for the whole population to see themselves as and behave as employees rather than citizens. Thus, education had to change from educating citizens to education for the labour market, for employability. Discourse and social technologies were developed in order to reinforce this educational development, first and foremost through the soft governance tools of transnational agencies like the OECD and the EC.

In education, international comparisons of test results, for example, by PISA as a frontrunner, were being 'sold' to the public as a relevant and complete measurement of student outcome, and implemented as a way of comparing a very diverse set of national educational programmes, therefore operating as a potent competition parameter. The employability aspect of education has been written into national legislation and resulted in this restructuring of schools

at all levels. This shift can be seen in the EU and in national government policy documents. One example is the way the European Commission expresses itself on demands on higher education, when it mentions as an aim: improving the quality and relevance of higher education, so curricula meet the needs of individuals, the labour market and the careers of the future, as well as stimulating and rewarding excellence in teaching and research.[1]

A problem?

Is it a problem to ask educational institutions to be 'relevant' and to care for the 'needs of the labour market', such as industry and healthcare and for careers of the future, as IT experts, policy advisers, carpenters, bricklayers, bookkeepers and so forth? No, it is not a problem in itself to reflect on the relevance, but it is a problem to focus exclusively on segments of society and life instead of the flourishing of human potential. It is a problem to look at young people only as resources to be utilised, and not as human beings in their own right. When thinking of life and society in connection to education, we need to consider different aspects: family life, working life, community life and life in leisure time, for example. Young people need to be educated to manage a full life.

A third way

The description of the aims of education as either personal development or employability is a false dichotomy and oversimplifies educational aims. These aims do not exclude each other and have to interplay continuously. It can even be argued that the two aims cannot exist without each other. Developing to your full potential includes qualifying for the labour market, because (for most people) working is an essential aspect of our personal life. On the other hand, preparation for the labour market certainly also includes nowadays important features of the Bildung ideal: helping people to understand their own potential and place in society and to empathise with the views of others.

The 21st Century skills and competencies for the labour market include problem-solving, empathic and reflective skills, and background knowledge of our culture and history. For democracy to operate, a thorough understanding of the history and background of our political system and the malfunctioning of others is more and more important. So in fact, these aims are two sides of the same coin, but it is difficult to include both in an educational system that is focusing exclusively on testing what are believed to be measurable skills.

[1] http://ec.europa.eu/education/news/20110920_en.htm.

Science Omega Review comment: AAU

The revolution in education is reflective of international phenomena, highlighted by changes to the approach of universities in many countries. The Association of American Universities (AAU) represents over 60 leading research universities in the US and Canada, and in July, AAU President Hunter R Rawlings III – together with individual university leaders – sent an open letter to President Obama urging him to close the innovation deficit that they believe the country faces.

"Our nation's role as the world's innovation leader is in serious jeopardy," the letter said. "The combination of eroding federal investments in research and higher education, additional cuts due to sequestration, and the enormous resources other nations are pouring into these areas is creating a new kind of deficit for the United States: an innovation deficit. Closing this – the widening gap between needed and actual investments – must be a national imperative."

"Ignoring the innovation deficit will have serious consequences: a less prepared, less highly skilled US workforce, fewer US-based scientific and technological breakthroughs, fewer US-based patents and fewer US start-ups, products, and jobs. These impacts may not be immediately obvious because the education and research that lead to advances do not happen overnight. But the consequences are inevitable if we do not reverse course."

It went on to say that "having witnessed this nation's success at turning investments in research and higher education into innovation and economic growth, countries such as China, Singapore and Korea have dramatically increased their own investments in these areas. Over the past decade, these other nations' investments have climbed at two to four times the rate of US research and development expenditures. It is equally troubling that the US has fallen to 12th among developed countries in the share of young adults who hold college degrees."[1]

Focusing on helping open the pathways required to fill highly skilled positions, the AAU has been a strong voice in the recent budget debate. Since 2011, it has also been driving a five year Undergraduate STEM Education Initiative to improve the quality of undergraduate teaching and learning in these fields, emphasising their importance to ensure graduates are equipped with the relevant skills for their environment.

[1] www.aau.edu

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The power of visual learning

Advancing the quality of education through visual media libraries…

The power of visual learning is about acquiring and communicating information. In this age of multimedia and mass communication, can a picture be worth a thousand words?

People learn and retain information more easily if presented visually. The impact of technology in the classroom cannot be denied. Computer-based learning has become a top priority for schools. And anything that can improve a pupil's interactive skills is important.

The digital education revolution

In this digital age, a media library offers education professionals a critical resource to assist educational activities. The Media Library from The Visual Learning Company provides a centralised, secure content management system that allows users – teachers, coaches and pupils – to store, index and retrieve digital footage.

What schools are saying about The Visual Learning Media Library

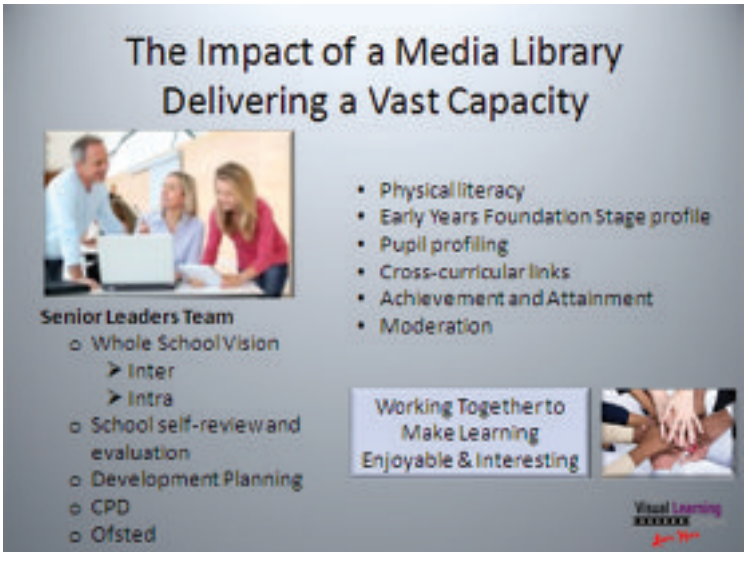
Kendrick School

"The media library has opened greater opportunities in all activities throughout the school."

St Crispin's School

"…embrace the use of visuals in order to enhance student progress and support assessment…"

A mathematics teacher was demonstrating the use of levers. Instead of using a door as an example, she used the Media Library to access footage on trampolining. This was more interesting to the pupils, and to further develop this learning activity, the teacher asked the pupils to film, using their mobile phones, more examples of day-to-day activities that demonstrate levers.



Footage can be imported into the Media Library from many different devices, such as digital cameras, iPads, mobile phones, DVDs and VHS videos. Once stored, the content is easy to locate and is available for play back by any number of students and teachers simultaneously.

Teachers will be empowered to use the library in the way that best suits them. All levels of education can be assisted by the use of video clips that aid learning and assist teaching within present teaching environments – generating a positive effect on the physical, social and emotional wellbeing of pupils. For example, the use of video footage can be used to demonstrate the progress made by a pupil in terms of their confidence and self-esteem.

A learning and teaching example would be footage of pupils undertaking peer assessment looking at each other's pieces of work and identifying areas of strength that relate to the learning outcomes for that piece of work. It inspires pupils to develop their own achievements and attainments, confidence and communication skills; therefore, maximising the impact that it can have on pupil performance.

Rich content

The Media Library should contain a rich source of clips that are extensively and intuitively indexed. These should include clips from: teachers, pupils, school DVDs, educational institutions, sporting bodies and publicly available clips such as on YouTube.

The BBC is also working closely with The Visual Learning Company in order to

bundle their educational content into the Media Library. ICT is always changing and it is vitally important that any system adopted by a school should remain up-to-date and make the maximum use of current technology.

Vast and diverse resource

In terms of capacity, the Media Library is vast and diverse. From the perspective of a school, it offers numerous benefits:

Pupil attainment

The use of digital footage for recording pupil development is an obvious tool to demonstrate their progress and attainment. The Visual Learning Media Library has a vast capacity in both learning and teaching including, but not limited to, pupil profiling, moderation, literacy (both physical and emotional), achievement and attainment and early years foundation stage profiling, as well as school self-review and evaluation, cross-curriculum links and learning and teaching strategies.

Whole school vision

The Media Library can be used as a tool to support the whole school vision, both within and externally to the school. In particular to staff and stakeholders, it can support the process of self-review and evaluation, demonstrating where activities and strategies have helped to drive up standards and change in the school.

Teacher training

The Media Library can be used in a training capacity – especially effective in the current climate when budgets for continuing professional development (CPD) are not as healthy as they were a few years ago. Internal training videos can be created and stored to support internal training opportunities, as well as assisting with Ofsted, SEND and CPD training. Moreover, as regards the Ofsted framework, the library can help in documenting the most valuable evidence to demonstrate school successes.

Teaching and learning

At the ground level, the Media Library can have an immense impact on learning and teaching. As an example, at achievement and attainment and the link to moderation can be looked at. Video footage can capture much more of what is actually happening, especially in a practical subject. It could, for example, enable a pupil in physical education to visually analyse the performance of themselves or others. This in turn could be captured on video and used to demonstrate a pupil's level within the national curriculum or against exam board criteria.

This video evidence could be added to the Media Library and then used internally and externally as part of a moderation process, not only enabling greater understanding than a photograph could ever provide but also helping to support a robust system for ensuring pupil progress.

The Visual Learning Company has run an extensive pilot programme to discover what was actually needed. Three schools (with parental permission) were able to share trampolining footage. They were each provided with quality clips of 'gifted and talented' pupils performing the activity, which has resulted in improved assessment within that sport.

Keeping families involved

The Media Library is a multifunctional and multi-user tool. Not only does it enable joined-up working by a number of agencies, but it also enables pupil progress and development to be enjoyed and seen by families, as we all know, children can be like chameleons and can appear different in different settings. It can open up the world of school, enabling pupils' families to really see and celebrate the work that they do in school. This may be in the form of a school production that they have not been able to attend.

School security is vital

The Visual Learning Media Library, and all of its content, is controlled by the school through the use of the VLC Appliance. The appliance is installed within the school premises and linked to the school's internal network or the cloud can be used, but this will depend on the bandwidth available and if it provides sufficient security. The Media Library is password protection so it can only be opened by those authorised to do so by the school.

The Media Library offers great pedagogical benefits and its use is set to grow. For further information, contact us on the details below.

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Space: the next generation

UK Space Education Resource Office Manager Dr Allan D Clements discusses using the context of space to enrich the teaching and learning of STEM subjects in the UK…

The European Space Education Resource Office in the UK (ESERO-UK) is based at the National STEM Centre in York, with its key objective to promote the use of space as an exciting and inspirational context to enrich the teaching and learning of STEM subjects – science, technology, engineering and mathematics.

The project is funded by the European Space Agency (ESA), the Department for Education (DfE), the Science and Technology Facilities Council (STFC) and the UK Space Agency (UKSA).

Right from the start of this project in 2010, the funders recognised that this work is not just about teaching space in the classroom, but more about using the excitement that space can create to encourage young people to study those STEM subjects that are vital to creating a vibrant growing space business within Europe and the UK.

The UKSA is at the heart of the UK's efforts to benefit from space. The UK space sector contributes £9.1bn to the UK economy, employs 28,000 people and, more importantly, is growing at 'Asian' rates of some 7.5% per annum.[1] The UK is now the third highest contributor to ESA's budget and this year announced its support of the human space flight programme, which will have a significant impact on raising the profile of space in the media and the education sector when Tim Peake, the UK's ESA astronaut, takes a flight to the International Space Station (ISS) in 2015.

The science curriculum in England is under review and at Key Stage 4 it currently proposes the inclusion of space physics. Students are expected to cover topics such as mass, weight, gravity, orbital motion and the history of the universe. It must be remembered that this is only a small part of the wider curriculum requirement in science – they also study chemistry and biology and this is why we encourage the use of space as a context – especially as it covers other areas of the curriculum, such as being taught how to work scientifically.[2]

Working scientifically includes the need for pupils to be taught:

- Experimental skills and how to conduct experiments;
- How to handle information and how to solve problems;
- Understand the ethics of science, how to assess risk and, above all, be objective in their scientific work;
- Understand measurements and be able to convert units.

All of these are vital to any space mission; hence, the broad ranging contextual link – folklore has it that some missions have failed due to the use of imperial units when the contractor should have been using SI units. ESERO-UK has, with the support of UKSA, developed a resource based on the current exploration of Mars using the Curiosity rover.[3] It introduces primary school children to working scientifically using a space programme that today is seeking the evidence for previous life on Mars.

Since its formation in 2010, ESERO-UK has:

- Worked with over 5,700 teachers from both primary and secondary schools;
- Collated 280 'Space Context' resources that teachers can access easily and download from the National STEM Centre eLibrary;[4]
- Facilitated with partners in the UK, the delivery of continuing professional development (CPD) for UK teachers that uses a wide range of space and astronomy contexts. A good example is the CPD course based on the context of the James Webb Space Telescope (JWST) mission, which runs at York and the Royal Observatory Edinburgh and introduces teachers to the scientists and engineers who are part of the project;
- Developed a website (www.esero.org.uk) where teachers can access news items, events and general information about the use of space as a context for learning.

ESERO-UK has developed a resource based on the current exploration of Mars using the Curiosity rover, introducing primary school children to working scientifically using a space programme that today is seeking the evidence for previous life on Mars, explains Dr Clements

Over the next three years ESERO-UK will continue to promote the use of the context of space in schools and focus on some high profile space missions including:

- ESA's Gaia mission, launching in September 2013, which will make the largest, most precise 3D map of our Galaxy by surveying more than a thousand million stars;
- ESA's Rosetta spacecraft, which is headed for an encounter with Comet 67P/Churyumov-Gerasimenko in mid-2014. Rosetta will despatch a lander on to the comet at a rendezvous point more than five times the Earth's distance from the sun. One of its objectives will be to search for evidence of early signs of life;
- Tim Peake's mission to the ISS will spark much interest in schools and the education community in general. The UKSA, ESA, ESERO-UK and other partners in the UK are now beginning to consult with schools in the UK to find out what form the outreach component of Peake's mission might be. When Dutch physician and ESA astronaut André Kuipers flew to the ISS, it had a great impact with schools and pupils in the Netherlands on their perceptions about science and technology.

Currently, the UK has a rich set of space related projects that schools and teachers can access – many free of charge. Good examples include STFC's Leading Space Education Programme (LSEP)[5] where schools with support can achieve the 'Space Quality Mark'. ESERO-UK is expanding this scheme to include more secondary schools and to also create a similar award for primary schools. The National Space Centre at Leicester delivers CPD to teachers and masterclasses to students via its National Space Academy project.[6] The UK is also blessed with a number of strong astronomy organisations that work with schools and allow them their own time on robotic telescopes to explore the stars.[7]

Whilst all of this is very exciting, it is worthwhile reminding ourselves of the importance of STEM to many of our growth and innovative businesses in the UK. We realise that today's young students won't all become astronauts, but encouraging and inspiring them to study STEM subjects will enable them to make a high contribution to the UK economy in the space sector and others. Some might even one day earn salaries that will enable them to take trips to space, thus achieving their wish of following in the footsteps of Gagarin and Armstrong.

[1] Source UKSA www.bis.gov.uk/ukspaceagency

[2] There is an abundant supply of resources using the context of space to enrich the teaching of biology and chemistry

[3] ESERO-UK: Is there anyone out there? www.nationalstemcentre.org.uk/elibrary/resource/5689/is-there-anyone-out-there

[4] This ESERO-UK collection can be accessed at: http://stem.org.uk/cx3nf

[5] School Science Review March 2012, 93(344); p. 41

[6] Ibid p. 33

[7] Ibid p. 53 and 63

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Saving lives with sensors

Mälardalen University's Shahina Begum sheds light on driver monitoring technology that uses physiological sensor signals to detect dangerous levels of stress and fatigue…

The safety and efficiency of today's road traffic is highly dependent on human behaviour. Specifically, psychological states such as mental load, stress, and fatigue have been identified as major factors in a large proportion of all traffic accidents.[1] In recent years, intelligent monitoring systems for drivers have emerged and become a popular topic among researchers. Due to the latest advances in car development, these solutions can be implemented in future. Also, people are more aware of their own safety than they were previously, and such solutions will be welcomed gradually by more safety-aware drivers. Driver monitoring will be valuable in helping to prevent potentially dangerous situations, provide and improve safer human-machine interaction, and help to build future semi-automatic cars that actively collaborate with the vehicle's driver and assist them in critical situations when necessary.

Today, researchers are exploring various techniques and algorithms to provide informative indications of a driver's state. There are systems available with techniques that monitor pupil response, eye blinking/closure/gaze and eyelid/face/head movements, etc. Previously, many researchers focused on identifying the risk factors or on classifying the condition of the driver based on external behaviour, e.g. lane position and reaction times. These techniques, though less intrusive, are still not as practical as the most accurate techniques for monitoring drivers' state based on physiological features, e.g. brain waves, heart rate, respiration, etc. Examples based on physiological measures include the IMod project.[2] Significant technological advancement has made it possible to monitor drivers' state using physiological sensor signals, for example electroencephalogram (EEG) or electrocardiogram (ECG), which provide more direct and early indication of fatigue and stress.

The envisioned intelligent driver monitoring system would continuously monitor drivers' psychophysiological state and use intelligent algorithms to provide an immediate warning (audio and visual) when possible signs of conditions appear that may

endanger the driver. The majority of systems monitor parameters, for instance, drowsiness or sleepiness and stress, as these are common causes of lack of attention while driving. Considering the system's fundamental functionality, a driver monitoring system based on physiological sensor signals performs two main, basic tasks: it takes data from the driver and provides them with feedback, which can be in the form of suggestions, cautions or warnings. Biological sensor signals (i.e. EEG, ECG, finger temperature, skin conductance) are collected through electrodes placed on the body of the skin.

Typically, signals, when collected – especially in driving situations – could easily be contaminated by noises or distractions due to movements and other interferences. Therefore, automatic algorithms are necessary to handle this unwanted data, which might otherwise produce misleading results. Feature extraction is another important aspect that is often applied in many such monitoring systems. Signal processing methods exist, e.g. Fast Fourier Transform (FFT) and Wavelet Analysis, that are able to capture significant characteristics of the original signal with a compact representation, and the features extracted are directly usable in the system. However, biomedical sensor signals have their own unique characteristics that are handled according to the problem at hand. The data gathered can then be used by intelligent monitoring systems to provide feedback to users. Since the psychological and behavioural conditions/status reflected by physiological sensor signals are so individual, personalisation of such systems is another important research issue.[3]

The number of driver monitoring systems using physiological sensor signals that have featured in different journals demonstrates the rapid growth of the field in recent times. Driver monitoring systems could be developed for specific users, for example, for professional drivers, personal car drivers, elderly drivers, etc. System inputs can involve single or multiple sensor sources to monitor the psychophysiological changes of drivers. System outputs can take the form of warning, decision, advice, or information-only messages. In the case of multiple sensor signals, the system can provide an individual outcome based on sensor signals, while some systems also show a combined result taking into account the sensor fusion technique.

Despite several challenges, e.g. light constraints and other interferences, video image technology is comparatively less obstructive during driving than physiological sensor signals. This is the most common form of driver monitoring system, and motor vehicle manufacturers including Toyota, Volvo, Mercedes-Benz, Nissan and Saab are involved in this research area. However, physiological sensor signals provide more reliable and robust information about drivers' health, relating more directly to the physiological and psychological state than video cameras. Sensor signals can detect drowsiness or stress even during dark or bad weather.

The envisioned intelligent driver monitoring system would continuously monitor drivers' psychophysiological state and use intelligent algorithms to provide an immediate warning…

Although there have been advances in sensor technology, many such systems are still in the research prototypical phase. Several challenges have to be overcome in developing a commercial product. First of all, the device should not interfere with normal driving tasks. It should also be low in cost for the purposes of mass production, able to record data continuously in real time, and take reliable measurements in case of light constraints, temperature, humidity and vibration, etc. It should be individualised and minimise false alarms.

Although driver monitoring systems using physiological signals have not exhibited any significant success in routine use or in widespread commercialisation, the field is continually improving. Moreover, the trends show that eventually, more sophisticated technology will be available to provide a more reliable, comfortable and unobtrusive product for drivers. In future, it could be applied as a reference-point with vision-based driver monitoring systems in intelligent vehicles.

[1] Taylor A H, Dorn L (2006), Stress, fatigue, health, and risk of road traffic accidents among professional drivers: The Contribution of Physical Inactivity. Annual Review of Public Health Vol 27, pp. 371-391

[2] Begum S, Barua S, Filla R (Emerging Technologies, Volvo Construction Equipment) and Ahmed M U, Classification of Physiological Signals for Wheel Loader Operators Using Multi-Scale Entropy Analysis and Case-Based Reasoning, Expert Systems with Applications Vol Accepted, Elsevier July 2013

[3] Begum S, Ahmed M U, Funk P, Xiong N and Schéele B V (2009), A case-based decision support system for individual stress diagnosis using fuzzy similarity matching. In Computational Intelligence (CI), Blackwell, Vol 25, Issue 3, pp. 180-195

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Getting to Know

Greg Foot

Science Communicator

Bringing a daredevil spirit to the realm of science, Greg Foot has undertaken many challenges in the pursuit of knowledge and discovery. From expeditions to Mount Everest to being buried alive, he focuses on tackling the difficult – and sometimes dangerous – scientific questions. Here, he tells Editor Amy Caddick what it is about extreme science that appeals to him and why science communicators are vital...

Where did your passion for science come from?
I remember being in the kitchen when I was young and performing science with my dad. My favourite was blowing custard powder over the hob of the oven. In fact, both my parents really encouraged me to look at the world and ask questions about it. I think it also helped that I had some fantastic teachers in school who really connected with me. I enjoy looking at the world and working out what makes it tick.

What inspires you?
I like to uncover science that actually matters to people, so taking an everyday topic and uncovering the science within it. For example, last year I looked

at the physiology and sports engineering behind the Olympics. Also, I enjoy looking into subjects that don't appear to involve science and technology, such as extreme sports.

I like answering people's questions about science. I do a weekly online show on the Head Squeeze channel on YouTube where people send in their questions and I respond. It's a great way to have instant interaction with the audience.

Do you think scientists have a responsibility to communicate science to young people?

I think it's important for young people to understand science, so that when something comes up in the news they have the tools to look at it, understand it, and make up their own mind. However, I don't think it's essential for all scientists to communicate their research. Some science is very pure and some science doesn't necessarily have an immediate application, but when science can be communicated it needs to be done in a clear fashion. That's why you have science communicators, like me.

Science communication is now a profession, and it is my full-time, freelance life. I work with many scientists who either haven't thought about communicating their subject or do not yet have the skills to communicate it effectively. I think the perfect way to communicate science is for science communicators and scientists to work together.

What is it about combining science and daredevilry that you enjoy?

I like immersive experiments and I like to get 'stuck in'. The best way to understand how something works is to throw myself in the middle of it and become a guinea pig. I think doing that makes it more visceral and engaging, and actually experiencing the science for myself means I can explain it more effectively.

What has been the scariest challenge you have undertaken?

Being buried alive was one. Because of health and safety, the BBC weren't allowed to actually cover me with soil, but I got into a coffin, they sealed the lid and we monitored my oxygen and carbon dioxide levels. We looked at how long I could survive before I essentially drowned in my own carbon dioxide levels. That was a pretty cool experiment.

Another one I think was really interesting was answering 'what do humans taste of?' It had never been scientifically answered, so I found a surgeon who was willing to take a biopsy of muscle from my leg. We then went to the University of Nottingham where we analysed all the aromas that came off in a mass spectrometer and, because flavour is about 80% aroma, we managed to track that back to different meats and work out what humans taste of.

Why is it important to push the boundaries of science?

Pushing the boundaries of science itself is something we leave to the scientists and the engineers, rather than the science communicators. It's the scientists themselves who do the real science; the real groundbreaking work. It's important not only from an intellectual pursuit, but also from a practical pursuit. We might not yet know the practical applications of the research being undertaken, but that's why it's important to keep pushing the envelope on what we know.

Saying that though, I'm trying to push the boundaries of science communication – trying to find new ways to communicate, engage and inspire people about science.

Which of your achievements are you most proud of?

I trained as a scientist, but I realised that my passion was communicating science to different audiences. At the time, I didn't know science communication was an actual job but I just followed what I was passionate about. When I left my employed job and branched out to freelance that was really nerve-wracking, but I'm very proud that it has grown into a career where I get to spend my time doing what I love.

Freelance is a hard life. It takes a lot of hard work. It took five years of making showreels and sending them out before I got my first TV show and then it took many years of work after that to build up to other programmes and prove myself in other forms of communication. So I think that is my proudest achievement – that I've managed to stick at this and build it into my career.

What are your plans for the future, and what ambitions do you have yet to fulfil?

I'm really excited that I start filming a new TV show in August for BBC Worldwide. It's essentially about the interesting science behind interesting stuff!

I'm still out touring my new Everest show, which is going down really well. It's great to do a live show about cutting-edge science. I've also got a plan for a new project that I want to launch next year, which will move into a different area of science communication. That one's top secret at the moment!

The Medical Faculty, University of Helsinki, has 5 research programmes starting from the beginning of 2013. One of these is the:

DIABETES AND OBESITY RESEARCH PROGRAMME

UNIVERSITY OF HELSINKI
FACULTY OF MEDICINE

To date, approximately 300 million people in the world have diabetes; in addition, 540 million adults are obese and 1.6 billion overweight. Over 90% of diabetic patients have Type 2 diabetes (T2D), but the incidence of Type 1 diabetes (T1D) has also increased manifold in most countries after World War II. An alarming concern is the growing presence of obesity and the metabolic syndrome in subjects with T1D and its impact on future cardiovascular risk. Diabetic complications, such as cardiovascular disease outcomes, diabetic neuropathy, amputations, renal failure and blindness result in increasing disability, reduced life expectancy and enormous health costs worldwide.

The mission of this research programme is to elucidate the molecular mechanisms underlying the various forms of diabetes and its complications, the metabolic syndrome and obesity and to translate this knowledge into novel treatment and prevention strategies for these conditions. The overall aim is to assess the role of genetic, environmental and lifestyle factors and their interactions in disease development and outcome in different types of diabetes, metabolic syndrome and obesity in the context of cardiovascular disease risk and microvascular complications. We aim to design biomarker panels based on specific phenotypes together with genetic and environmental risk factors to predict the development of diabetes/obesity, treatment success and disease complications. We will utilise cross-sectional, prospective and longitudinal epidemiological study cohorts with extensive data on environmental and lifestyle factors and studies based on families with extensive information on phenotypes.

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C·M·H·P
College of Mental Health Pharmacy

Building a better picture of mental health

The College of Mental Health Pharmacy (CMHP) has the overall objective of advancing education and research in the practice of mental health pharmacy. Although mainly aimed at pharmacists and pharmacy technicians, anybody can register to be an associate member of the CMHP, enjoying access to education and networking opportunities such as e-groups, bulletins and the annual conference. We also support pharmacist members to be recognised experts in their field through a process of accreditation.

We have two strategic aims, which are:

- To sustain and further develop educational events and resources, which enhance the practice of mental health pharmacy; and
- To foster Research into the Optimisation of Medicines for Mental Health (ROM-MH), disseminate results widely and promote implementation, for individual benefit.

To find out more, call us now on 0191 404 6875 or visit our website www.cmhp.org.uk

The CMHP works in collaboration with: the Royal Pharmaceutical Society of Great Britain; the Royal College of Psychiatrists; and the Centre for Postgraduate Pharmacy Education
The CMHP has academic links with: Aston University; and The University of Bath
The CMHP works in partnership with: Lundbeck Ltd; Janssen-Cilag Ltd; Otsuka Pharmaceutical Co. Ltd.; and Shire Pharmaceuticals Ltd.