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INSPIRE

RESEARCH AUSTRALIA SHOWCASES HEALTH & MEDICAL RESEARCH

Frontiers edition

UNLOCKING
Australia's potential with Frontiers research

Foreword by the Minister for Health

RESEARCH AUSTRALIA

CONNECTING • ENGAGING • INFLUENCING

Message from CEO

Whilst I'm all for living in the now – when it comes to health and medical research I'm all about the future hence dedicating this issue to the very real possibilities of our future, and bringing Australian health innovation to the frontiers of science and technology.

This initiative follows Research Australia's calls for the Government to use the Medical Research Future Fund to boost research at the limits of our application of human health science and technology. I'm delighted they agreed and the $240 million-dollar allocation in the May budget gave us just that in the form of the Frontiers Health and Medical Research Programme.

The Health Minister, Greg Hunt MP, expands on this in his foreword of this special Frontiers issue. It's a different approach to the usual grant process and its designed to use the economies of scale model to really push for a frontier outcome. Importantly, as a global player with a solid research excellence track record, it's an opportunity for Australia to signal its intention to lead in an area we know is a gamechanger on how we approach health outcomes in and beyond our lifetimes.

And yes, it is ambitious … and it needs to be.

Our goal with this issue is to showcase the range of potential frontiers research already underway in our institutions that could indeed be ground breaking and of course we intend to use future editions of INSPIRE to highlight other frontier potential research.

Acknowledging the talent, progress and excellence of our member's research is a key part of Research Australia's role in advocacy for the health and medical research sector and a sincere thank you to all who submitted extracts for this special edition. The committee was greatly challenged to select a range to showcase and from targeted nanotechnology for precision disease treatment, protein nanobots to target cancer, growing your own organs and repairing your own tissues, biodegradable bone implants, AI to decipher big data and find answers in a lifesaving fraction of the time the possibilities are endless. What they all have in common, is the potential to transform the way we treat or eradicate diseases forever, bringing tomorrow into sharp focus for us all.

A special thanks to Enrico Coiera for his 'Last Word' piece on moving healthcare to the Artificial Intelligence Frontier – certainly an interesting global perspective and one which fully supports the urgency of the need for investment in Frontiers research.

As the nation's alliance for discoveries in health we trust you find this issue enlightening, inspirational and above all – we encourage you to think big when it comes to this significant and bold new funding programme.

Enjoy!

Nadia Levin
CEO & Managing Director

Publisher
Research Australia Ltd

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INSPIRE ONLINE
issuu.com/researchaustralia

INSPIRE is a publication of
Research Australia Ltd
ABN 28 095 324 379
384 Victoria Street
Darlinghurst NSW 2010

Who can submit articles?
Any current member of Research Australia who would like to share a relevant story that affects their organisation including, philanthropic donations and their outcomes, research findings, and any other related health and medical research topic that affects the Australian population.

Submission guidelines & deadlines
For information regarding how to submit and publishing deadlines visit the Research Australia website.

RESEARCH AUSTRALIA
CONNECTING • ENGAGING • INFLUENCING

FOREWORD

A NEW FRONTIER IN HEALTH AND MEDICAL RESEARCH

The single best way to prepare Australia for the health care challenges of the future is through health and medical research. It is today's investment in the world-class health care of tomorrow.

The Federal Government is providing unprecedented funding in this space. The $20 billion Medical Research Future Fund is a significant funding contributor of the new $1.3 billion National Health and Medical Research Industry Growth Plan, which will drive the next era of better health care, foster research translation and entrepreneurship, and fuel jobs and growth in new firms and industries through research.

The Frontier Health and Medical Research (Frontiers) Program is a key part of this Plan. It will provide $240 million over the next five years to create a landmark investment scheme to enable opportunities for researchers and collaborations to explore innovative out of the box ideas and new to world discoveries of great potential. **Frontiers** will unlock ground breaking research with the potential to enable new treatments for disease for Australians and, indeed, the world.

Strengthening Australia's competitive edge in global innovation requires nurturing the skills of Australian scientists and clinical researchers. Success will depend on job adaptability and an increased awareness of entrepreneurialism as it applies to discovering and realising products and treatments that can be translated and commercialised. Collaboration between researchers and business is associated with a 70 per cent achievement of new to world innovation, but Australia is a poor performer here – we are last among 27 economies measuring research and business collaboration. This needs to change.

Frontiers will create an opportunity for blue sky thinking in the health and medical research sector. Australia has the potential to lead markets and create new ones by applying cutting edge science and technologies to new applications that improve human health. However, to achieve or even entertain these possibilities, we have to take a bold step and adapt our current approach to funding to reach an economies of scale ideal.

Frontiers will allow our best and brightest to put forward big and bold ideas that can fuel an ecosystem of discovery and industry. It will support them to investigate how to turn these ideas into a research program that has the potential to spin out frontier technologies that will revolutionise global health care and create new industries in Australia.

In order to encourage disruptive thinking and new approaches to problems, the structure of the Frontiers Program is unlike the normal grant model employed in traditional research funding. This approach will involve some risk taking but is essential to identify unique opportunities for Australia to create new global markets. The program will operate using a two-stage elimination process.

STAGE ONE will be an expression of interest where researchers will articulate their idea and its merit, demonstrating its novel aspects

Nadia Levin CEO Research Australia (left)
Minister Greg Hunt (middle)
Chris Chapman Chair Research Australia (right)

and competitive and transformative nature. An internationally selected assessment panel will then assess the idea.

Ten great ideas will be identified each year and successful applicants will have one year and $1 million to bring their idea to life and have it ready to put forward for stage two – investment.

STAGE TWO provides an opportunity for applicants to receive a further five years of funding. Proposals will be reassessed after their initial seed funding by an expert international panel specialising in identifying new to world opportunities. Successful stage two applicant funding will typically be in the range of $10 to $20 million a year. Successful applicants will need to demonstrate partnerships across disciplines and sectors (public and private), as well as the ability to build capacity and training of Australia's research talent and provide a return on investment. It is estimated that around six big and bold ideas will be progressed under stage two over the next four years.

The program design is currently under development and the opportunity will open for researchers in the coming months of 2019.

Australia has a long and strong history and excellent reputation for health and medical research. We are recognised internationally for punching above our weight when it comes to medical breakthroughs. I am confident programs like the Frontier Health and Medical Research Program will demonstrably enhance that reputation, supporting our world-class researchers in their life transforming and lifesaving endeavours.

I commend this edition of Research Australia's INSPIRE magazine to you and congratulate Research Australia on taking the initiative to draw together these great examples of Research Australia members working at the frontier of health and medical research.

Greg Hunt MP
Minister for Health

CONTENTS

Australian Health & Medical Research

STEM CELL TECHNOLOGY AT THE FRONTIER OF TOMORROW'S MEDICINE

Regenerative medicine holds the promise of revolutionising patient care in the twenty-first century. Sitting at the convergence of stem cell science, gene therapy, synthetic biology and bioengineering, it provides novel ways to restore normal organ function.

The following are examples from work being undertaken by Research Australia members.

STEM CELLS COME OF AGE

Bone marrow transplantation remains the most widely available stem cell therapy. This is about to change as stem cell therapy for the eye's surface (cornea) has been commercialised in Europe and clinical trials around the world are using stem cell-derived tissues to treat many conditions – including blindness, neurological disorders, heart diseases and diabetes.

Stem cells are unspecialised cells capable of making copies of themselves and differentiating into the more specialised cells of the body. There are two main types of stem cell: tissue stem cells and pluripotent stem cells (PSCs).

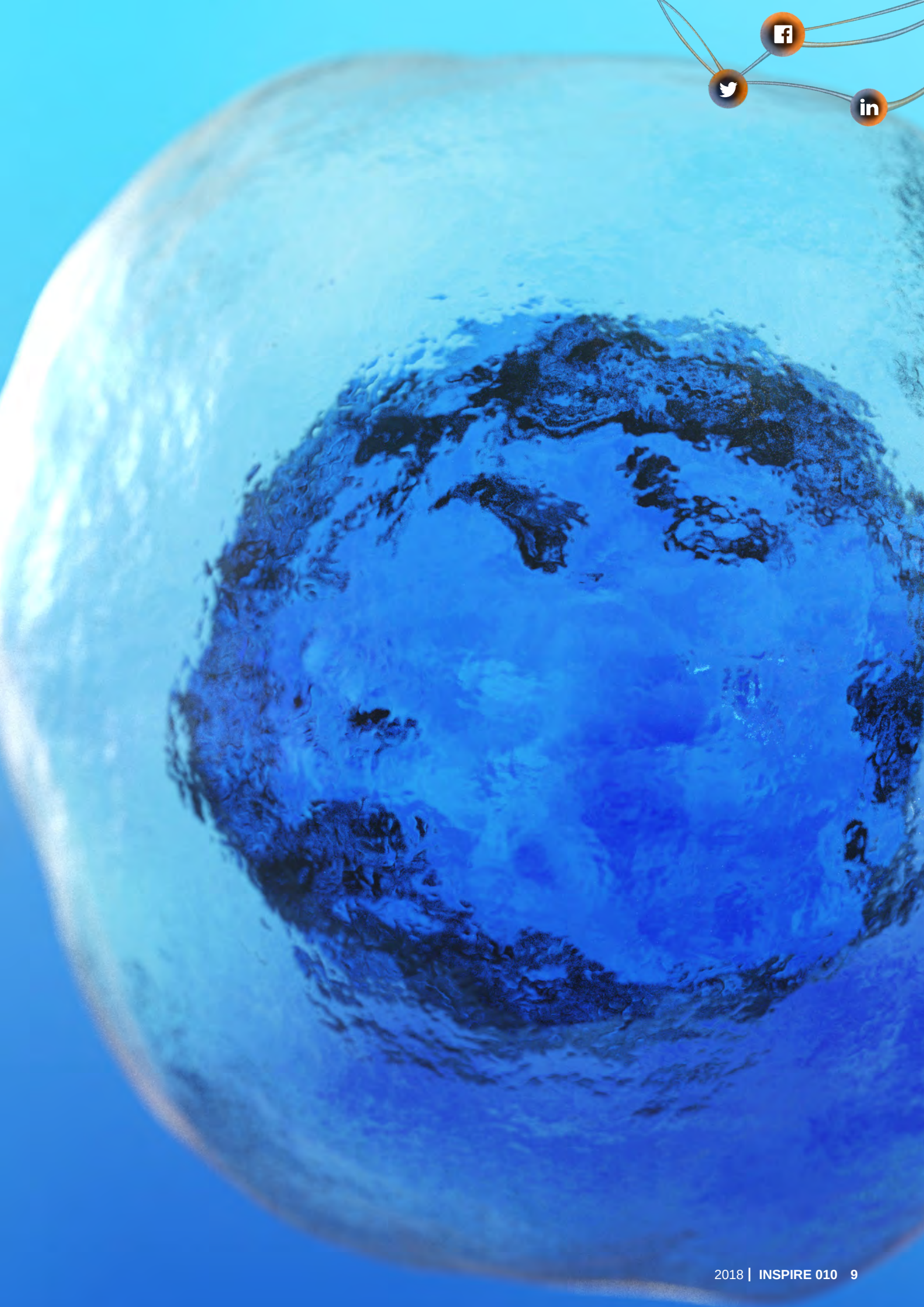
STEM CELLS IN YOUR TISSUES

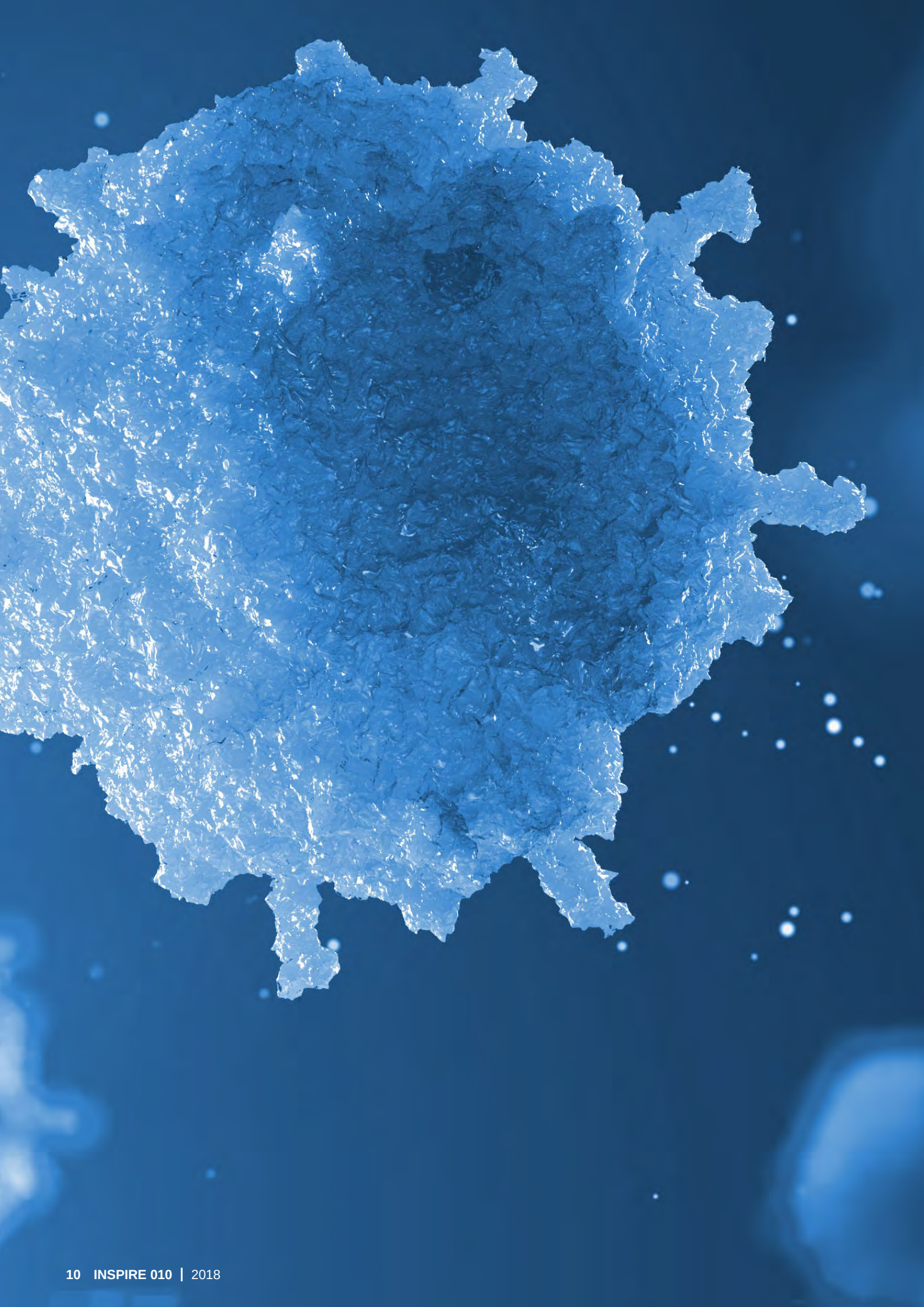
Your body is able to maintain and repair your tissues due to the 'tissue stem cells' found in many of our organs. The skin, the lining of your intestinal tract and the blood, for example, have robust stem cells that can give rise to the required cell types for that tissue. Being able to harness these stem cells or improve their capacity to keep responding to injury, disease and/or aging is a major focus of tissue stem cell research.

PLURIPOTENT STEM CELLS

Def: the master cells that can make cells that can potentially produce any cell or tissue the body needs to repair itself.

In contrast, a PSC is able to generate any cell type in the body - thereby creating a sustainable source of stem cells for research and potential clinical use. Until the mid-2000s, embryonic stem cells derived from fertilised eggs were the only type of PSC available. However in 2007, new technology was developed that enabled any cell in the human body to be reprogrammed into a pluripotent stem cell, so-called induced pluripotent stem cells (iPSCs) – technology that won the Nobel Prize in 2012. iPSCs circumvented ethical concerns related to embryonic stem cells and opened up the option of "self" stem cell treatments, avoiding the need for life-long immunosuppression. Precise methodologies are now available for differentiating pluripotent stem cells into specific cell types for tissue repair.





Mending a broken heart: Bob Graham and Richard Harvey at the Victor Chang Cardiac Research Institute are working with James Chong at the University of Sydney to assess how hormones and growth factors can be used to regenerate the injured adult heart partly by stimulation of stem cells. Enzo Porrello and David Elliott at the Murdoch Children's Research Institute and James Hudson at the Queensland Institute of Medical Research are identifying the genes that control the proliferation of heart muscle, to enable them to screen for new drug candidates that activate these genes. They are also testing whether new heart tissue generated from iPSCs can be used to repair heart damage in large animal models, ready for potential use in children with congenital heart disease.

Seeing is believing: Every 7-10 days the surface of the cornea is replenished. Specialised stem cells in the eye maintain clear sight by providing the replacement cells for the cornea. Sight is rapidly lost if these stem cells die or are damaged through disease or trauma. Stephanie Watson at the University of Sydney and Nick Di Girolamo at the University of New South Wales have successfully restored sight in Australian patients with corneal blindness, in a world-first clinical trial that delivered corneal stem cells on the inside of a contact lens to the damaged eye. They are now working to further enhance the effectiveness of this treatment.

An aide-mémoire and lifting the mood: Perry Bartlett demonstrated the existence of stem cells in the adult brain over 25 years ago. Now at the University of Queensland, he and his colleague Dhanisha Jhavari have found ways to activate brain stem cells to improve memory, mood and cognition. They are testing drugs for their ability to stimulate these cells in animal studies and have a clinical trial underway assessing how exercise can improve cognition in elderly people.

Building a kidney: With chronic kidney disease diagnosed in 4000 Australians annually, there is an urgent need to develop new treatments. In 2015, Melissa Little at the Murdoch Children's Research Institute produced the world's first kidney-in-a-dish from iPSCs. This technology is being used now to study genetic kidney disease to improve diagnosis and develop treatments. In 2017, she started using Australia's first 3-dimensional bioprinter to 'print' different cell types (derived from iPSCs) to create a more accurate 3D kidney structure. The ultimate aim of this tissue engineering is to build a functional mini-kidney.

Brain repair: Parkinson's disease was one of the first targets for cellular therapy, with early clinical trials in the 1980s demonstrating that human foetal tissue transplants into the brains of patients could alleviate symptoms for decades. Now the focus has moved to generating precisely the right sort of dopamine nerve cell to replace those that degenerate in the disease. Clare Parish and Lachlan Thompson, at the Florey Institute of Neuroscience and Mental Health, have developed methods for efficient and reproducible production of these dopamine cells using human PSCs and are now advancing these studies ready for local clinical trials.

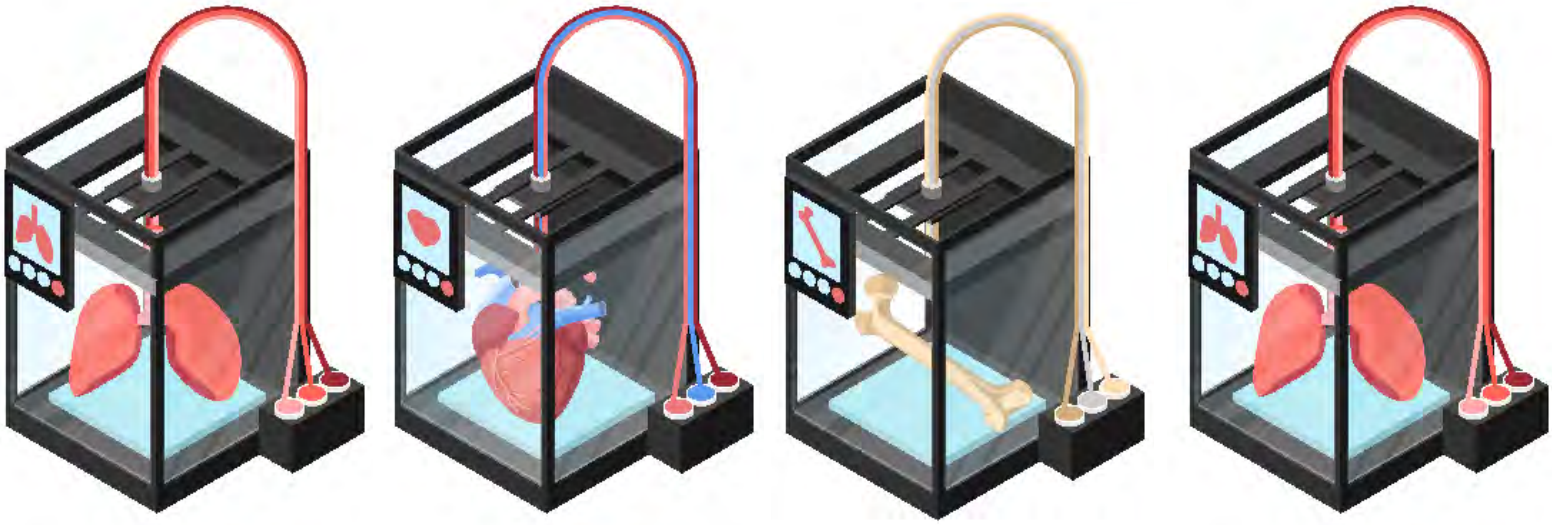
New blood: Modern stem cell technology can also assist traditional treatments such as bone marrow transplantation. Ed Stanley and Andrew Elefanty at the Murdoch Children's Research Institute are engineering human blood stem cells from PSCs for patients without suitable donors. Lars Nielsen at the University of Queensland has made immune-boosting neutrophils by expanding stem cells in umbilical cord blood in a 'bioreactor' and then encouraging them into becoming neutrophils. The licensed technology will provide a new treatment to help chemotherapy patients fight infection.

AUSTRALIA AT THE FOREFRONT OF STEM CELL MEDICINE

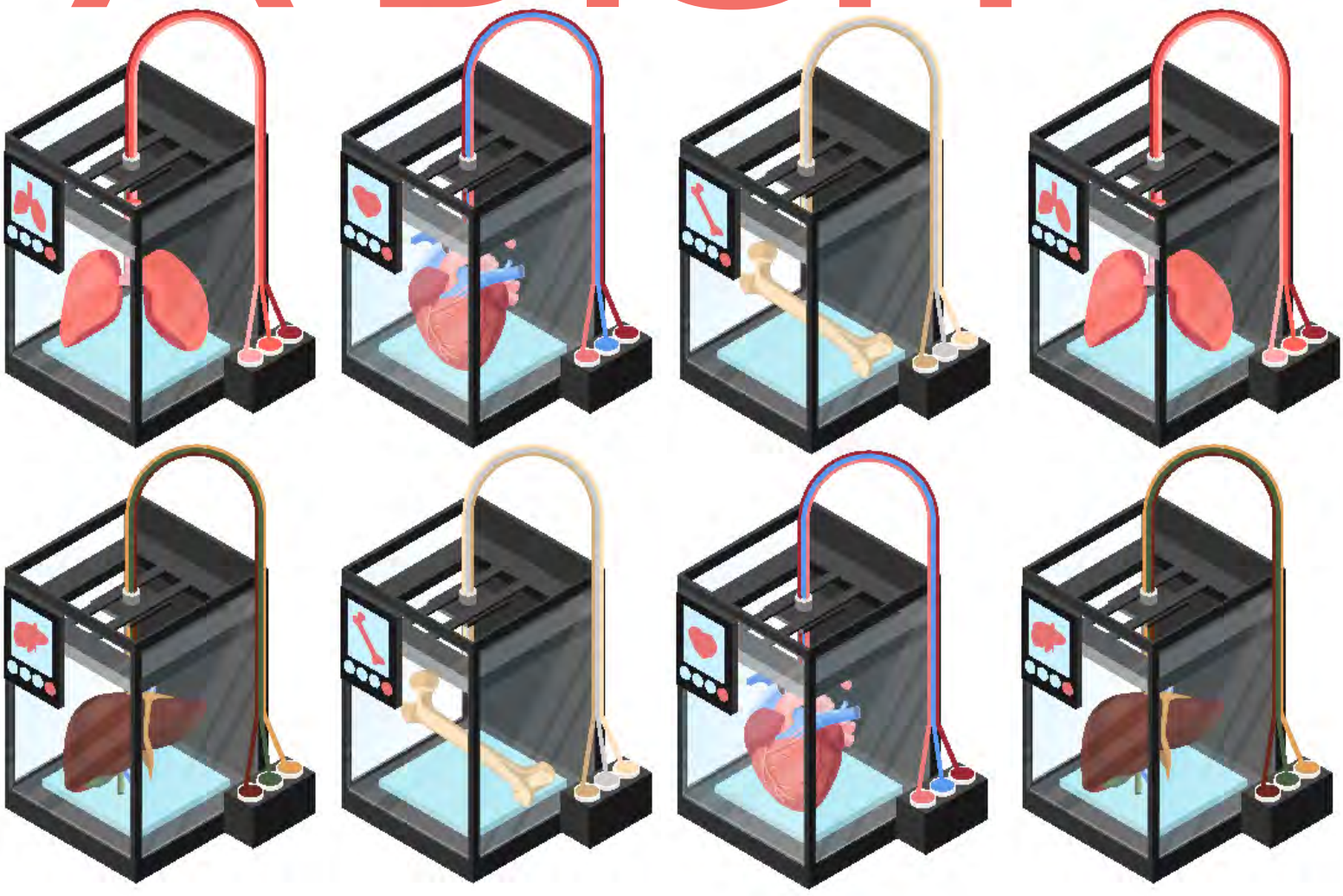
Stem cells and regenerative medicine have the potential to transform healthcare, thereby improving patient outcomes. Based on our ongoing understandings of cell identity and techniques for cell reprogramming, therapies are advancing along the pipeline. What is now required is support to move from bench to bedside, with the involvement of the patients, clinicians, regulators, the community and biotechnology industry.

Stem cell-based treatments will reshape medicine by providing completely new ways to restore normal cell and tissue function in many conditions with unmet clinical needs, including in chronic and rare diseases that are currently untreatable with drugs. In some conditions, stem cell therapy has the potential to be curative.

Authors: Stephanie Watson, University of Sydney.
James Chong, University of Sydney. **Clare Parish**,Florey Institute of Neuroscience and Mental Health.



LIVER IN A DISH



The 1982 classic film 'Blade runner', set in LA in the year 2019, brought to life a world in which artificial humans could be engineered in a lab. Now, the real world is catching up with Ridley Scott's imagination and we are working on the potential of patients growing their own liver using their own cells.

The O'Brien Institute Department at St Vincent's Institute (SVI) leads the way in reconstructive microsurgery and tissue engineering, with the aim of tackling issues such as lymphoedema, cardiac dysfunction and liver disease.

"Since its genesis 60 years ago, SVI has been at the frontier of research innovation", says Director, Professor Tom Kay. "We study common diseases that affect many Australians, and our researchers bring a diverse range of techniques and experience to the table. SVI's work spans the research spectrum, from fundamental research, right through to clinical studies, with improved health of the patient always at the forefront of our work."

ORGANOIDS TO GROW LIVER TISSUE

In 2016, Associate Professor Geraldine Mitchell and her long-time colleague Professor Wayne Morrison, were awarded an NHMRC Project Grant to fund the development of what they call a 'liver in a dish.' The ultimate aim of their work is to grow an 'organoid' (a miniature, simplified version of an organ) derived from a patient's own cells, to be used as a source of tissue for liver transplantation.

Geraldine says that liver disease is more common than is generally recognised in Australia. It is associated with common conditions such as obesity, diabetes, viral hepatitis, excessive alcohol intake and cancer.

> ***"The only current treatment for advanced liver disease is transplantation and, because there are not enough organs to meet demand, many patients die before they can get a transplant," says Geraldine.***

Geraldine's research involves a multi-disciplinary team, including scientists and surgeons, whose focus is on using human cells to 'grow' a liver that could be up-scaled in the future to be used for transplantation, or as a platform on which to test drugs to treat the disease.

Geraldine explains that without the involvement of surgeons at St Vincent's Hospital, and in particular, her PhD student, Surgical Fellow, Dr Kiryu Yap, the project would not be viable.

"Kiryu is often called, both in and out of hours, to collect liver tissue from patients having surgery who have agreed to us using very small segments of their liver for our experiments. For this project, access to human cells is paramount."

With the consent of Hepatobiliary Unit patients at St Vincent's Hospital Melbourne, Dr Yap attends surgeries to remove cancer in the liver and harvests a small sample of healthy tissue.

Kiryu says that one of the major hurdles is the need for cells in the organoid to get enough oxygen. The team are approaching this problem by engineering a vascular system within organoids, derived from human endothelial cells and support cells that form blood vessels and facilitate liver development.

Other components include a porous scaffold, provided by PolyNovo Ltd. Melbourne, that provides a physical support upon which the cells can grow and a special gel, which provides other factors that promote the cells' survival.

FROM DISH TO TRANSPLANTATION

Ultimately, the team intend to use stem cells from a person with liver disease to grow liver tissue for transplantation. Geraldine says that this is the most clinically feasible method to generate the millions of liver cells that would be required for personalised organoid generation. "Organoids represent the most advanced approach to creating structures with the complex architecture and diverse functions of the liver, and may allow relevant drug testing and disease modelling in addition to their use in liver tissue replacement,"says Geraldine.

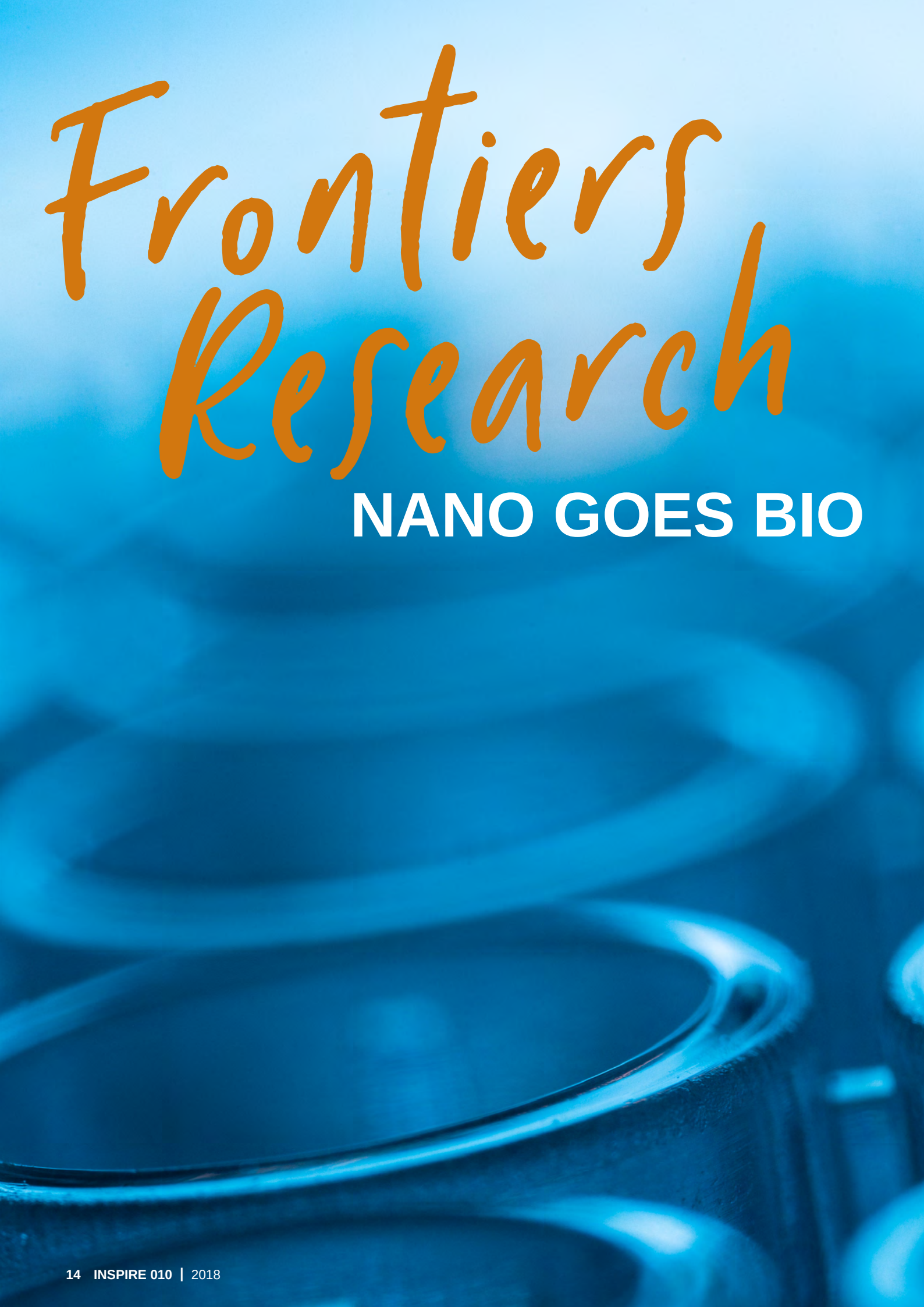
> ***"This research, using human tissue, wasn't happening 10 years ago, but technological advancements in vascular biology and bioengineering mean that it is now moving in leaps and bounds."***

The promise of genetically identical replacement body parts may not just be the stuff of science fiction and the way is being paved by Geraldine and her team.

Authors: Associate Professor Geraldine Mitchell is the Head of SVI's O'Brien Institute Department's Vascular Biology Unit.
Dr Kiryu Yap is a PhD student at SVI, and a Surgical Fellow at St Vincent's Hospital, Melbourne.

Frontiers Research

NANO GOES BIO



DESIGNED DRUGS AND TAILORED PROTEIN PARTICLES

Frontiers Research leading to the provision of cutting-edge targeted nanotechnology that can deliver drugs and imaging tracers with high precision and less adverse effects.

The emerging field of nanomedicine holds great potential for new forms of precision disease treatment.

"The main advantage of nanomedicine is that nanoparticles can load a lot of drug and deliver it to the tissue of interest, rather than randomly distributing it throughout the body quite as with current treatments," says Associate Professor Hagemeyer, Head of the Nanobiotechnology Laboratory at Monash University. "So you can reduce the off-target or side effects."

However, in order to reach their intended target, nanoparticles need to fly under the radar of the immune system, which would otherwise identify them as foreign and destroy them. Typically, low-fouling polymers such as polyethylene-glycol (PEG) are used to shield the particles from the immune system but because the field is so young, the possible side-effects of sending these tiny coated nanostructures into the human body are still unknown.

There are increasing concerns about their safety as the body cannot degrade most polymeric nanoparticle structures. Thus, new particle formulations combining stealth and biocompatible features are required to advance this field. The team at Monash University has developed a low-fouling particle platform with superior hydrophilic characteristics provided by the amino acid repeat proline, alanine, and serine (PAS) crosslinked into particles with lysine (K) and polyglutamic acid (E). The so-called PASKE protein particles are completely degraded after 24 hours as the cells recycle and re-use the amino acids they are made from.

MAJOR ISSUES WITH CURRENT NANOPARTICLE FORMULATIONS

Nanoparticles are approximately the size of cellular structures and are therefore easily recognised in vivo as pathogens. They are rapidly covered by proteins once in the bloodstream, forming a protein corona, which further promotes their recognition by the immune system. To overcome this challenge, the field has developed "stealth" coatings to prevent protein absorption and clearance. This is typically achieved with highly hydrophilic and neutral polymers that reduce the interactions with the charged surfaces of biomolecules.

The gold standard in the field is the Food and Drug Administration (FDA) approved polymer PEG that has been successfully used to improve the bioavailability of various nanomaterials. However, the administration of PEGylated compounds raises several concerns such as those about adverse immunological responses, oxidative damage and accumulation of these non-biodegradable polymers in lysosomes causing a disruption of normal cell functions.

> ***"Previous research had shown that the plastic-like particles formed deposits in the kidneys of mice repeatedly exposed to them so they appear not to break down in the body," Associate Professor Hagemeyer says.***

Also concerning is that the fact that the adaptive immune system can generate anti-PEG immunoglobulin M that detect and eliminate eliminates PEGylated materials upon subsequent injections.

The limitations outlined have driven the quest to discover alternative low-fouling materials that prevent the build-up of non-degradable materials in the body. Protein-based materials are of specific interest because they are biodegradable and lysosomal proteases can easily degrade the particles into small amino acid oligomers which can subsequently be metabolised and recycled by physiological pathways.

THE SOLUTION: GO BIO – TAILORED NANOPARTICLES THAT ARE COMPOSED SOLELY OF PROTEIN MATERIAL

One of the most interesting combinations comprises repeats of the three amino acids Proline (P), Alanine (A) and Serine (S) that result in the biosynthesis of long hydrophilic and highly soluble polypeptide chains strikingly similar to PEG. The Monash team set out to generate nanoparticles out of PAS and crosslinked the building block via lysine (K) and polyglutamic acid (E) to generate PASKE particles. For their studies, they also used PEG particles for comparison as well as particles made from the natural serum protein albumin.

As expected, the PEG particles showed very low cell uptake when exposed to cells of the phagocytic system. The PASKE particles show a similar favourable association profile to the PEG particles while surprisingly, the particles made from the natural blood component albumin associated strongly with the cells.

Next, the researchers tested the particles in vivo in mice and also showed that the albumin particles were cleared rapidly from the circulation, with less than 10% of the injected doses present in the blood only a few minutes after injection. The PASKE particles, however, exhibited prolonged blood clearance times and were slowly taken up by spleen macrophages and Kupffer cells of the liver.

On a cellular level, using cutting-edge imaging flow cytometry analysis, the team showed that the phagocytosed PASKE particles were preferentially localised in the lysosomes and showed signs of degradation in vitro and in vivo. “We showed that PASKE particles fly under the radar of the immune system and circulate in the blood for an extended period of time. More importantly, once they enter the tissue our protein particles were completely gone after 24 hours,” Associate Prof Hagemeyer said.

> ***“The cells in the body had the ability to digest the particle and basically recycle and re-use the amino acids they are made from.”***

The work is of importance for the clinical translation of nanomaterials as it demonstrates optimised clearance of the injected materials from the body thereby avoiding unspecific accumulation and potential long-term toxicity. The recent FDA guidelines for the assessment of nanomaterials toxicity specifically highlights the concerns regarding the risk related to the chronic accumulation of non-biodegradable components. “This is one of the first reports in which tailored protein particles have been used as a true alternative to classic polymers,” Associate Professor Hagemeyer points out.

"One of the other advantages of our platform is that you can design it very precisely by changing the amino acid sequence.”

> ***“This could mean that treatments could be personalised better to individual patients by loading several different molecules in the particle specifically suited to the patient’s disease.***

This work is a step towards overcoming the biocompatibility and biodegradability issues seen with current nanoparticle formulations. The PASKE particles largely preserve the low-fouling features of PEG that provide good blood clearance kinetics and ensure full biodegradability within 24 hours, which is not achievable with PEG particles.

This project was a collaboration between the Australian Centre for Blood Diseases (ACBD) and University of Melbourne scientists led by world-renowned material scientist Professor Frank Caruso and was published recently in the leading nanotechnology journal ACS Nano. Bonnard, Thomas; Jayapadman, Anand; Putri, Jasmine; Cui, Jiwei; Ju, Yi; Carmichael, Catherine; Angelovich, Thomas; Cody, Stephen; French, Shauna; Pascaud, Karline; Pearce, Hannah; Jagdale, Shweta; Caruso, Frank; Hagemeyer, Christoph. *Low Fouling and Biodegradable Protein-Based Particles for Thrombus Imaging.*

The first author Dr Thomas Bonnard received funding from the People Programme (Marie Curie Actions) of the European Union to conduct this work in Australia. The work was also supported by the National Health and Medical Research Council, and the Australian Research Council.

Authors: Associate Professor Christoph Hagemeyer, a chemist by training, is Head of the NanoBiotechnology Laboratory at the Australian Centre for Blood Diseases (Monash University) and also an adjunct Associate Professor of Nanotechnology at RMIT.

RESEARCHERS BUILD NANOROBOTS THAT STOP CANCER GROWTH

QIMR Berghofer's Professor Greg Anderson is helping to drive a new scientific frontier with microscopic nanorobots demonstrating what may be the future of drug delivery

Scientists are tackling cancer on a new frontier, using tiny nanorobots made of DNA and protein to kill tumour cells.

The study was led by researchers at the National Centre for Nanoscience and Technology in Beijing and the University of Chinese Academy of Sciences and involved Professor Greg Anderson, head of the Chronic Disorders Research Program at QIMR Berghofer Medical Research Institute.

The team found that the targeted nanorobots reduced the growth of breast cancer and melanoma in mice.

"It shows just what is possible with contemporary biomedical technology and hints at what may be the future of intelligent drug delivery," Professor Anderson said.

The nanorobots were made using a technique called "DNA origami", where specially constructed sheets of DNA were folded up and bound together to form a tube.

TARGETING TUMOURS WITH BLOOD CLOTS

The group embedded the blood-clotting agent thrombin within the lumen of the tubular nanorobots.

"Thrombin is a naturally-occurring protein that causes blood clots to form," Professor Anderson said.

"This ability can be harnessed to kill tumour cells by developing a system where the thrombin only causes clots in the blood vessels that are feeding the tumour, and not elsewhere in the body.

When that happens, the tumour cells no longer receive essential nutrients and they die.

The nanorobots were designed so that thrombin was released only after it was "unlocked" by a particular protein found within the blood vessels of tumours.

"The nanorobot keeps the clotting agent disguised until it reaches the place where we want it to act. In this case, that's the tumour," he said.

"That's why this is such a clever delivery system."

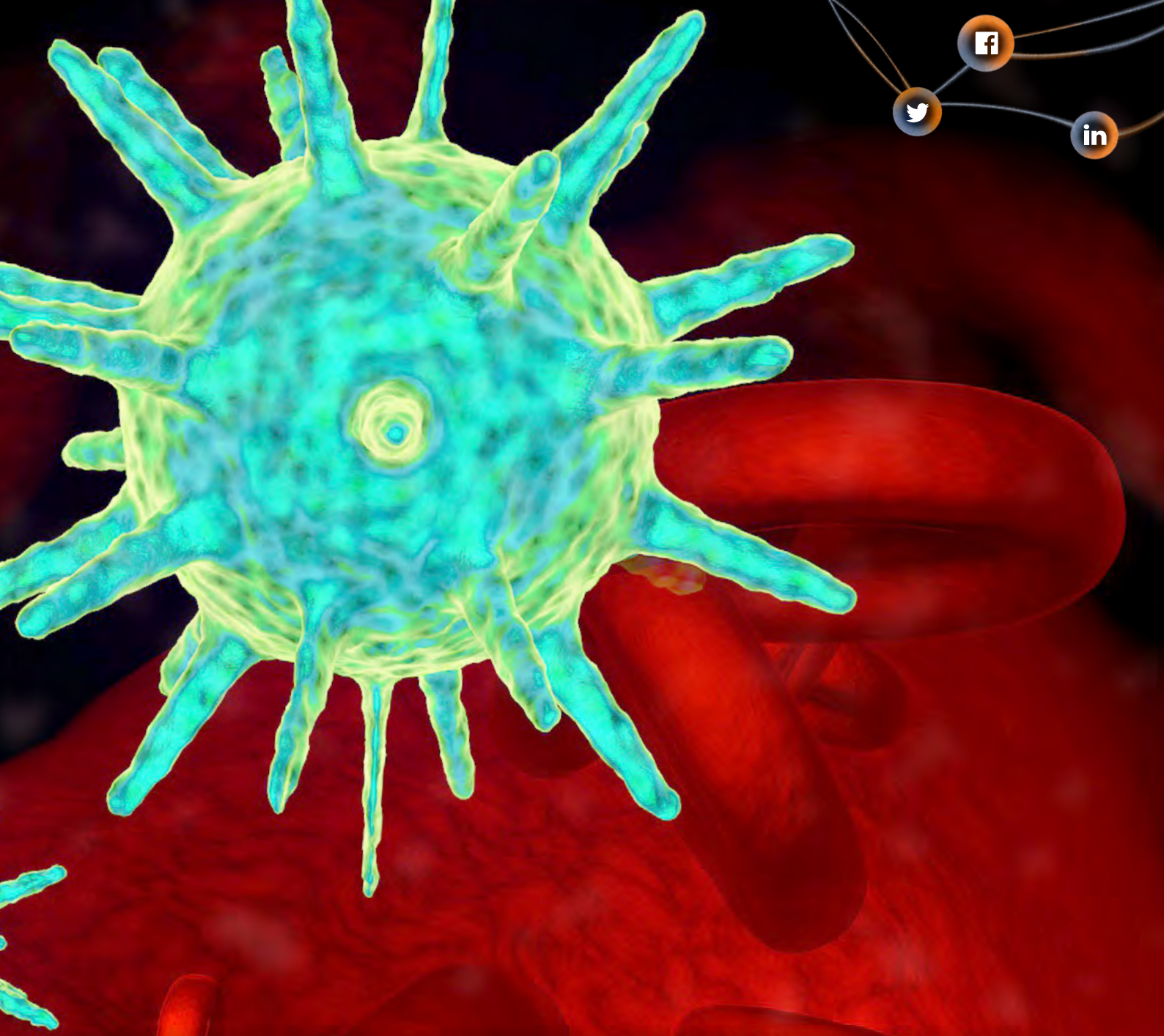
NOVEL APPROACH

Professor Anderson said it was a highly-innovative example of nanotechnology being used to target tumours.

"This approach is novel in the way the team has combined a number of existing but different elements of nanotechnology to enable the controlled and targeted delivery of the blood-clotting agent," he said.

"Methods like this could potentially be used to deliver a wide range of drugs, and even multiple drugs at once.

"There are really limitless combinations of technologies and drugs that could be tried. The applications of the technology are certainly not restricted to tumour development either."



MORE TO BE DONE BEFORE TESTS IN HUMANS

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There are really limitless combinations of technologies and drugs that could be tried.

The applications of the technology are certainly not restricted to tumour development either."

Professor Guangjun Nie, from the National Centre for Nanoscience and Technology in Beijing who led the work, agreed the study was an exciting first step.

"Through accurately controlling the dose of nanorobots, we should be able to improve their tumour-targeting efficacy while minimising side effects," he said.

"We have moved to the pre-clinical trial stage now and we hope to finish all pre-clinical studies over the next few years."

This research means that it may now be possible to deliver cytotoxic drugs in a very controlled way directly to the site of a tumour. This gives patients a broader range of options for the treatment of their tumours and could potentially become the standard way of delivering drugs to tumour in the future. The technology could be equally applied to any health problem where the delivery of a drug to a particular tissue is required.

Our research shows what it is possible to achieve by combining innovative thinking with contemporary nanotechnology approaches. Improved tumour therapies will have a clear benefit for the health of Australians as cancer remains a leading cause of death both nationally and globally.

Author: Professor Greg Anderson BSc, MSc, PhD
is coordinator of the Chronic Disorders Program at QIMR Berghofer Medical Research Institute in Brisbane, Australia.

MEDICA
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CANCE

Gathering the world's first data to evaluate safety and tolerability of intravenously administers, genetically-modified bacteriophages – a novel approach to accessing the cell shifting current research and clinical paradigms.

Researchers at Monash University are preparing for a clinical trial using genetically modified bacteriophages (protein nanobots) which they describe as the Swiss army knife of nanomedicine.

ANCIENT ORIGINS

Embedded in many faiths and cultures for millennia are myths about sacred waters with the power to heal. In the Hindu faith, followers drink and bath in revered waters from the Ganges River in the hope to have their sins washed away. However, over a century ago it was discovered that the river water contains bacteriophages that are extremely effective at killing Vibrio cholerae, the bacterium responsible for cholera, partly accounting for the water's healing and preservation properties.

Bacteriophages are naturally occurring viruses that target bacteria but not humans and so have been used to successfully treat diseases in humans caused by bacteria. It has been suggested that bacteriophages are slowly released from the Himalayan permafrost at the origin of the Ganges held captive in frozen seawater since India collided with Eurasia approximately 45 million years ago.If water containing bacteriophages have had healing properties for eons, then wouldn't it be amazing if we could apply these properties to other areas of health and chronic disease – even cancer!

We know that the likelihood of developing cancer increases with aging and most cancer deaths are due to the cancer spreading throughout the body. Unfortunately, there are many cancers that are difficult to treat because they have already spread by the time of diagnosis. This means that difficult to treat cancers will contribute significantly to the disease burden of cancer in Australia which is forecast to cost the health system more than $8 billion per annum by 2030; however, there are some promising solutions.

We are fortunate to be living during a period of innumerable biomedical advances. Nanomedicine is one advancing field and within it there are many innovative technologies that will improve health during our lifetimes. When the term "nanomedicine" was originally coined, many envisaged tiny robots flowing in our blood that could selectively kill cancer cells and even repair our tissue. One technology with these potential abilities currently being evaluated by researchers from Monash University is genetically modified bacteriophages (GMBs).

ABUNDANT, SAFE AND USEFUL

Naturally occurring bacteriophages, "wild-type phages" mainly found in saltwater, are the most abundant "organism" on the planet estimated to have a population of over 10^{31} and have mind bogglingly diverse genetic compositions. It is this diversity and adaptability that makes the phage ideal for delivering therapeutics.

The most promising aspect of GMB technology is due to the phages' evolution and innate design as a protein particle with the capacity to deliver cargo. After a century of research, phages are not considered pathogens for eukaryotic cells (that is they do not harm humans) and so are essentially inert within a sterile environment such as the bloodstream. This property ranks GMBs very highly both as the choice of delivery vectors for therapeutic products and for a myriad of other systemically administered applications.

> ***As a comprehensively studied genetic structure, the bacteriophage, with its malleable genome, could prove to be the gift that keeps on giving within the realm of nanomedicine.***

Extensive research into bacteriophage genetic structure and their functions has built the foundation for genetic modification and genetic engineering, as depicted by Nobrega et al. and shown in Figure 2. Phage display libraries are well-known as the manufacturing powerhouse of biologic drug discovery, namely in immunotherapy and protein engineering, however, phages are really the Swiss army knife of evolution and their applications are much more diverse.

WHY NOW AND WHY AUSTRALIA?

The discovery and application of CRISPR/Cas-9, an enzymatic gene editing tool, is proving to be the fulcrum of technological advance and could be compared to man's discovery of fire. However, even before the advent of the CRISPR/Cas-9 system, plasmids played a huge role in the editing of genes. With intense development spanning more than 20 years, a product (Metavec) has

been developed using plasmid technology to genetically modify a lambda bacteriophage so that it can both target metastatic cancer cells and deliver a gene that can signal suicide in numerous cancer cell line types.

Metavec, a saltwater buffer containing the GMB nanobots, was engineered in New Zealand by Dr Armand Sinclair and although brilliant in development, the technology has not been able to progress there due to clashes between environmental and gene technology policies. One of the many benefits of conducting GMB research in Australia is that we classify the GMB as a product from another organism. This is because GMBs are manufactured from genetically modified bacteria and those bacteria do not leave the manufacturing laboratory.

CLINICAL TRIAL

The technology meets current Australian regulatory safety guidelines for use in humans making the clinical trial a world first. Preliminary data was presented recently, at the Global Summit on Oncology & Cancer, in Singapore, and reported at least one patient with end-stage ovarian cancer was administered Metavec without any significant adverse event.

Dr Keith Potent from the Australian Centre for Blood Diseases' NanoBiotechnology Laboratory lead by Associate Professor Christoph Hagemeyer, said "We must now capitalise on the promising pilot data to ascertain whether Metavec could be a new therapy in combating cancer and improve the lives of millions of patients. The phase I clinical trial aims to prove that Metavec is safe and well-tolerated in humans and we also hope to gather preliminary data to show that the nanobots do what they were designed for –kill (apoptose) cancer that has spread. Not only will this be a landmark clinical trial, it will also pave the way for numerous other phage-based technologies that have applications in areas such as multi-drug resistance infections, stem cell therapy, and rare diseases."

> ***"There are more than 40 biotechnology companies around the world that produce bacteriophage technologies; 18 of them from the United States of America, none of which are in the Southern hemisphere.***

With Australia's strong biotechnology industry, we are well placed to build a GMB industry, putting us on the brink of a revolution that promises to yield technologies limited only by imagination. Many Australian researchers, academics, and clinicians are taking an interest in this fascinating field. At the recent Australian Society of Microbiology Annual Scientific Meeting in Brisbane, the first meeting of the Bacteriophage Special Interest Group was held comprising experts who are keen to pursue clinical developments within the realm of bacteriophage technologies.

WHERE TO FROM HERE?

Australia's high regulatory standards and our Research and Development Tax Incentive create an excellent environment for us to lead the GMB field and ensure that high standards of clinical research can be maintained when collaborations with other countries are developed in the future.
We should direct much more funding towards research and development of GMB applications. If we seed and support this field, then we could develop targeted therapies for cancer, therapies for:

- **infections** (including multi-drug resistant infections, microbiome dysbiosis, and even stubborn infections due to biofilms),
- **rare genetic diseases;** and even to deliver crucial signals to stimulate stem cells for tissue regeneration.

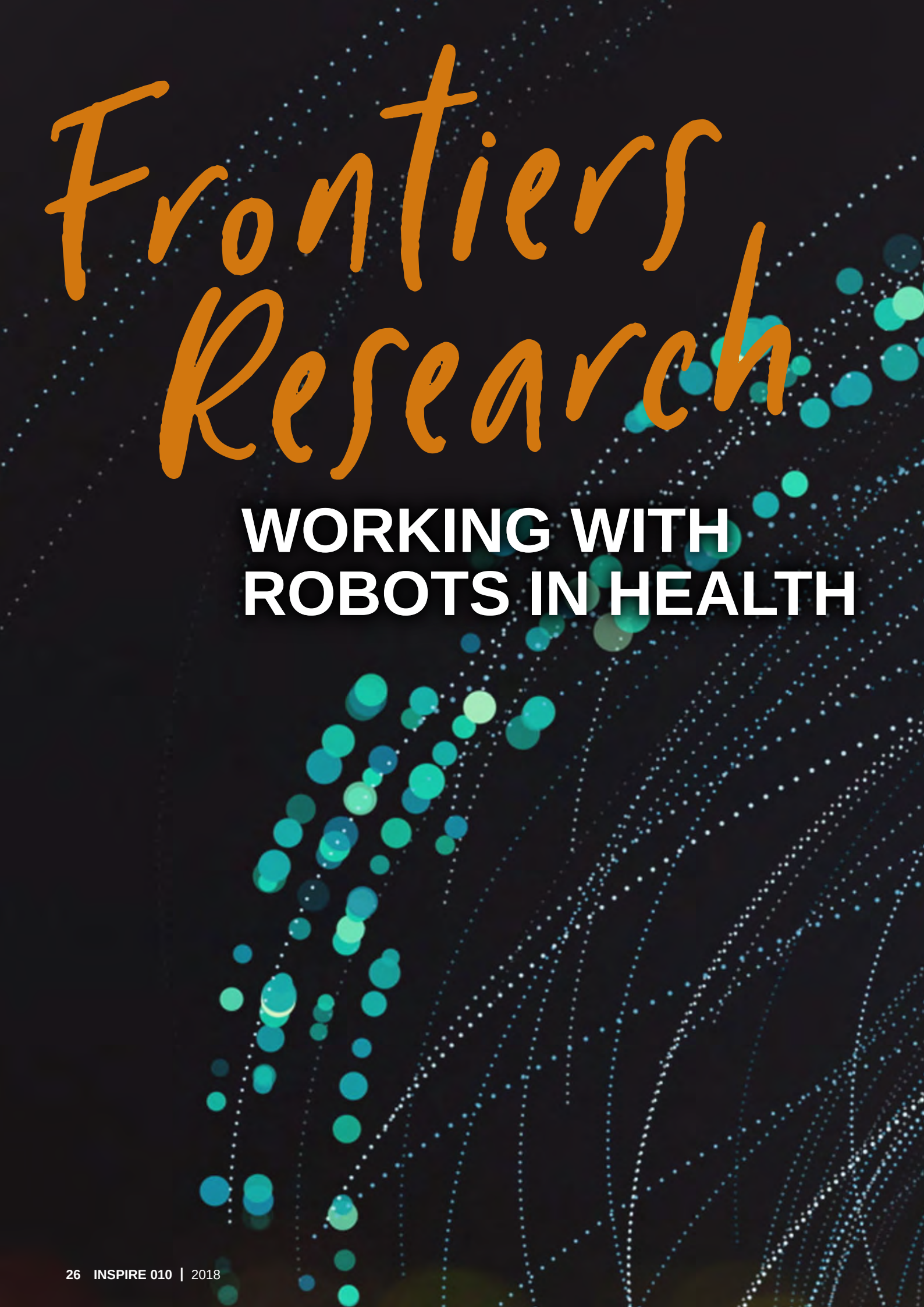
And this isn't even scratching the surface. Supporting the development of these technologies will make Australia an engine of phenomenal biomedical and economic output, benefit millions of patients and become an important industry. Nanobots in water with the power to heal – it is not a myth, it is science and it's on our doorstep!

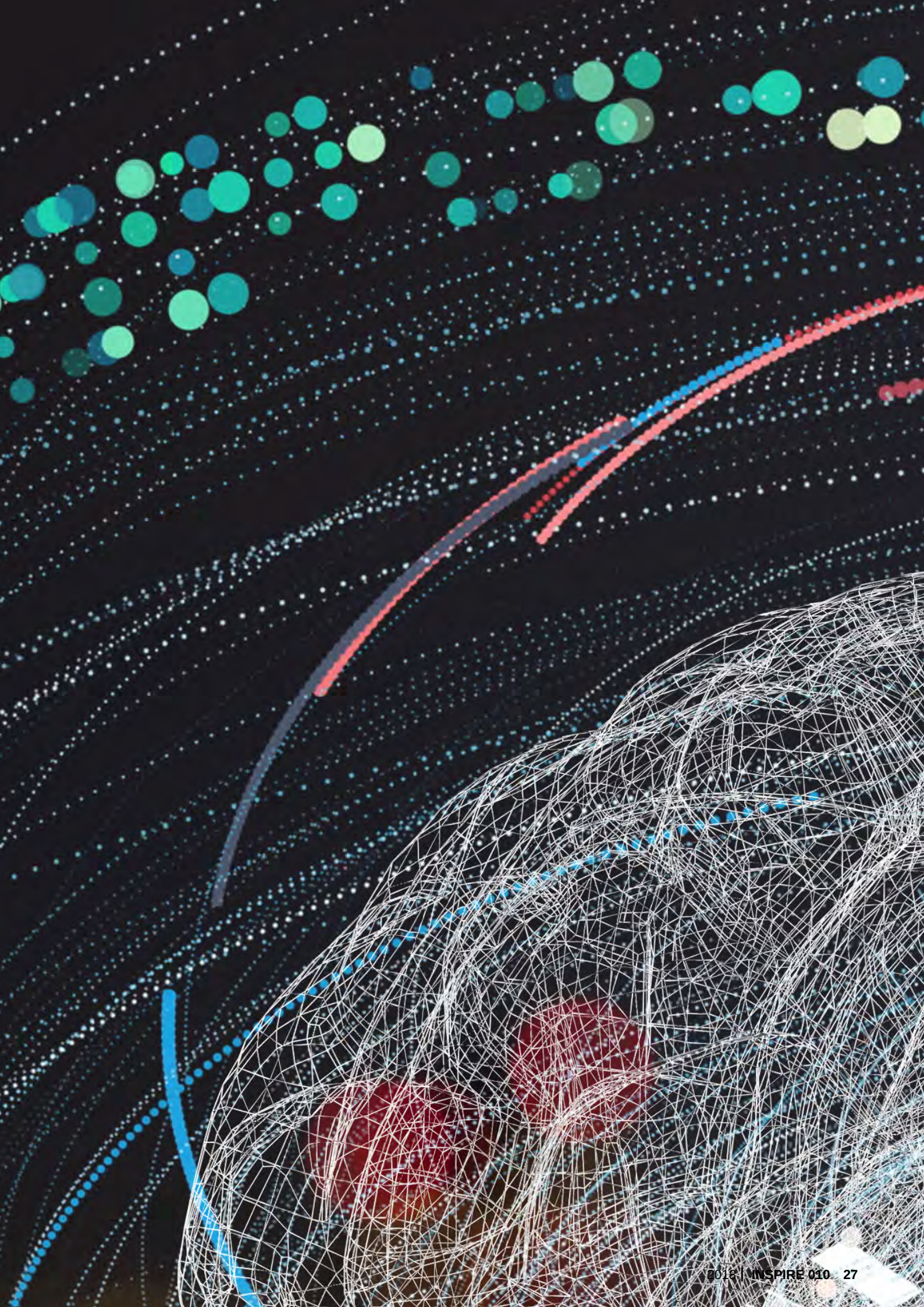
There is currently a global race to develop genetically engineered technologies like MetaVec and our clinical research, demonstrating safety and tolerability, will not only prime the Australian gene and therapeutic regulators, but it will also be the vanguard for other technologies to follow. With Australia leading the translation of gene technologies, this will cause an influx of international companies wanting to develop their products and run more clinical trials in Australia and create an economic powerhouse of jobs involving the gene technology outputs.

Authors: Dr Keith Potent MBBS(Hons) BSc BMath AMA(Q) is a Lecturer with Griffith University's Clinical Trials Unit, School of Pharmacy. He is also a PhD (Translational medicine) candidate at Monash University.

Frontiers Research

WORKING WITH ROBOTS IN HEALTH





WILL A ROB

OT

REPLACE YOUR NEUROLOGIST?

Research leveraging the power of machine learning algorithms to automatically identify epileptic spikes from a patient's EEG (a record of the tiny electrical impulses produced by the brain's activity)

THE CHALLENGE

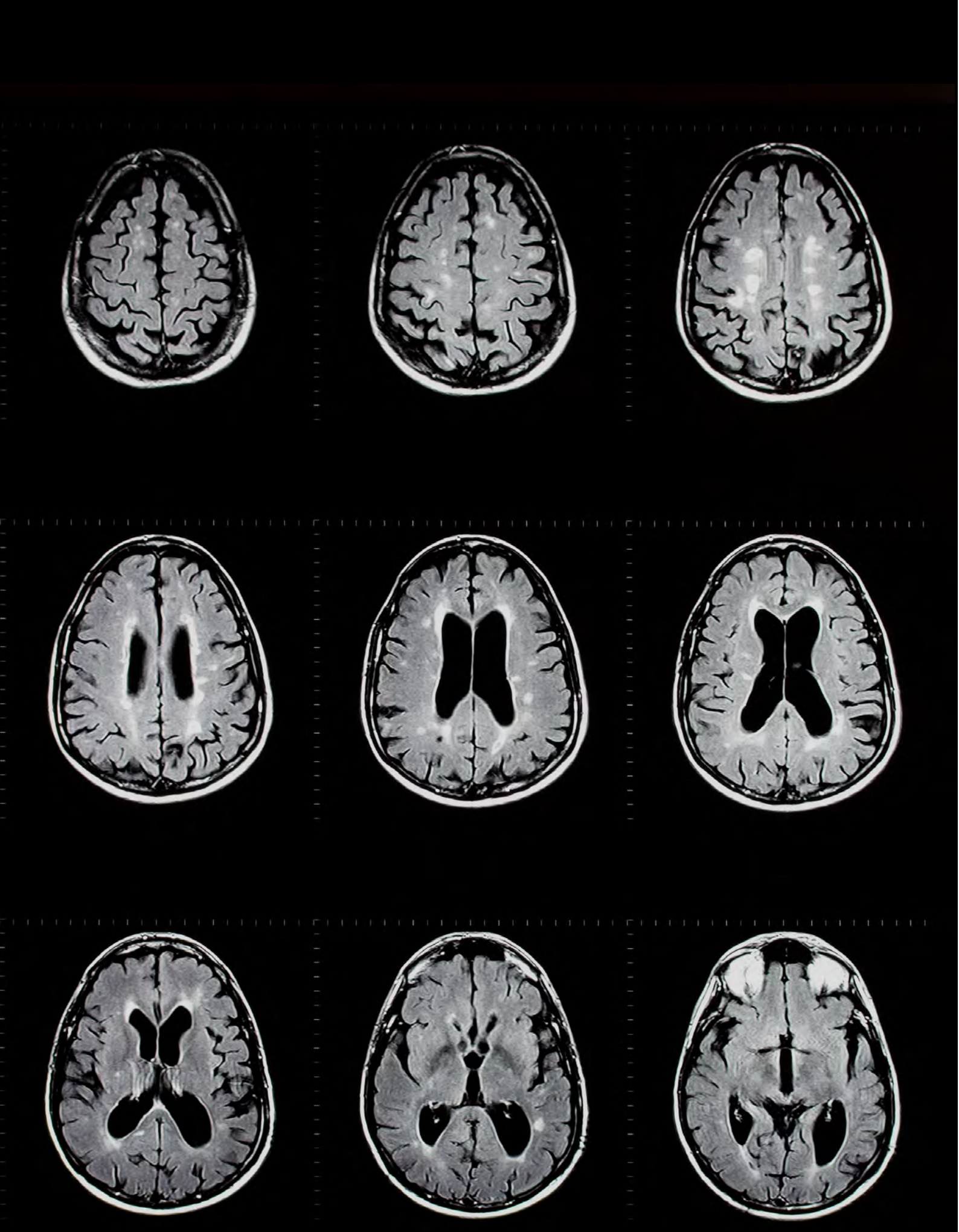
Refractory epilepsy, also called drug-resistant epilepsy, is a term used to describe a situation where patient's seizures won't resolve after trials of different anti-epileptic medications.

Obviously, this outcome is extremely disappointing and frustrating for patients, their families and their treating neurologists. Adding to the frustration, there is often no clear suggestion for the next stage of treatment.

In these patients, the best chance of a cure is achieved by carefully targeted surgery, where only the 'abnormal' brain areas that drive the epileptic seizures are removed. Importantly the brain regions responsible for speech, vision, movement, memory and other vital day-to-day functions must be spared.

To locate the seizure origin, patients may undergo a simultaneous EEG-fMRI scan. EEG shows when an abnormal electrical activity (so-called spike) happens in the brain and fMRI shows where the activity occurs in the brain. The fMRI scans are acquired on the Siemens 3T Skyra scanner at the Florey node of the National Imaging Facility (NIF).

EEG-fMRI recording is usually limited to one hour and requires the patient to lie motionless inside the MRI scanner. The neurological team then goes through the EEG recording 'by hand' to find possible spikes, very short EEG changes which typically last less than one second. The marked spikes are finally combined with simultaneous fMRI through a complicated mathematical procedure to provide a map of epileptic brain regions.
EEG-fMRI analysis is not widely used in epilepsy clinics,



mainly because of its technical complexity and its challenging EEG markup stage. Usually processing of a one-hour EEG recording takes several hours of a specialist at its quickest and can be subjective and costly. Obviously, a better solution is required.

A FASTER AND MORE ACCURATE APPROACH

This is where Dr. Amir Omidvarnia, Professor Graeme Jackson and a talented PhD candidate, Magdalena Kowalczyk, come in. They are *developing an EEG-fMRI analysis software package* which enables non-technical users to automatically detect most EEG spikes and perform EEG-fMRI analysis after a few clicks.

As soon as a patient's scan is complete, they use artificial intelligence and machine learning for any 10-15 spikes 'pointed out' by the human in any study, and the computer does the rest – crunching EEG-fMRI data and making brain maps in just minutes.

The team has analysed data from 16 refractory epilepsy patients, and in 11 of these, the software package has led to more extensive epileptogenic brain networks in contrast to the networks obtained by human mark-up. The newly revealed brain regions are meaningful and in line with the other types of clinical data from patients.

"Even better – it turns out that when comparing the computer's performance to the current 'gold-standard' of manually marked recordings by a neurologist, the software performs not only hundreds of times faster but can sometimes identify additional problematic parts of the brain from the data.

So, will the EEG-fMRI software package replace your team of neurologists any time soon? Amir says the answer is a resounding 'NO' – but we will work closely with it.

"EEG-fMRI analysis and automatic spike detection results will not be the only piece of information in the decision-making process of epilepsy surgical planning" says Amir. "The results still need to be considered in the context of other clinical information like PET, SPECT, anatomical MRI and pharmacological responses."

The Florey and Austin Health epilepsy teams meet every Friday to discuss all these results. "Our automated analysis will speed this process up significantly, helping the neurologists to concentrate on the best outcome for every patient."

OTHER BENEFITS

Dr John Archer, a neurologist with Austin Health and the University of Melbourne, who was not involved in the study, sees additional advantages of the work.

"By speeding up the laborious and time-intensive task of scoring a patient's inter-seizure EEG data we will be able to better measure a patient's response to anti-epileptic medication, without having to wait for them to experience a seizure.

In that way, we can;

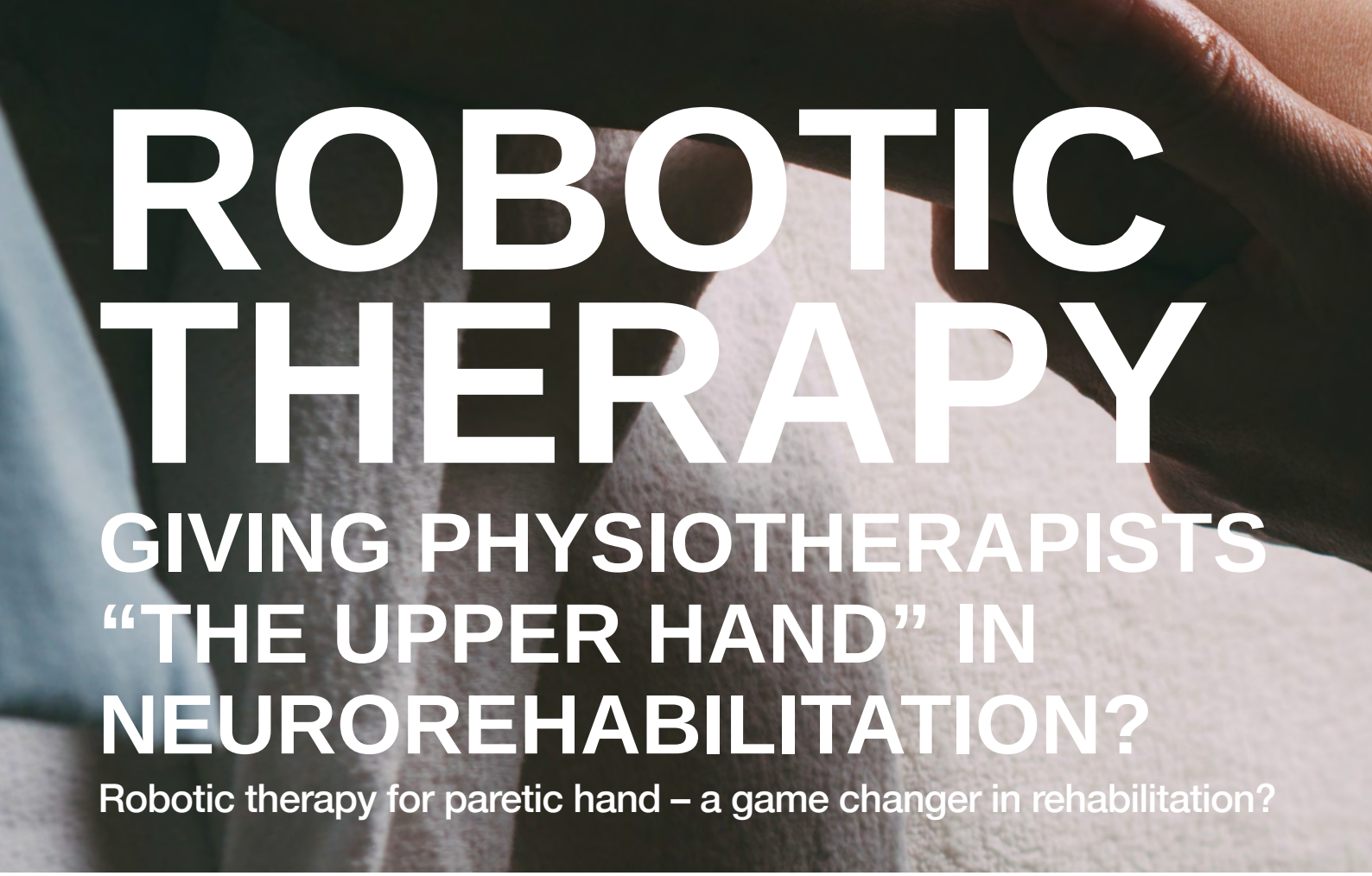
- titrate medications to find the optimal dose
- make faster decisions about switching to alternative medications, or
- decide to surgically remove the tissue.

This automated spike detection algorithm could also mean more patients have access to the simultaneous EEG-fMRI technique. At the moment, this technique is not used as widely in the clinic as it might be because of the time needed for mark-up and analysis, but it's an important and precise tool in targeting the often-tiny brain regions giving rise to focal epileptic seizures.

"Any research that helps us give patients more options, and reduces what we all know can be a frustrating waiting period for an accurate diagnosis can only be a good thing."

Amir and his colleagues will make the software freely available for the rest of the epilepsy research community, in order to facilitate its rapid validation and more widespread use, in yet another example of Australian research having a global impact.

Authors: Dr Tom Keeble. Tom completed his PhD and postdoctoral work in developmental neurobiology. Tom now translates specialist neuroscience jargon into plain English.



ROBOTIC THERAPY

GIVING PHYSIOTHERAPISTS "THE UPPER HAND" IN NEUROREHABILITATION?

Robotic therapy for paretic hand – a game changer in rehabilitation?

The hand plays a unique and critical role in the many everyday activities required to live independently such as feeding, grooming, dressing, showering, transfers and bed mobility. Hand paresis (weakness) is a common consequence following damage or injury to the upper motor neuron such as stroke and cervical spinal cord injury (SCI). In fact, two thirds of stroke survivors and over 50% of patients with SCI experience severe motor impairment of the hand which causes significant challenges or even an inability to perform daily activities [1, 2]. Without appropriate rehabilitation, functional impairment can persist or worsen over time, leading to increased dependence and burden on caregivers and the community. As such, hand paresis is considered a major source of long-term disability among stroke survivors and adults with tetraplegia.

> ***Therefore, successful rehabilitation of the hand is of paramount importance and is highly linked to improve quality of life and functional independence.***

Motor recovery of the hand after stroke and SCI is the slowest and most challenging and often remains unsatisfactory despite intensive rehabilitation training. As such, research in neurorehabilitation continues to investigate treatment alternatives to improve motor recovery of the hand. Unfortunately, this effort is hindered by our incomplete understanding of the precise neurobiological mechanisms that underlie motor recovery. **The increasing global burden of stroke – and SCI-related disability has led to the pursuit of robotic therapy devices to improve effectiveness of current rehabilitation practice.** Compared to conventional physical therapy approach, robot-assisted therapy has several distinct advantages:

1. robotic therapy can achieve a higher dosage of repetitive task practice in the same amount of time in a consistent, reproducible manner.
2. robotic therapy is labour-efficient as patients can perform robotic-aided exercises with minimal supervision and is suitable for patients with profound weakness or complete paralysis, who may not be able to perform conventional exercises without manual assistance.
3. Lastly, majority of robotic devices incorporate game-based training activities, with visual and auditory feedback to engage and motivate patients during the rehabilitation process, whilst keeping track of training intensity, volume and adherence.

Robotic therapy can be precisely controlled and standardised making it an attractive intervention for studying functional recovery after stroke and SCI. High-intensity repetitive practice, task specificity, patient engagement and feedback are all well-documented ingredients necessary to promote neural re-organisation or "neural plasticity" in the brain which is thought to play a critical role in motor recovery after stroke and SCI [1, 3].

> ***Not surprisingly, robotic devices have been progressively integrated in neurorehabilitation programs for stroke survivors and incomplete tetraplegics with the intend to drive neural plasticity."***

However, the nature of neural plasticity induced by robotic training remains unclear and the underlying neurobiological mechanisms mediating motor recovery post stroke and SCI remain to be elucidated.
Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological tool commonly used in clinical neurology to study the excitability or efficacy of important motor pathways and neural circuits in the brain. Previous studies using TMS has demonstrated that both the lesioned and non-lesioned side of the brain undergo significant neural re-organisation within days of a stroke [4]. Furthermore, motor recovery is associated with functional re-organisation in both the lesioned and non-lesioned hemispheres [4].

Studies in both animal and human SCI have also demonstrated extensive re-organisation in remote cortical and subcortical structures. However, it is currently unclear whether these changes are necessary (i.e., adaptive) or an obstacle (i.e., maladaptive) to achieve maximum functional recovery. Dr Michael Lee and Dr Alana McCambridge from the Discipline of Physiotherapy at the University of Technology Sydney (UTS) are currently conducting clinical research using TMS to better understand the neurophysiological mechanisms that underlie recovery of hand function post stroke and cervical SCI.
In recent years, a number of upper limb robotic devices have been developed specifically for post-stroke rehabilitation. However, the majority only focus on movement about a specific joint or segment of the arm. Considering the fact that many activities of daily living require precise control and coordination of multiple upper limb segments, robotic therapy that promotes movements

across multiple joints in a functional way may be more beneficial. Tyromotion® (Tyromotion® GmbH, Graz Austria) have developed a suite of robotic therapy devices capable of training the entire upper limb (shoulder, elbow, wrist, hand and fingers) using separate devices to target each body segment.
The Tyromotion® system incorporates computer gaming and virtual reality technologies that provide multiple real-time sensory feedback to engage the patients in their rehabilitation. Neuroscientists Dr Michael Lee and Dr Alana McCambridge at UTS Physiotherapy is currently conducting research using TMS to better understand the nature neural plasticity associated with Tyromotion® robotic training.

Currently, very few robotic devices have been designed specifically for patients with paretic hand and there is very limited data on the feasibility and efficacy of robotic hand rehabilitation in stroke survivors and tetraplegics.

“The Amadeo robotic hand system by Tyromotion® is the only device that provides robot-assisted exercises for the finger flexors and extensors.

Amadeo can be categorised as an end-effector external manipulator and is capable of performing passive, active-assisted and active-resisted training targeting the fingers and thumb.
Amadeo hand therapy is delivered via interactive computerised games emphasizing finger/thumb flexion and extension movements with real-time visual feedback of performance. Several pilot studies have established that Amadeo is a safe and feasible therapy for hand paresis post stroke [5, 6], but there are currently no studies which have investigated whether Amadeo is also applicable for people with cervical SCI. Research of this kind will make a meaningful contribution to our current understanding of the underlying neurobiological mechanisms mediating motor recovery after SCI and clinically effective robotic rehabilitation protocols.

This research is at the frontier of translational brain science. Our Clinical Neurostimulation Laboratory at UTS is the only tertiary institution in the southern hemisphere equipped with state-of-the-art robotic therapy devices (Tyromotion® GmbH, Graz Austria) and sophisticated transcranial magnetic brain stimulation system.
This new knowledge will consolidate the need to conduct further randomised controlled trials to properly evaluate the clinical effects of robotic therapy in stroke and SCI survivors. It has the potential to transform current neurorehabilitation practice and reduce the global burden of stroke- and spinal cord injury- related disability.
If we can demonstrate the clinical benefits of robotic therapy with our research, we will be in an ideal position to influence the Australia’s health system to make robotic devices more readily available. As such, our research has the potential to revolutionise rehabilitation approach for patients with stroke and SCI and establish Australia as a world leader in translational neurorehabilitation research.

Author: Dr Michael Lee, Dr Alana McCambridge
Graduate School of Health, Discipline of Physiotherapy, University of Technology Sydney

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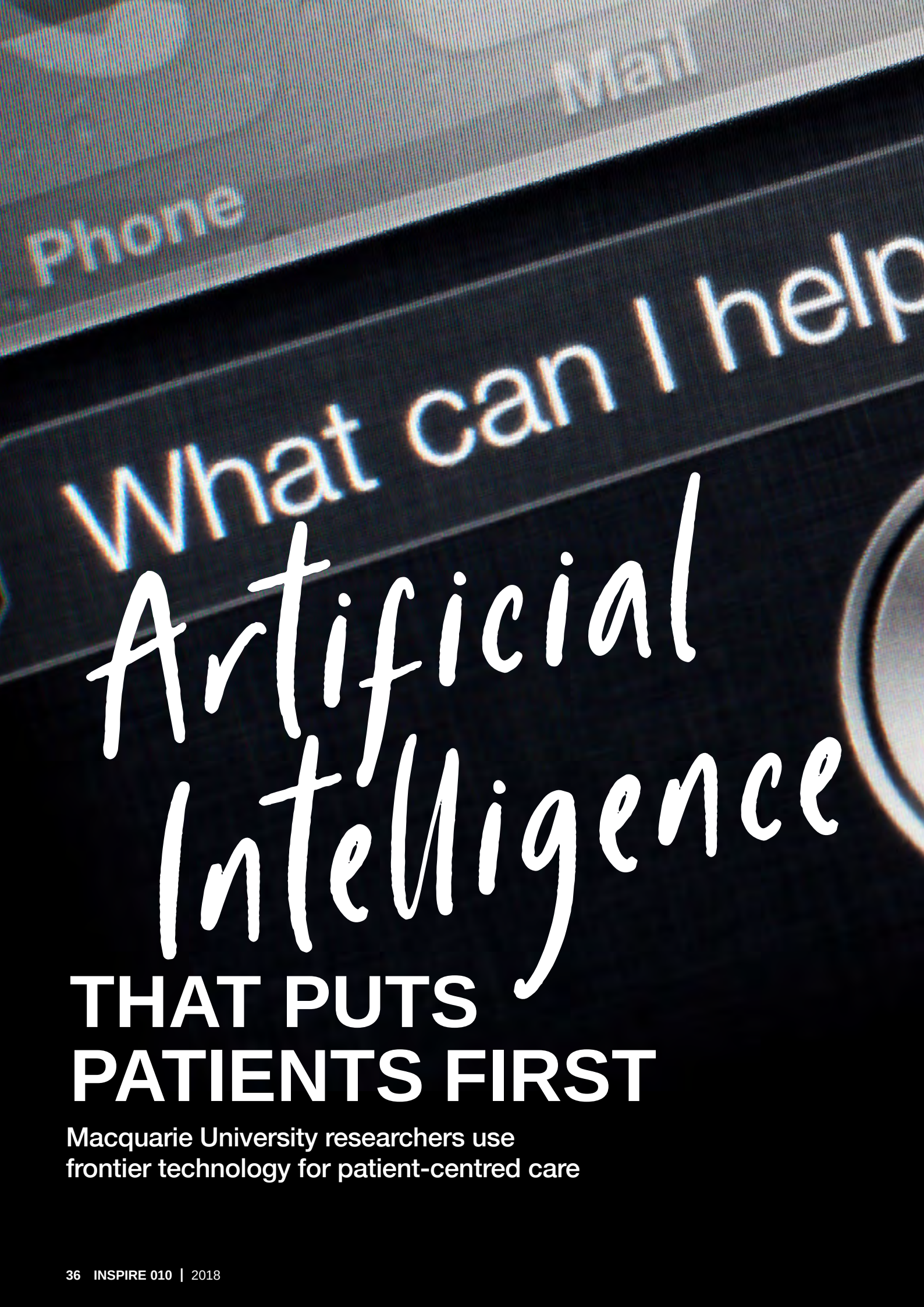


Artificial Intelligence

THAT PUTS PATIENTS FIRST

Macquarie University researchers use frontier technology for patient-centred care

Siri and Alexa. They are embedded in our modern lives. If they don't already reside with you, you probably have friends who rely on these two for everything from music selection to car navigation and online shopping. They are artificial intelligence (AI) engines that act as virtual assistants, designed to make life easier and save time.

What if we could harness that same idea and enhance it? Then introduce it to the doctor's consultation room? Remember the last time you visited a doctor or took a child or an elderly relative to an appointment? The doctor spent a lot of time typing on their keyboard. They had to look up notes, check medication history, find pathology results, read pharmaceutical guidelines, type a prescription, and finally update the notes for next time. That's a lot of time spent looking at a computer instead of looking at you.

At Macquarie University in the Centre for Health Informatics (CHI) at the Australian Institute of Heath Innovation, researchers are inventing Digital Scribe. At the heart of this endeavour in frontier technology is the desire to unlock the powerful potential of a true doctor patient relationship. Allowing the clinician to focus on the patient and providing data that will support an informed and shared decision-making process.

Artificial intelligence is a frontier technology poised to disrupt many aspects of healthcare. At the very bleeding edge of AI in healthcare research sit fundamental questions about how these technologies will transform clinical work and allow new, previously impossible, models of care.

The challenge is to think beyond data and algorithms to ask hard questions about what clinical care will look like in the next two decades. The Digital Scribe program is using AI to help reimagine how data is captured and used in the clinical interaction. To do that frontier questions are faced about the ability of machines, to understand human speech, actions, and biomedical and clinical processes.

The Digital Scribe research team includes Director of CHI and lead investigator Professor Enrico Coiera and CHI researchers Dr Baki Kocaballi, Dr Liliana Laranjo, Dr Dana Rezazadegan and Dr Juan Quiroz.


VOICE ASSISTANT

PUSHING THE FRONTIER

With digital scribe technologies, one of the foundational bottlenecks to building truly learning health systems can be solved – access to rich and high-quality data from clinical records. The clinical encounter is also reengineered to release clinical time and effort from data gathering and recording to be redirected to clinical care. Indeed, it is hard to imagine how completely different healthcare will be when the tyranny of data collection is disrupted, and a truly learning health system emerges.

A DIGITAL PARTNER

Digital Scribe is more than another manifestation of the electronic health record. This is a partner that will listen, understand, interpret and apply the information gained from a verbal exchange between the doctor and the patient. In the US, human scribes perform part of this role, sitting in the consultation room with the doctor and patient and transcribing conversations and instructions. The Digital Scribe ultimately will not only prepare notes from a consultation by capturing what is said, it will also harness the vast amount of medical intelligence that is available but underutilised, assisting clinicians to arrive at the best diagnosis and treatment plan.

Professor Enrico Coiera says: "The Digital Scribe has the potential to enhance clinical encounters and improve the quality of care, contributing to a health system that is more patient-centred."

PATIENT SAFETY

Running alongside CHI's leading-edge technology is a dedication to patient safety. As with all clinical inventions, Digital Scribe will have governance issues to address. There will be new patient safety issues, the potential for automation bias, the temptation to create more detailed records, and a change in the nature of the record with medico-legal ramifications.

CHI has a team of clinicians, software engineers, interaction designers, and machine learning and natural language processing experts working on developing the first prototype of the Digital Scribe. The guidance of patient safety experts is also essential to the process.

Dr Laranjo explains: "We are working in close collaboration with primary care clinicians and conducting field observations to assist in the design and development of this exciting technology."

While some people may not immediately feel comfortable with the idea of a technology that listens and records their conversation, strict protections and parameters will be put in place to ensure data remains confidential.

Dr Kocaballi says:

> ***"It's easy to forget that when paper form medical records first began there were similar concerns around privacy, but the recording of a person's medical history went on to become an essential part of the medical process."***

Digital records, which have been common place in many other sectors for decades, will need to be protected and secured just the same.

FOCUS ON THE PATIENT

Digital Scribe will alleviate what is known to be clinicians' most common frustration. While electronic health record taking makes for improved clinical documentation, it forces the clinician's focus away from the individual sitting in front of them and patient satisfaction decreases. Inputting can be time consuming and cumbersome.

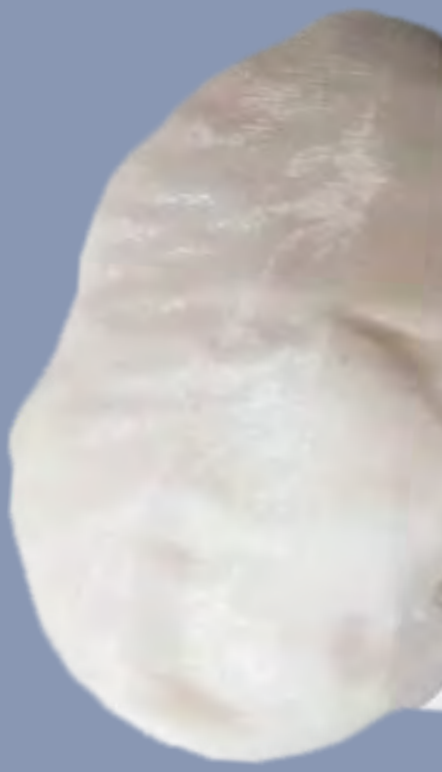
While Digital Scribe will be more than a repository for patient case histories, guidelines will be built-in to ensure records are meaningful. Decisions will be made about when and how raw data from the consultation is retained (e.g. full audio, video and sensor record of the clinical encounter or just the summary generated by the machine); the level of clinician involvement in creating and signing off on the summary; and the need for explicit patient informed consent for having their record created in such a way.

Although Australia is a laggard in the level of investment currently devoted to AI in healthcare, focussing on bleeding edge applications to transform health service delivery has huge potential to make our own healthcare system more agile, safe and effective. It also allows us to exploit what is one of the world's great national healthcare systems to create new 21st century industries that utilise AI to reinvent healthcare.

Harnessing the world of medical knowledge will be Digital Scribe's ultimate contribution – resulting in a more patient-centred approach married with in-depth knowledge to transform the health system of the future.

Professor Enrico Coiera is Foundation Professor of Medical Informatics at Macquarie University and Director of the Centre for Health Informatics, Australian Institute of Health Innovation. He is also the Director of the NHMRC Centre of Research Excellence in Digital Health.

3D PRINTED SHIN BONE IMPLANT AN AUSTRALIAN FIRST



We were the first in the world to save a patient's leg using a 3D printed biodegradable implant combined with the patient's own tissue

Researchers, clinicians and industry have come together in an Australian first, providing a Gold Coast man with a 3D-printed biodegradable shin bone implant. The surgery's success has led to approaches from German surgeons seeking to conduct similar operations.

The young man received the implant last year, replacing bone that he lost through infection. Eight months after the surgery, the patient was able to put some weight on the leg and doctors saw signs of bone regeneration.

A transdisciplinary team of researchers at QUT's Institute of Health and Biomedical Innovation (IHBI) led the design and prototype fabrication of the implant, as well as a 3D printed model of the bone defect for surgical planning.

Distinguished Professor Dietmar W Hutmacher mentored the team, composed of Dr Marie-Luise Wille, Dr Nathan Castro and PhD candidate Sebastian Eggert, and worked closely with Brisbane plastic surgeon Dr Michael Wagels.

The research team works at the ARC Industrial Transformation Training Centre in Additive Biomanufacturing, based at IHBI, and collaborates with Queensland company 3D Industries and industry partner Osteopore International.

ADDITIVE BIOMANUFACTURING

Teams at the training centre aim to develop the next generation of additive biomanufacturing and train future leaders.

The research aims include overcoming challenges and developing bioprinters capable of using multiple material types and meeting strict processing needs. Other considerations include being able to move towards the scaling up of manufacturing processes.

Researchers are developing bioinks in multiple forms, such as hydrogels, polymers, ceramics and metals for different biomedical applications, while ensuring they are compatible with both printing processes and biological processes.

Clinical translation of the research involves collaborating with industry partners and clinicians to advance medical applications of 3D printing, particularly in radiotherapy, customised titanium implants and novel therapies for treating cartilage defects.

At the core of the recent surgery in Brisbane was a patient-specific implant, designed in the form of a biodegradable scaffold. "A 3D printed scaffold can be customised to the patient, with a specifically designed internal architecture guiding the new bone formation and maturation," Professor Hutmacher said. "After the bone has been formed, the scaffold slowly degrades and only the patient's own bone remains."

Dr Wagels performed the surgery at the Princess Alexandra Hospital, with Professor Hutmacher in attendance. The scaffold was implanted along with a tibial nail for stability using a new technique that involved a tissue flap developed by Professor Hutmacher's research group, including PhD candidate David Sparks.

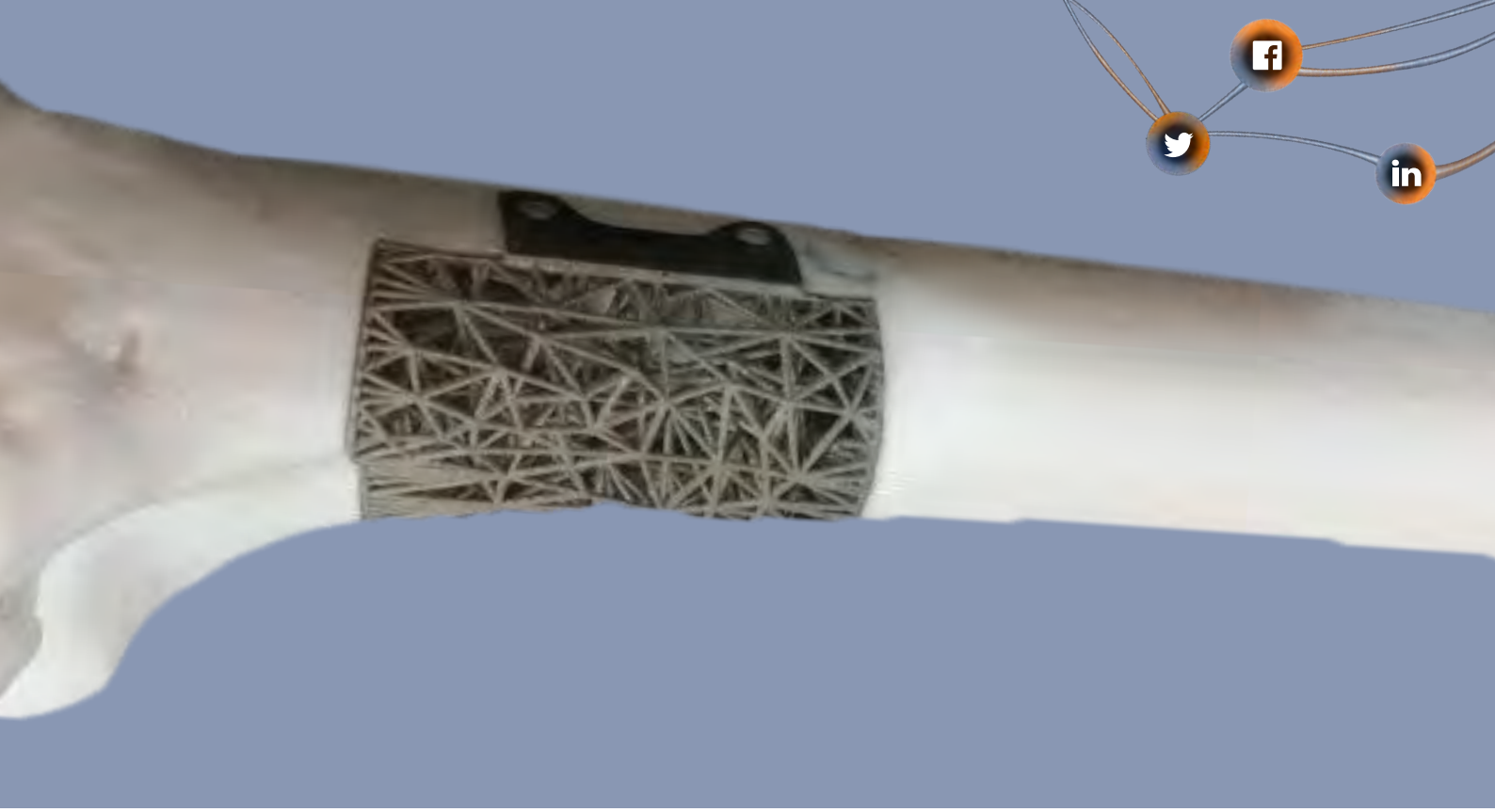
The tissue flap was designed to promote bone regeneration, provide a blood supply and include the patient's own cells to facilitate regeneration across the length of the scaffold. The flap comprises the top layer of a bone's surface and surrounding tissue.

Doctors reported no infection in the eight months since the operation.

PATIENTS, SURGEONS AND RESEARCHERS WORKING TOGETHER

Members of Professor Hutmacher's team benefited from research and training activities at IHBI's Medical Engineering Research Facility (MERF), based at the Prince Charles Hospital, providing assessment and validation for the biomaterials and surgical techniques. The researchers conducted pre-clinical studies at MERF ahead of the surgery involving the Gold Coast man.

"The needs of both surgeons and patients are important considerations in translational research," Professor Hutmacher said.



"Our research team consists of engineers and designers. We collaborate with surgeons so we can meet their needs, designing and delivering a scaffold that they can implant easily, using existing equipment and surgical techniques."

INTERNATIONAL INTEREST

Its success led to approaches from German surgeons seeking to conduct similar operations. IHBI Adjunct Associate Professor Boris Holzapfel led one such operation at the University Hospital of Würzburg in November. In that instance, the patient had a tumour, resulting in a 20cm section of his tibia being surgically resected.

Another operation was conducted in Munich in February, involving another tumour patient. Professor Hutmacher's research team designed a modular scaffold that could be length-adjusted during the November operation. The process involved developing a computer model and 3D printing a series of physical models from CT scans of the patient's tibia bone.

"Our team used a 3D printer from 3D Industries to print the anatomical models for pre-operative planning of the surgery and implant placement," Professor Hutmacher said.

"The final scaffold designs were sent to Osteopore International, a partner with a clinical track record for their FDA-approved and CE-marked biodegradable scaffolds."

In each instance, a hospital ethics committee provided approval and the patient's consent was obtained ahead of the surgery.

Professor Hutmacher and Dr Wagels have started a PhD training program partially funded by the Princess Alexandra Foundation to train young surgeons to perform cutting-edge research to meet Australia's need to build capacity in 3D printing in medicine.

A RESEARCH COLLABORATION

Among the IHBI chief investigators of the training centre are;

- bone and tissue engineering expert Professor Yin Xiao
- biomaterials and biofabrication expert Professor Mia Woodruff
- cartilage regeneration expert Associate Professor Travis Klein
- Professor Prasad Yarlagadda, an expert in tooling for non-traditional manufacturing.

The centre involves chief investigators from RMIT, Deakin, the University of Wollongong and the University of Melbourne and partner investigators from Shanghai Institute of Ceramics in China.

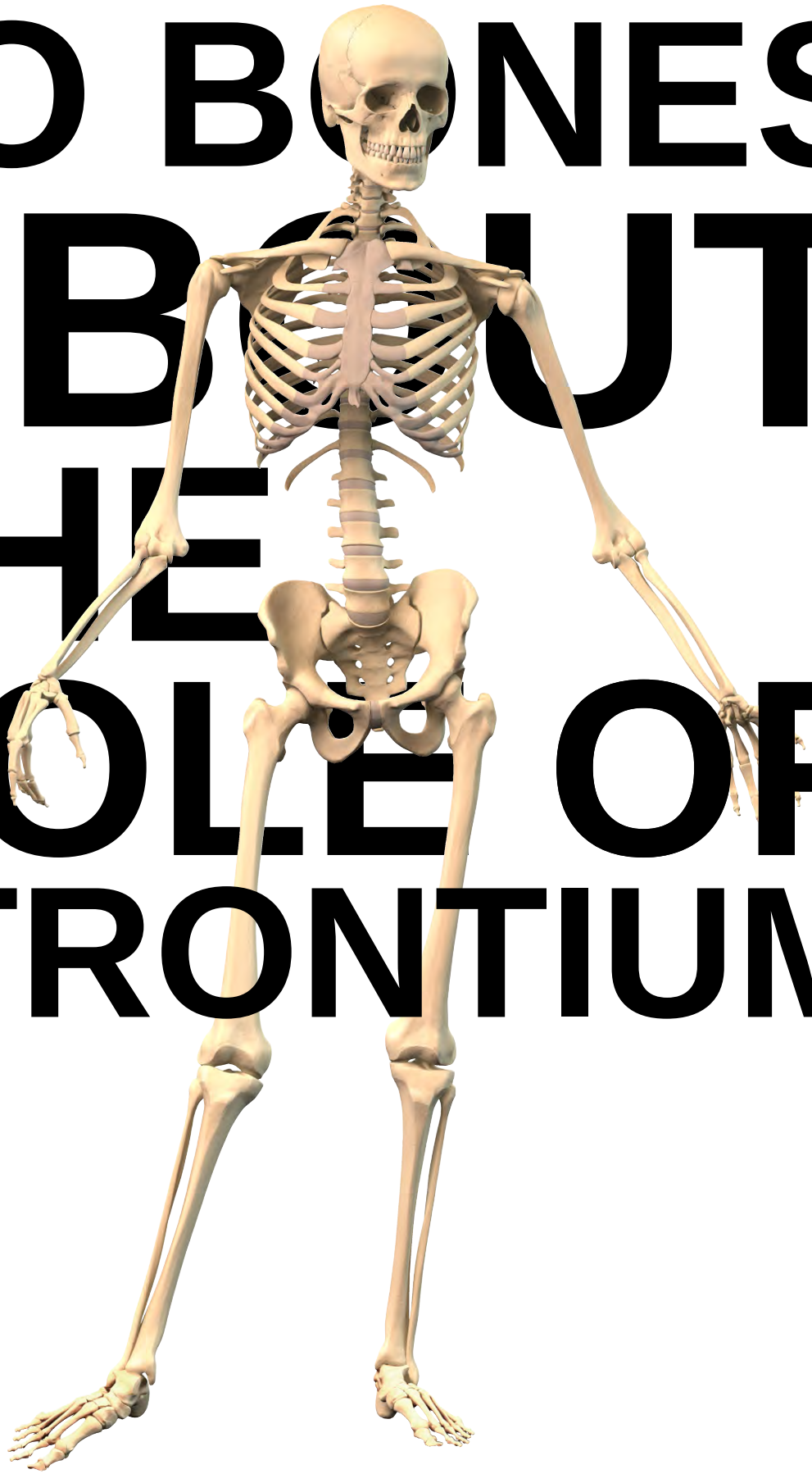
THE OUTCOME

Limbs that have previously been lost due to disease or trauma can now be saved by using tailored 3D printed implants combines with the patients own tissue to encourage full bone regeneration. The patient will experience a better quality of life through improved healing, reduced risk of infection, less pain and ultimately full use of the limb.

We are changing the paradigm, addressing clinical need using a multidisciplinary approach that combines the best minds, innovative thinking and cutting-edge technology.

Author: Erik de Wit, Communication Program Coordinator, Institute of Health and Biomedical Innovation, QUT

MAKING NO BONES ABOUT THE ROLE OF STRONTIUM



Frontier research using novel artificial intelligence and machine learning methods to identify important genes to coax the body's own cells to regenerate bone.

KEY FACTS

Bone loss due to injury, cancer or ageing is a significant factor in morbidity, and is an important problem for ageing populations, greatly increasing the risk of breaks compared to healthy bone. It is common in Australia, with 1.2 million people having the disease and another 6.3 million having low bone density.

Biomaterial design of biomaterials for regenerative medicine is hindered due to lack understanding of how cells respond to them. New methods for objectively probing cell-materials interactions are needed. We showed how genome-wide expression data, AI-based feature selection, and holistic experiments elucidate how strontium-containing bioglass drives differentiation of mesenchymal stem cells from bone, providing a new paradigm for biomaterials design.

REGENERATING BONE, BUT HOW?

The biomaterial Stronbone™ is a useful treatment for osteoporosis and injuries or other diseases involving bone loss. It consists of a bioactive glass containing the active ingredient, strontium ranelate, the strontium salt of ranelic acid. The material stimulates the body's mesenchymal stem cells (MSCs), causing them to preferentially differentiate into bone, thereby coaxing the body's own cells to regenerate lost or damaged bone.

There are several theories about how strontium ranelate achieves this but no consensus about the correct mechanism, inspiring experiments to confirm or refute the validity of these theories.

In collaboration with Stronbone's inventor, Professor Molly Stevens of Imperial College London, Eileen Autefage (now at the Karolinka Institute) and Eileen Gentleman (now at Kings College London) and coworkers, my colleague Frank Burden and I analysed the gene response of MSCs donated by three patients treated with Stronbone using a novel statistical method called sparse feature selection.

This identified only 11 genes from over 35 000 candidates that were most important in stimulating the growth of bone. Those genes revealed biochemical pathways that had not been previously associated with differentiation of MSCs down the osteogenic (bone forming) pathway.

"The study predicted that chemical processes in the body that produce sterols and fatty acids, essential for formation of cell membranes and cell signalling, are central to strontium-mediated bone regeneration. This was subsequently confirmed by standard molecular biology techniques that showed that Stronbone indeed stimulated sterol production and the modification of proteins to allow them to attach to cell membranes.

We were able to detect increases in cholesterol in cells and their membranes, identify changes in lipid raft compositions, and in natural chemicals that control muscle function. Lipid rafts are very important domains in cell membranes that help assemble and process essential signalling molecules, control cell membrane fluidity and regulate transmission of signals in nerves.

> ***By providing a better understanding of how specific biomaterials influence cell behaviour, our research has also opened up a new way to design more effective and less toxic drugs to limit bone loss.***

For example, identifying the chemical pathways that are modified when stem cells are stimulated to generate bone provides new targets for drugs that could slow bone loss or replace bone lost by disease or injury.

Our proof of concept study has also shown the benefits of combining modern mathematical methods with objective biochemical experiments to gain a deeper understanding of global cell– material interactions. These discovery-driven, non-reductionist methods provide alternative research modalities for evaluating biomaterials and improving their design without making prior assumptions about mechanisms.'

Our research has clearly demonstrated that AI/ML methods are capable of discovering new, important information about biological systems that previous statistical and computational methods, and even human scientists, have not. The diversity of potential applications of AI, and the implications of AI-driven discoveries in chemistry, materials, biology and many other areas of science and medicine, are truly paradigm shifting and exciting.

Authors: Autefage H., Gentleman E., Littmann E., Hedegaard M.A.B., Von Erlach T., O'Donnell M., Burden F.R., Winkler D.A., Stevens M.M. Proc. Natl Acad. Sci. USA 2015, 112, 4280–5).

FRONTIERS RESEARCH STARTING AT THE PATIENT END OF THE PIPELINE.

Focussing on the patient as an end-user can fast-track translation into the clinic of a cell transplantation therapy to repair the injured spinal cord.

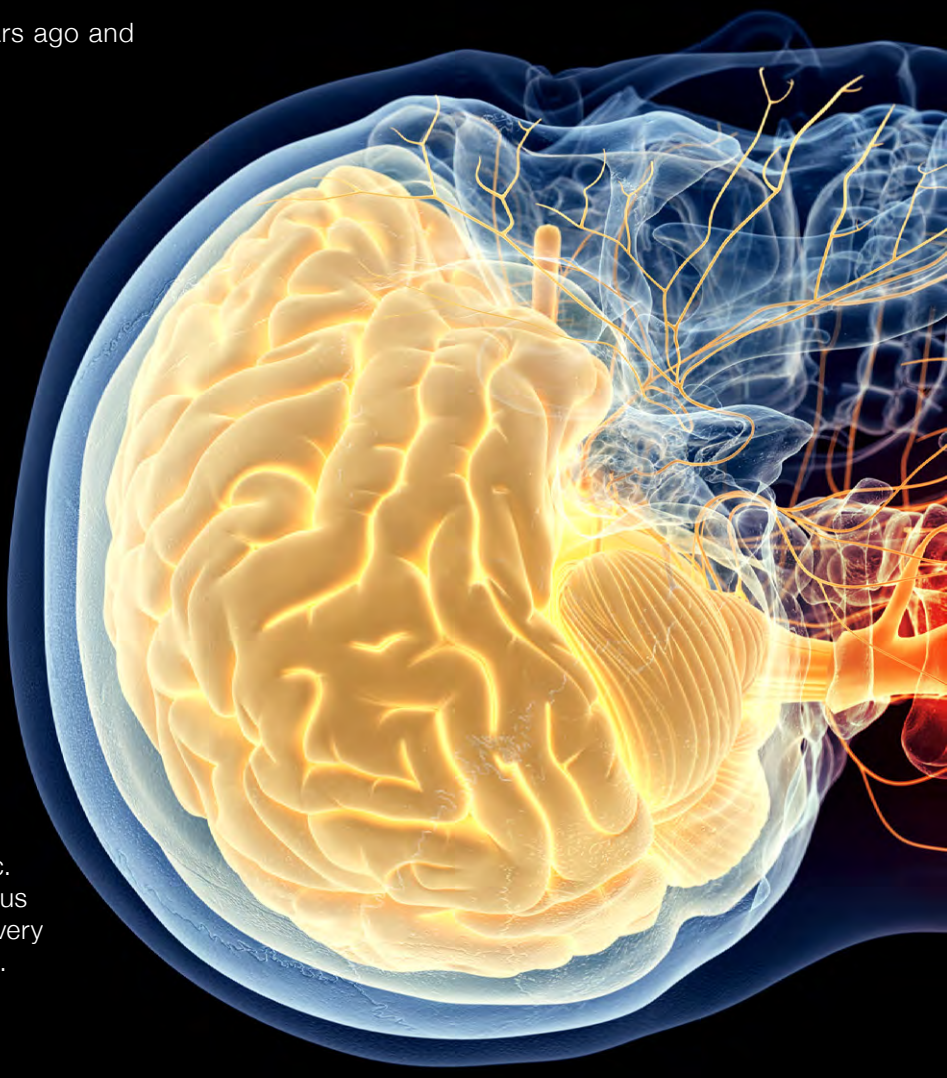
THE CHALLENGE TO DELIVER

Perry Cross looked us in the eye a few years ago and asked,

> ***When are you, as scientists, going to translate the olfactory cell transplantation therapy for spinal cord injury into a clinical product?'***

Perry Cross is a ventilated quadriplegic and director of the Perry Cross Spinal Research Foundation so he knows what the spinal cord injury community wants.

Perry has seen research and media releases showing that olfactory glial cell transplantation to repair the injured spinal cord has produced some very promising results. He has seen Professor Emeritus Alan Mackay-Sim awarded Australian of the Year in 2017 for his work in 2002 that tested the safety of olfactory cell transplantation for spinal cord injury in humans. Yet while recent lab-based research was creating great discoveries, it was not addressing the key bottlenecks needed to translate the therapy into the clinic. It was Perry's direct message to the heart of us scientists that changed us from being discovery researchers to being translational researchers.



Coinciding with Perry's question was Australia's Chief Scientist Alan Finkel's message about innovation being the pipeline which creates a product and delivers it to market. Rather than commencing with the discovery, the starting point in this process is actually at the opposite end of the pipeline - the end-user. We need to know what is demanded by the market, how it is going to be paid for and at what price, and the constraints of product formulation in order to generate the product profile. It is only at this point that we should embark on the translational research to develop the product; otherwise we are likely to create products that cannot be delivered to the clinic.

With this background and unmet need, we embarked on the entrepreneurial and innovation pipeline research approach to fast-track delivery of a therapy for treating the chronically injured spinal cord. With strong support from the Queensland Government, the Perry Cross Spinal Research Foundation and the Clem Jones Foundation we have been able to assemble a large team at Griffith University to drive this therapy forward.

IDENTIFYING THE NEED

So, what it is that people living with spinal cord injury want and need? Ultimately, complete regeneration is ideal, but that may mean we are aiming too high. Improvements to the quality of life can be achieved by smaller outcomes – the ability to breathe unaided or regaining function control of fingers, bowel and bladder.

Importantly, sensory function, not just motor function, must be restored too as the ability to feel again brings back the ability to feel a loved one, or to feel the initial stages of a pressure sore that can be so devastating. While robotics and other devices can aid restoration of

movement, it is only a regenerative cell therapy that can restore both motor and sensory function. As this is what is wanted by the end-user we must focus on delivering such a therapy.

THE BUSINESS CASE

How does the business case stack up? There are around 15,000 Australians living with spinal cord injury and another 300-400 are added to that each year. The total socio-economic cost to Australia was $2 billion per annum in 2008 and is likely to be much higher now. It is therefore easy to see that an effective therapy that may cost some $300,000 or more per patient is worth the investment. But we need to deliver the therapy at the lowest possible price to ensure that it is available to those most in need, and we need to design it so it can be delivered within the existing frameworks of health departments and insurance companies as these are the most likely to be paying for the therapy.

FIT FOR CLINIC

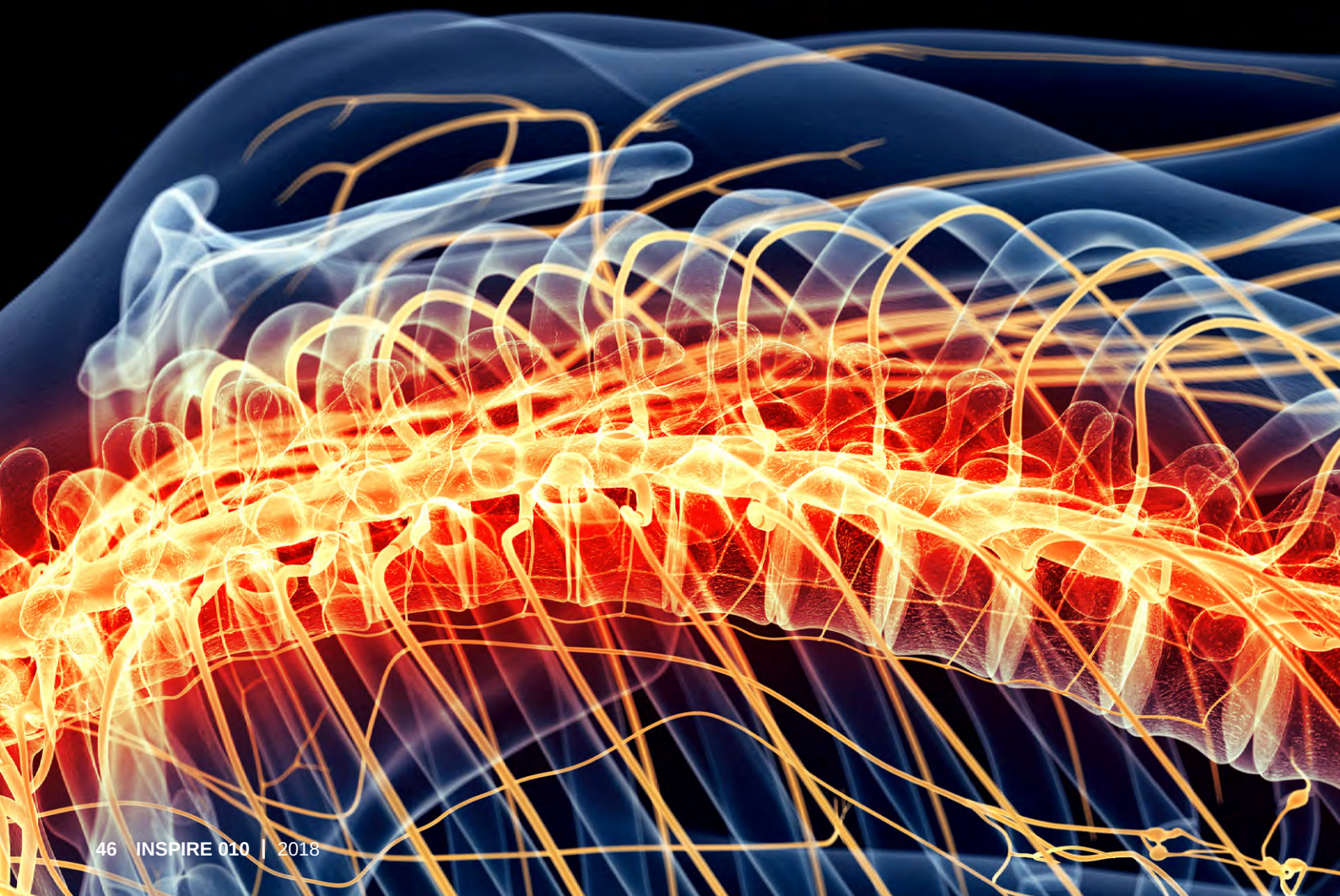
The next step in the innovation pipeline is the clinician who must transplant the cell product into the patient. There is no point creating a lab-based product that clinicians cannot effectively use. This means we are limited by numerous constraints including the ethics of the degree of intervention, the devices that are needed to transplant the cell product, and the physical dimensions of the injury site. If a minimally invasive procedure is the preferred clinical option then we need to create a product that suits.

From this point in our translational approach, we set about creating the production systems that would allow us to target the key bottlenecks as quickly as possible. Rather than a linear production, we have established five teams of 5-8 researchers working simultaneously on the different aspects: high quality cell production, drug discovery, nerve bridge generation, transplantation technique, and post-transplantation stimulation of cell activity.

Together this is the intense lab-based research component that is central to success and we have set milestones that need to be achieved within strict timeframes. From our point of view, the entrepreneurial team-based approach that we have established generates an enthusiasm and motivation to drive the translational research towards our clearly defined targets.

PHYSICAL ACTIVITY NEEDED TOO

Yet the therapy does not stop with the cell transplantation, as nerve regeneration is a long process. For best outcomes, activity-based therapy is likely to needed for months and years and at an intensity that is much higher than is currently provided for most rehabilitation.



Our health departments recommend that everyone in the community does at least 30 minutes of exercise a day, so clearly people undergoing regeneration of their spinal cord need considerably more than 30 minutes. Yet, is it reasonable to expect people to endure intensive long-term activity-based therapy when the outcomes are uncertain? Will they cope psychologically and how can they fit it into their existing lifestyles? How do we deliver the service and who is going to pay for it? All these issues must be addressed and support services put in place to promote success.

THE RIGHT PATH TO MARKET

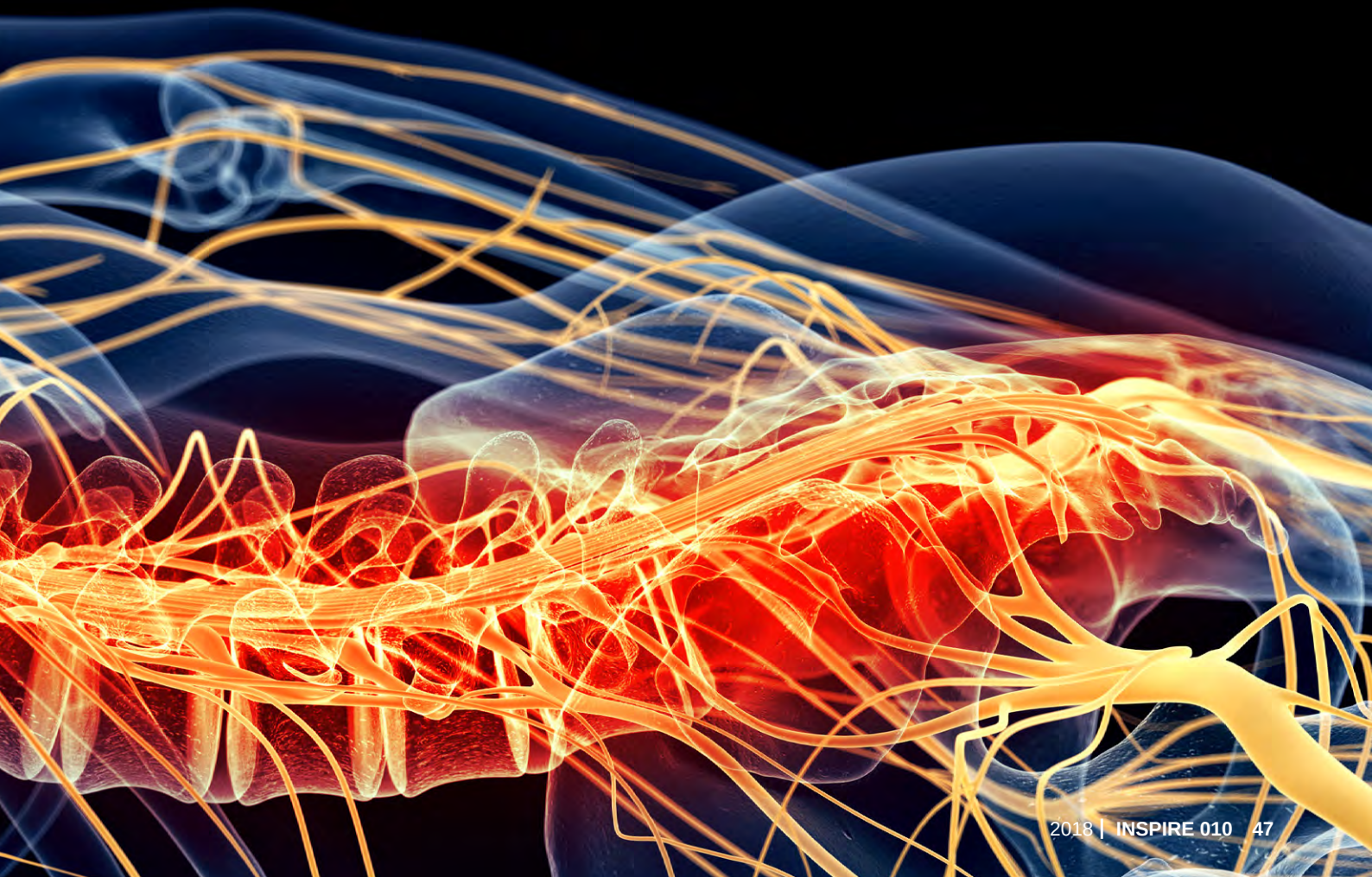
Getting a new therapy to market can cost a billion dollars or more and hence investment in potential products needs to be protected via patents and trade secrets. This in turn means that the primary output of translational research is intellectual property. But not all intellectual property is protected by patents, as it can be more advantageous to retain the IP as a trade secret or know-how. Careful judgement supported by commercialisation experts is needed to know the appropriate IP pathway to take.

So what is the over-riding characteristic of translational researchers? They are risk-takers. They take the risk that the project will be successful because without success they are left without a strong publication track record. They take the risk that the trade secrets and know-how that are not patented or published are worthy outcomes that will be properly considered by future employers and grant panels. In our team, we are fortunate to have these risk-takers who want to create a benefit for the community. While we feel the pressure of the community expectation, it is a strong motivating factor that makes the difficulties of research so much more enjoyable.

THE MOON IN OUR SIGHTS

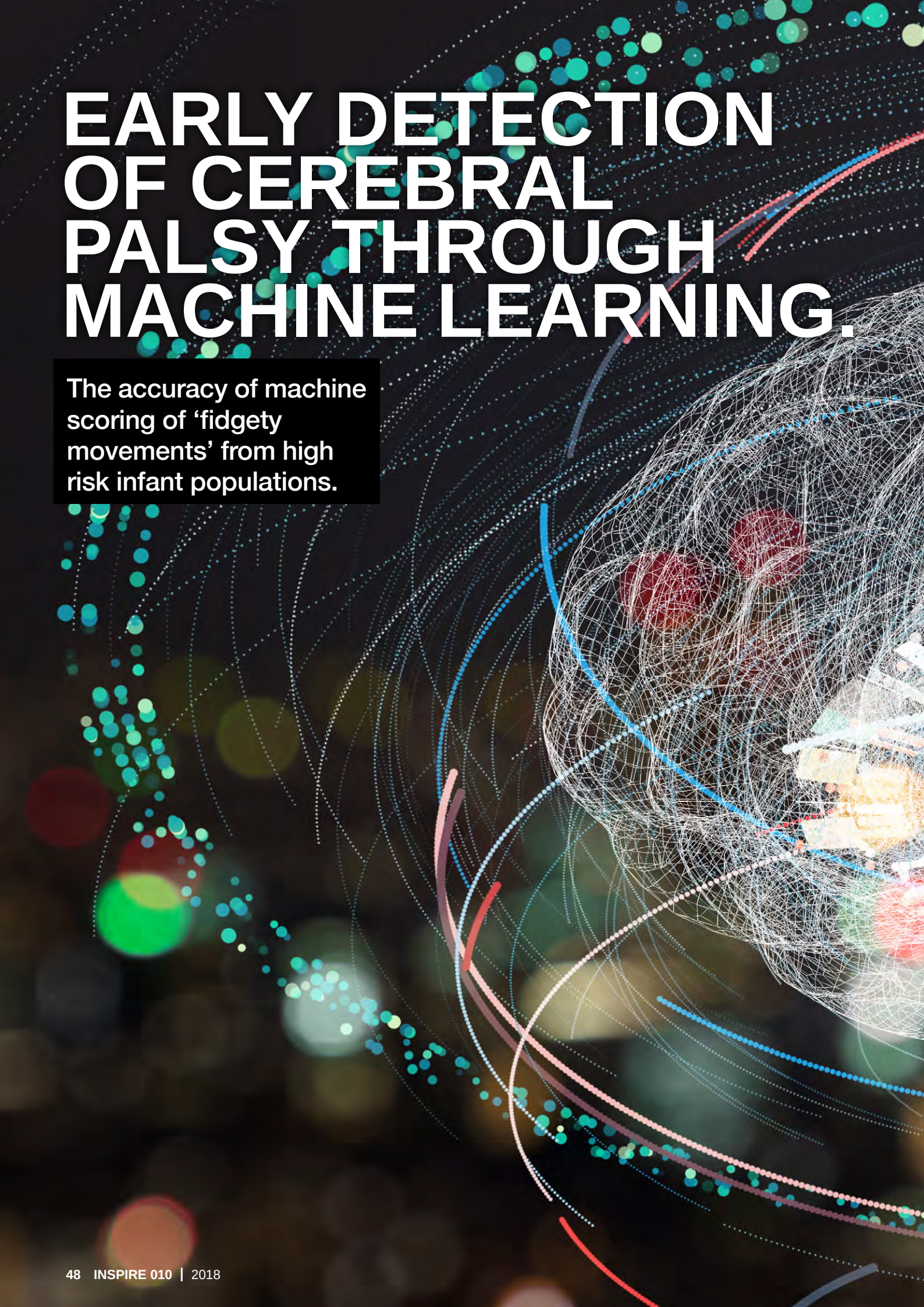
When the Americans decided to send humans to the moon they embarked on a decade of innovation pipeline research targeted specifically to solve key bottlenecks, with the full support and excitement of the community. It is now time that we as a community use this same approach to fully support risk-taking biomedical researchers to solve the big problems of our time. That way, when Perry and all the others in our community ask us researchers what we are doing to translate a therapy, we can confidently say that we have the moon in our sights.

Authors: A/Prof James St John,Head of the Clem Jones Centre for Neurobiology and Stem Cell Research, Griffith University.
A/Prof Jenny Ekberg, Menzies Health Institute Queensland.



EARLY DETECTION OF CEREBRAL PALSY THROUGH MACHINE LEARNING.

The accuracy of machine scoring of ‘fidgety movements’ from high risk infant populations.



The Cerebral Palsy Alliance Research Institute has achieved a 20% reduction in the incidence of cerebral palsy, from 1 in 400 to 1 in 600 Australian live births, and effectively reduced the severity of cerebral palsy.

Australia is one of the first countries in the world to achieve this breakthrough. We have significantly reduced the average age of cerebral palsy diagnosis (previously 19 months), now possible at 12 weeks, opening a vital window for early intervention and neuroplasticity for babies at risk.

17 million people worldwide have Cerebral Palsy (CP). It is Australia's 5th highest cause of childhood death and the most common childhood physical disability, with no cure. CP imposes a severe physical, emotional and economic burden on affected individuals, families and communities.

EARLY INTERVENTION REQUIRES EARLY DETECTION

Recent neuroscience research supports intensive, repetitive, task-specific early intervention for CP, which should commence very early while the brain is most plastic. CP is often diagnosed as late as 12-24 months of age at which time the maximal opportunity for brain development (neuroplasticity) has already passed.

Detecting CP early in high risk babies is essential if we are to make evidence based interventions possible during the critical window of optimal neuroplasticity, thus reducing severity.

Existing human rated scores of general movement are time consuming and access to skilled practitioners is limited, particularly in poorer countries. Methods that can automate this process or reduce the human effort will vastly improve early detection.

A ROLE FOR MACHINE LEARNING

Machine learning and pattern recognition is the theory and practice to learn from, and predict patterns in data. Rooted in statistics, it separates signals from noise, learns linear and non-linear models from complex, spatial and temporal data, and uses them to derive groups, find similarities/dissimilarities, predict the future, and categorise data.

Machine learning and pattern recognition have had phenomenal recent success in diverse tasks such as search, recommendation and face recognition. These methods offer promise for the construction of data driven accurate analysis of diverse media including video and text.

Motivated by this recent success, our research examines the use of advanced machine learning methods to classify and separate normal versus (abnormal + border) fidgety movement from high risk infant populations. Once this has been achieved the results can be incorporated into early detection platforms for scalability and global impact.

NEW METHODS FOR ANALYSIS

The innovation in this project is the construction of new machine learning methods to analyse videos of fidgety movement from high risk populations. The innovation involves solving problems that are specific to this problem: learning and estimating subtle differences between classes of movements in highly noisy and non-standard video captured by cheap handheld devices. This work has not been attempted before with such videos and will result in new algorithms and systems.

The impact is significant and far reaching.

a) The results can be incorporated into automatic early detection platforms. Such platforms can reduce the amount of human effort and help triage costly human attention to the neediest cases. The distribution of these platforms will positively impact the community.
b) These platforms can be accessed worldwide including by people in poorer demographics, and/or with limited access to specialists.
c) From a research perspective it will create new multidisciplinary capacity and advance the field of automated analysis in CP.

While the primary objective is to construct new methods to classify videos of fidgety movement, other objectives are understanding the underlying factors in motion that are discriminating between the two classes, and constructing an effective video standardisation technique that accounts for the great variation in video quality.

PROGRESS

A one year preliminary project has been completed, resulting in a prototype that can read a new video and produce a classification score. The accuracy of automated analysis has been established at 72.9%.

The next stage is to obtain more data and improve the automated analysis accuracy rate before further trialling. The performance of machine learning algorithms is known to improve with increase in data, especially in initial stages where training sets are much smaller in size. We are hopeful that with more data, and more unbiased data, more complex algorithms can be designed and the performance of the algorithm will improve.

This project and its impact has the potential to grow to deliver global benefit through the distribution of early detection platforms. However, further funding is required if this is to be achieved.

Authors: Professor Iona Novak, Head of Research, Cerebral Palsy Alliance Research Institute, The University of Sydney. PhD MSc (Hons) BAppSc
Professor Svetha Venkatesh, Australian Laureate Fellow, Alfred Deakin Professor and Director of Strategic Research Centre for Pattern Recognition and Data Analytics

NEW PERSPECTIVES ON THE PROFOUND INFLUENCE OF SOCIAL AND ENVIRONMENTAL CONDITIONS ON OUR BIOLOGY AND THE HEALTH OF FUTURE GENERATIONS

The science of epigenetics is providing evidence for completely new perspectives on how early environments may possibly give rise to semi-stable traits that can be passed on to future generations.

The central problem confronting the early pioneers of epigenetics was how cells choose which genes to express, (since all of the 200+ cell types in the human body have the same DNA sequence) and how cells remember their identity.

1970'S

By the 1970's, scientists noticed that some DNA sequences contained additional chemical modifications (methyl groups), which occurred non-randomly in the genome, correlated with cell lineage and were copied over to daughter cells during cell division. Thus, DNA methylation was proposed as a potential transcriptional regulatory mechanism that was heritable across cell division.

Today we understand epigenetic processes such as DNA methylation to be important influencers of the way DNA is organized into chromatin fibers within the nucleus of the cell. Chromatin organisation represents a second dimension to the genome and is the basis for cellular memory. Chromatin state changes are directed by families of proteins that deposit, remove or copy covalent modifications to DNA or DNA associated proteins (histones) which has the effect of altering the accessibility of DNA to transcription factors, and hence the propensity for genes to be transcribed.

Extracellular signals (metabolic, stress related, inflammatory etc) are translated into chromatin state changes through these epigenetic processes, allowing for a range of potential phenotypic outputs from the same genome sequence. Together these mechanisms allow cells and tissues to adapt to their environments in a stable manner by storing that information in the form of chromatin changes and passing on that information to daughter cells.

1980'S

The significance of epigenetic processes changing cell specific gene expression patterns according to an organism's environment, and the potential for these mechanisms to alter the risk for disease was quickly realised. The first human disease to be linked to epigenetics was cancer in 1983, and interest in epigenetic mechanisms of tumorigenesis continues to this day.

> ***"Specific attention was given to understanding the role of DNA methylation in cancer genome instability, tumour development and resistance to therapy. We now appreciate that cancer cells exhibit genome-wide changes in DNA methylation, histone modification and chromatin organization."***

The mechanistic basis for cancer epigenetics includes the disruption of homeostatic chromatin balance, which can prevent the induction of tumour suppressor programs or allow oncogenic activation.

Two translational areas of research that have emerged from epigenetic research into tumorigenesis include clinical biomarkers and novel cancer therapies. Recent research has shown that aberrant DNA methylation profiles found in tumours have astonishing utility for classification and subtyping with a view to introducing molecular classification of tumours into routine practise. Other applications under development include predicting relapse or response to therapy with early signs that DNA methylation signatures have utility for more personalized approaches to cancer treatment.

Targeting aberrantly regulated genes has also been the focus of drug development, with novel classes of DNA de-methylating agents and histone de-acetylases and inhibitors of histone methyl-transferases now developed, and FDA approved for clinical trials on blood and solid tumours. Efforts in this area will no doubt bring benefits to patients both in terms of improved diagnostics and broader treatment options in the foreseeable future.

1990'S

In the late nineties epigenetic science intensified in complex disease research following evidence that some germline epigenetic changes could be inherited by offspring across multiple generations. This surprising new form of non-Mendelian inheritance was particularly exciting as it suggested not only a strong role for the early environment in shaping human development, but in shaping the development of future generations. Several landmark animal studies demonstrated that particular exposures (dietary, toxins, endocrine disruptors) had the potential to disrupt epigenetic marks in the gametes.

A shift from the more traditional view of epigenetics with an emphasis on cellular memory, to the inheritance of phenotypes that were independent of changes in DNA sequence ensued. This was particularly appealing as proof that the mechanisms for the transmission of environmental experience were possible. Improvements in technology allowed epigenetic researchers to study these phenomena on a genome-wide scale, prompting the first wave of EWAS (Epigenome Wide Association Studies).

The initial finding from the first wave of EWAS suggested that transgenerational epigenetic changes in humans were remarkably difficult to detect, and generally of small effect size. Partly this is attributed to the difficulties in studying epigenetic changes, which by definition change over time and vary in different cell types, posing logistic challenges for cohort-based studies. The field is eagerly awaiting sufficiently large, well-designed multigenerational cohorts that might allow for robust detection of transgenerational epigenetic changes.

NOVEL LEARNINGS

Despite this, novel learnings that emerged from EWAS led to new paradigms of developmental plasticity and the predictive adaptive response. These ideas encompass the entire social conditions of our lives, the contexts we live and the way we live them, and challenge notions of determinism, whether social or biological. We are beginning to understand news mechanisms for the transmission of environmental experiences that can begin to address the complexity of human development as the interplay between social and biological life.

Developmental mismatch occurs when the predicted postnatal environment (nutritional scarcity) differs from the experienced environment (nutritionally dense, such as in Western cultures), and in such cases foetal epigenetic adaptations may increase the risk for metabolic disease and obesity in adult life. This thinking is foundational to the Developmental Origins of Health and Disease (DoHAD) field providing a mechanistic framework through which to understand the rising rates of chronic disease worldwide.

Numerous case-control and cohort studies have demonstrated associations between the molecular hallmarks of epigenetic control and allergic, autoimmune, neurological and cardio-metabolic disease. Since most disorders are likely to show a change in cell identity it has been difficult to separate cause and effect, but there is now clear evidence that exposures such as maternal smoking and in utero growth restriction induce epigenetic change during foetal development, which may increase the risk for disease.

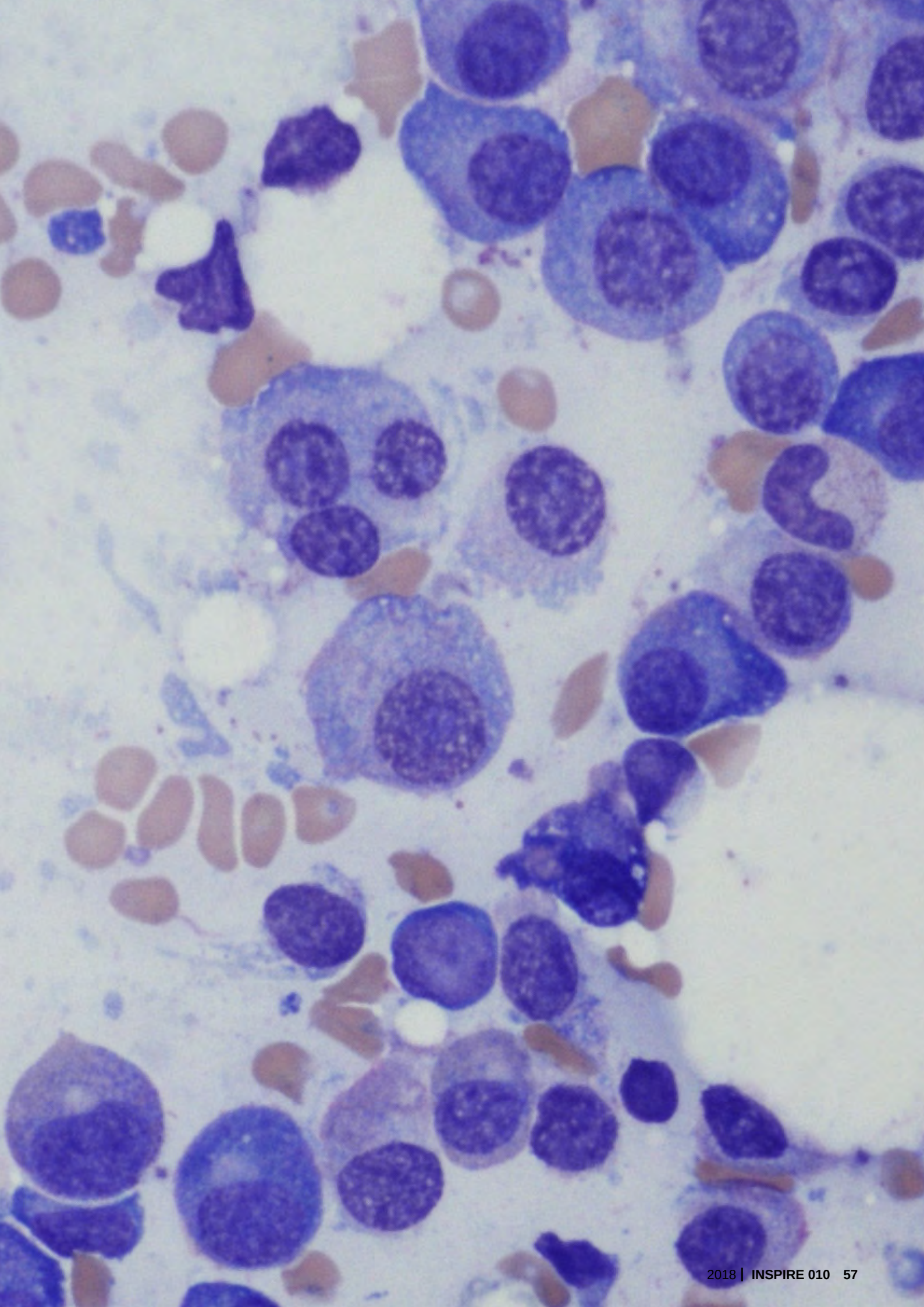
Discovering these epigenetic changes will no doubt lead to novel DNA-based biomarker and diagnostics with utility for identifying at-risk populations, as well as revealing novel gene targets for therapy.

Our research serves to increase the scientific and public awareness of emerging arguments around the importance of preconceptual health for the well-being of future generations, and for public health more broadly. Further investments and efforts in the epigenetics domain could position Australia as a global leader in this area.

Authors: Dr David Martino is a biomedical research fellow and head of the Clinical Epigenetics team at Telethon Kids Institute. He is engaged in exploring the links between epigenetic processes and childhood disease.

Frontiers Research

FOCUSED ON THE EARLY YEARS



A FIRST IN THE WORLD

Probing how environmental exposures from pregnancy through early life impact gene expression and the development of type 1 diabetes.

The ENDIA Study Team at the 2018 ENDIA Symposium held in Adelaide in February 2018.

© Kim Chapman

THE INCIDENCE OF TYPE 1 DIABETES HAS DOUBLED OVER THE LAST 30 YEARS IN AUSTRALIA AND HAS BEEN INCREASING BY 2-5% PER YEAR GLOBALLY.

Each day in Australia five children and two adults hear the words 'you have type 1 diabetes'. Lives are changes in that moment but the events leading to the diagnosis may have their origins as far back as pregnancy.

Type 1 diabetes is a major, chronic autoimmune disease that affects over 120,000 Australians. The social and economic burden of this disease is a significant cost to the Australian healthcare system. The direct treatment cost is estimated to be $600 million annually and the indirect costs much higher, with the personal cost immeasurable.

The dramatic rise implicates the modern environment as being increasingly relevant in promoting the disease process that leads to type 1 diabetes. The condition is typically diagnosed when the symptoms and signs of persistently high blood glucose levels develop. This clinical presentation, however, follows a long period of months to years during which the immune system is attacking the insulin-producing beta cells in the pancreas.

EARLY SIGNS

The majority of children who develop type 1 diabetes have immune markers of beta cell destruction detectable in their bloodstream by the age of five with an early peak before 12 months. This suggests that the environmental factors that drive type 1 diabetes are acting at the earliest stages of life – even during the pregnancy.

Discovering the modifiable environmental factors that might contribute to, or protect against, the development of type 1 diabetes will inform strategies for prevention of this disease in future generations. To this end, the world's first pregnancy to early childhood cohort of genetically at-risk children, the Environmental Determinants of Islet Autoimmunity (ENDIA) study was launched in Australia in 2013.

ENDIA is the first study globally with recruitment during pregnancy to investigate the developmental origins of type 1 diabetes and how the environment interacts with the genome to drive the development of autoimmune beta cell destruction.

The cohort is nearing its recruitment target of 1,400 mother-infant pairs from early pregnancy. The infant is at genetic risk for the disease by having a first-degree relative with type 1 diabetes. Study visits occur at each trimester of pregnancy, at the time of and just after birth, every 3 months during the first two years of life, and 6-monthly thereafter. Multiple biological specimens are collected from the mother during pregnancy (swabs, faeces, urine, blood), from the baby once born (swabs, faeces, urine, blood), as well as breast milk from the mother. Blood and faecal samples are also collected from other family members to provide a complete picture of the family's genetic and environmental risk profile.

Making these resources available to the wider research community will stimulate broader thinking around novel analytical, predictive, and therapeutic strategies targeting type 1 diabetes.

SPECIMENS UNDERPINNING FUTURE RESEARCH

In excess of 40,000 biological specimens have already been collected from ENDIA participants with >100,000 samples remaining to be collected as part of the ENDIA protocol. The ENDIA biorepository, held at the University of Adelaide's BioBank Facility, represents an invaluable resource that will underpin future national and international collaborative efforts to elucidate the developmental origins of type 1 diabetes. In recognition of this, the ENDIA Study Team has developed a policy for providing reasonable access to samples and/or clinical data generated by the study that will contribute towards ENDIA's goal of identifying environmental factors and gene-environmental interactions that modify disease risk.

MULTIPLE APPROACHES AND A DIVERSE TEAM

While still early days, the first results are revealing differences in the composition of the microbiome and virome of individuals who do and do not have type 1 diabetes. Such 'omics investigations are game-changing but expensive and further funding will be required to complete the analysis of the 'big data' generated from ENDIA samples. From 2019, investigation can begin of the interactions between genes and environment through the 'omes during pregnancy and the first year of life in the ENDIA children who develop the first stages of type

2 Epigenetics and immune regulation,

3 Nutrition and growth

4 Virology and the virome

5 Epidemiology and toxicology

6 Genetics

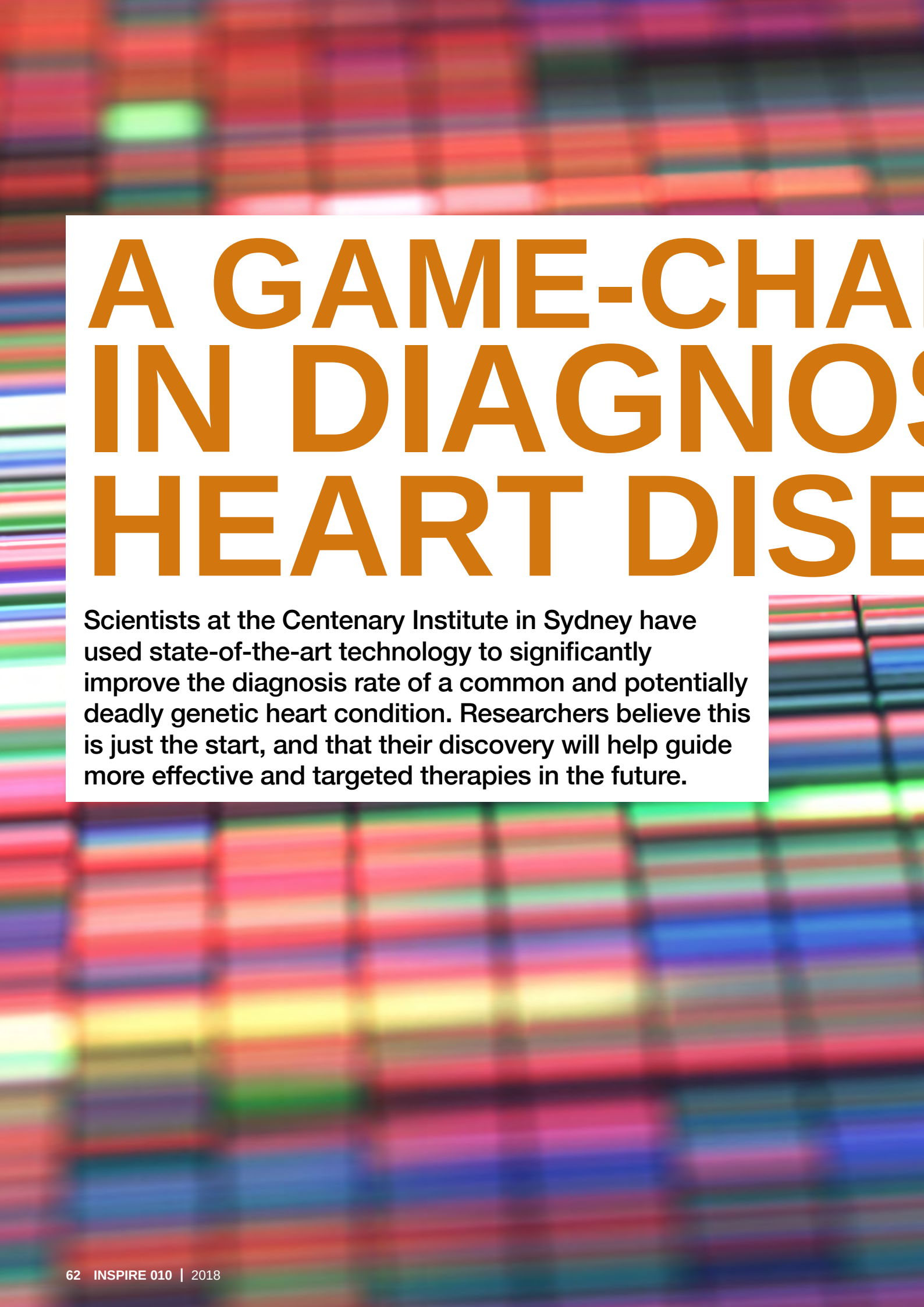
1 diabetes. These children are at similar risk of coeliac disease. Therefore ENDIA will also offer the unique ability to investigate the developmental origins of this very common disease in Australia. Realising the full value of the cohort however, will only be possible with continued investment in the follow-up of the children beyond infancy and into childhood.

The administration and scientific directions of ENDIA are driven within six Group of 8 (Go8) universities (University of Adelaide, University of WA, University of Queensland, University of Sydney, University of New South Wales and University of Melbourne) and four Australian medical research institutes (Walter and Eliza Hall Institute, Robinson Research Institute, Telethon Kids Institute and Harry Perkins Institute). The Australian ENDIA network is one of the largest collaborative groups of type 1 diabetes researchers in the world. It is well placed to run clinical trials aimed at preserving insulin production, preventing the high rates of diabetic ketoacidosis at presentation of type 1 diabetes, reducing diabetes complications, and ultimately, preventing the disease itself.

The ENDIA study was established with funding from the NHMRC with subsequent support from JDRF Australia, the recipient of the Australian Research Council Special Research Initiative in Type 1 Juvenile Diabetes, The Leona M. and Harry B. Helmsley Charitable Trust, JDRF International, and Diabetes SA. ANZCTR registration number: ACTRN12613000794707. Understanding how the environment interacts with genes from conception to increase a child's risk of developing type 1 diabetes will enable prevention strategies that should eventually eliminate the disease in children.

This would change the lives of countless children and alleviate a major health burden.

Authors: Dr Megan Penno, University of Adelaide; **Prof Len Harrison**, Walter and Eliza Hall Institute; **Prof Jenny Couper**, University of Adelaide.



A GAME-CHA
IN DIAGNOS
HEART DISE

Scientists at the Centenary Institute in Sydney have used state-of-the-art technology to significantly improve the diagnosis rate of a common and potentially deadly genetic heart condition. Researchers believe this is just the start, and that their discovery will help guide more effective and targeted therapies in the future.

NGER SING EASE.

Hypertrophic cardiomyopathy (HCM) is a common genetic heart condition which can affect men and women at any age. HCM occurs when the heart muscle thickens, making it difficult for the heart to pump blood, and in some cases results in sudden cardiac death. HCM is caused by single genetic variants in any one of at least eight different genes encoding structural proteins of the heart muscle filament. Immediate family members of a person with HCM have a 1 in 2 chance of inheriting the causal variant.

BETTER TARGETED SCREENING

Current guidelines recommend that immediate family members receive ongoing clinical screening for the disease. However, if the genetic cause is found in a person with HCM, family members can undergo genetic testing for the same variant. Family members who *do not* have the variant can be reassured that they are very unlikely to develop the disease, and can be released from life-long clinical surveillance. This reduces the burden placed on family members, their clinicians and the healthcare system. Those family members who have inherited the causal variant can be targeted for closer clinical surveillance and given an appropriate disease management plan.

GENOME SEQUENCING TO IMPROVE DIAGNOSIS

Current clinical genetic testing approaches for HCM typically screen the protein-coding regions of the established disease-causing genes. Such targeted DNA sequencing performs particularly well for the majority of HCM when there is a strong family history of disease. However, for some families, no genetic cause is found.

We have previously shown that extending screening to the protein-coding regions of all 22,000 genes, using an approach called exome sequencing, only yields a genetic diagnosis in a few additional families. Since the protein coding regions represent a mere 1% of our entire complement of DNA, these results suggest that we may need to look deeper into the genome; specifically, within the non-protein coding regions, which were once termed '*junk DNA*' as they mostly consist of repeated sequences.

Genome sequencing in its current form is a state-of-the-art technology that can determine all 3.2 billion letters of our DNA code in a matter of weeks for less than AU$2,000. This is an impressive feat considering that sequencing of the first human genome took an international consortium two years at a cost of more than US$500 million. Genome sequencing also detects most types of genetic variation, ranging from single nucleotide changes up to structural

alterations of a chromosome. This breadth of genetic testing usually requires different cytogenetic analyses, quantitative chromosomal assays, and DNA sequencing approaches, each incurring time, money, and anxiety for the patient.

With funding from the NSW Office of Health and Medical Research, Professor Chris Semsarian of the Molecular Cardiology Program, Centenary Institute, Sydney, assembled a state-wide team of cardiologists, clinical geneticists, genetic counsellors, research scientists, and bioinformaticians. We explored whether genome sequencing could find additional genetic causes of HCM in families where the underlying cause of disease was not found with prior genetic testing.

NEW CAUSES IDENTIFIED

In four families of cohort 1, we found a disease-causing variant deep within the non protein-coding regions of a major HCM causal gene. These variants cause errors in RNA splicing – the post-transcriptional 'cut and paste' processing of protein-coding sequences into a continuous protein-coding template. We also found a variant in the small circular genome of mitochondria, which are organelles that generate energy for the cell and are in high demand in the heart muscle. This finding has important implications for inheritance risk and genetic counselling of family members, as mitochondria and their genome are passed on through the maternal lineage only.

OTHER DISEASES

The broad net cast by genome sequencing also identified variants in protein coding regions of genes causal for diseases that can be misdiagnosed as HCM. In two families we found variants causing Noonan syndrome, which is associated with heart muscle thickening, as in HCM, but can also include mildly unusual facial characteristics, short stature, and hearing and vision impairments. The variants were missed with prior genetic testing because the genes causative of Noonan syndrome were not included in the genetic test. This suggests that we might be misdiagnosing milder forms of Noonan syndrome, and that we should include Noonan syndrome genes in genetic testing of HCM. We also found a disease-causing variant in a gene that was very recently

WE PERFORMED GENOME SEQUENCING IN THE LARGEST PUBLISHED COHORT OF HCM TO DATE

COHORT 1

62 people from 46 families who had prior genetic testing of at least 46 cardiac disease genes, with no causal variant found

COHORT 2

We also genome sequenced 12 unrelated people with HCM who had never received prior genetic testing.

TOTAL OF 58 HCM FAMILIES STUDIED

associated with heart muscle thickening *and* prominent electrical rhythm problems of the heart, in a family with both of these clinical features.

In 42% of cohort 2, we identified genetic variants in protein coding regions of established HCM genes, as are typically found with current genetic testing approaches, thus showing genome sequencing can also detect run-of-the-mill HCM variants.

UP TO 20% IMPROVEMENT

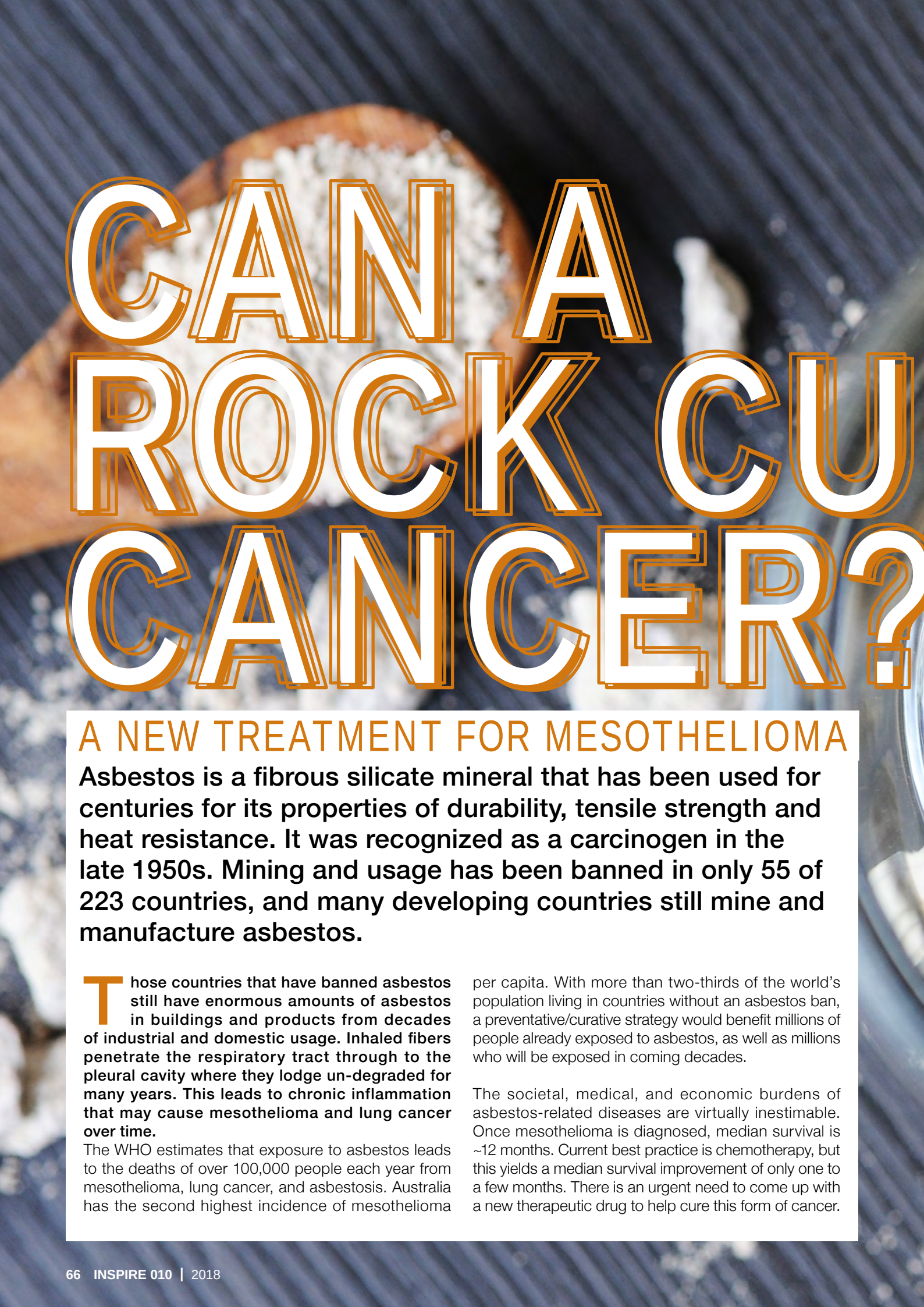
Overall, our findings, now published in the *Journal of the American College of Cardiology*[1], show that genome sequencing improves genetic testing outcomes for families with HCM by up to 20%. Our demonstration of disease-causing variants in non protein-coding regions, and mitochondrial genome variants, should encourage other researches using genome sequencing to delve into these genome regions in search of additional causes of disease. For our families who received a genetic diagnosis, we have established the genetic cause of their disease, provided a precise genetic test to identify other family members at risk of developing the disease, and enabled the possibility to guide future reproductive options. For our families without a genetic diagnosis, we will continue to further explore their genomes for the cause of their disease.

THE WAY FORWARD

Despite our successful outcomes with genome sequencing, there are some challenges for incorporating this technology into clinical care. For many families, genetic testing of a small panel of HCM disease genes performs adequately, and when compared to genome sequencing, is a cheaper option, and the data are smaller and quicker to analyse. However, because genome sequencing can detect most types of genetic variation, it is poised to replace many clinical genetic tests currently available, greatly simplifying the decision about which test a clinician should order. This is particularly relevant when there is uncertainty in the clinical diagnosis, or when a genetic test is inconclusive.

Overall our research has demonstrated how genome sequencing is a game-changing technology that is poised to transform the healthcare system of Australia and overseas, by dramatically improving early diagnosis of inherit heart disease. Having a one-size-fits-all genetic test will translate to more accurate diagnosis and management of disease, not just for families with HCM, but most likely for families with other diseases too.

Dr Richard Bagnall, Senior Researcher at the Centenary Institute



CAN A ROCK CU CANCER?

A NEW TREATMENT FOR MESOTHELIOMA

Asbestos is a fibrous silicate mineral that has been used for centuries for its properties of durability, tensile strength and heat resistance. It was recognized as a carcinogen in the late 1950s. Mining and usage has been banned in only 55 of 223 countries, and many developing countries still mine and manufacture asbestos.

Those countries that have banned asbestos still have enormous amounts of asbestos in buildings and products from decades of industrial and domestic usage. Inhaled fibers penetrate the respiratory tract through to the pleural cavity where they lodge un-degraded for many years. This leads to chronic inflammation that may cause mesothelioma and lung cancer over time.

The WHO estimates that exposure to asbestos leads to the deaths of over 100,000 people each year from mesothelioma, lung cancer, and asbestosis. Australia has the second highest incidence of mesothelioma per capita. With more than two-thirds of the world's population living in countries without an asbestos ban, a preventative/curative strategy would benefit millions of people already exposed to asbestos, as well as millions who will be exposed in coming decades.

The societal, medical, and economic burdens of asbestos-related diseases are virtually inestimable. Once mesothelioma is diagnosed, median survival is ~12 months. Current best practice is chemotherapy, but this yields a median survival improvement of only one to a few months. There is an urgent need to come up with a new therapeutic drug to help cure this form of cancer.


RE

THE REALITY

Mesothelioma is an incurable disease. Our research outcomes to date are both innovative and potentially promising for translation to the clinic and mesothelioma patients.

A ROLE FOR ZEOLITE?

Over 250 mesothelioma clinical trials have been reported, but the results have not translated into advances in the clinic. However, these past few years have seen an explosion of interest in immunotherapy, which involves treatments that stimulate the body's own immune system to fight the cancers. This has enjoyed some early successes with some types of cancers, particularly melanoma. However, trials with two of these immunotherapy drugs have proved to be unsuccessful, or of only marginal use in slowing the growth of mesothelioma tumours.

The present study began with the notion that zeolites would scavenge iron released from, or bound to, asbestos and thus ameliorate the onset and/or progression of asbestosis and mesothelioma. Zeolites are hydrated microporous crystals containing AlO_4 and SiO_4 tetrahedra linked by oxygen atoms. Over 130 natural and synthetic zeolite structures are known, with major industrial and agricultural uses.

> ***Treatment with zeolite is the first intervention able to reduce asbestos-induced damage and reduce the onset and progression of mesothelioma.***

Using zeolite to both prevent and treat asbestos-induced cancers has the potential to impact a significant global problem. The main aim of our project was to test the efficacy of a natural silicate mineral zeolite, clinoptilolite, in moderating or reversing asbestos-induced mesothelioma in a mouse study. The outcomes demonstrated that this compound was able to reverse cell damage and provide protection against the devastating effects of asbestos, leading to 83% survival with no tumour formation in treated mice over a period of 30 weeks.

So far, it appears that the common mineral zeolite, which has heavy metal scavenging properties and can be safely used in humans, can counter the biological harm caused by asbestos. It is able to ameliorate asbestos-induced damage in human lung epithelial and mesothelial cell lines, and greatly reduce both the onset and progression of asbestos-induced mesotheliomas in a mouse trial.
The notion of using one type of silicate mineral (zeolite) to counteract the deleterious effects of another (asbestos) is seemingly antithetical, but clearly innovative in concept, approach, and potential.

Finding a treatment and possible cure for an incurable disease should be a world first in ground-breaking research and patient treatment. Our treatment may be combined with traditional chemotherapy to activate a more rapid reversal of tumour growth.

> ***Our preliminary cell and mouse model data indicates that this concept has the translational potential to treat mesothelioma and lung cancer in existing patients, and to slow or prevent the onset and progression of tumours in persons already exposed to asbestos.***

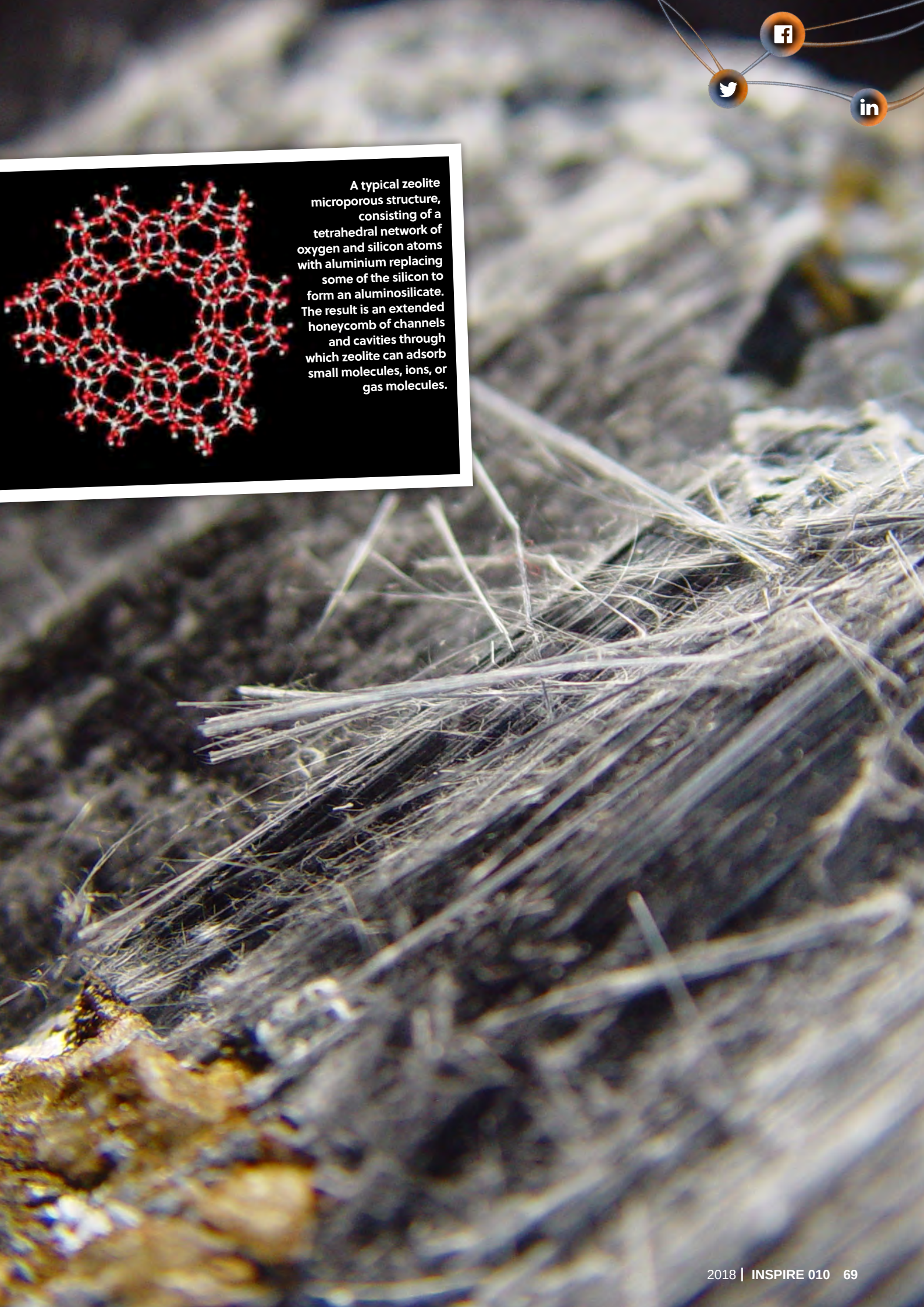
NEXT STEPS

Our work establishing the propensity of zeolites to slow and/or arrest mesothelioma tumours in mice, might pave the way for trials in mesothelioma patients. We now need to complete a full toxicology profile for the zeolites and conduct a mouse respiratory trial. The project will enable the use of zeolite as a prophylactic and/or alleviator of mesothelioma, in bimodal combination with current chemotherapeutic interventions. This bimodal approach will be more potent against tumours if the zeolite component of therapy reduces the cascade of signals that lead to tumour development, allowing the cytotoxic drug to better inhibit tumour growth.

> ***The health benefits are manifest in the alleviation of suffering, quality and length of life, and economic and medical savings.***

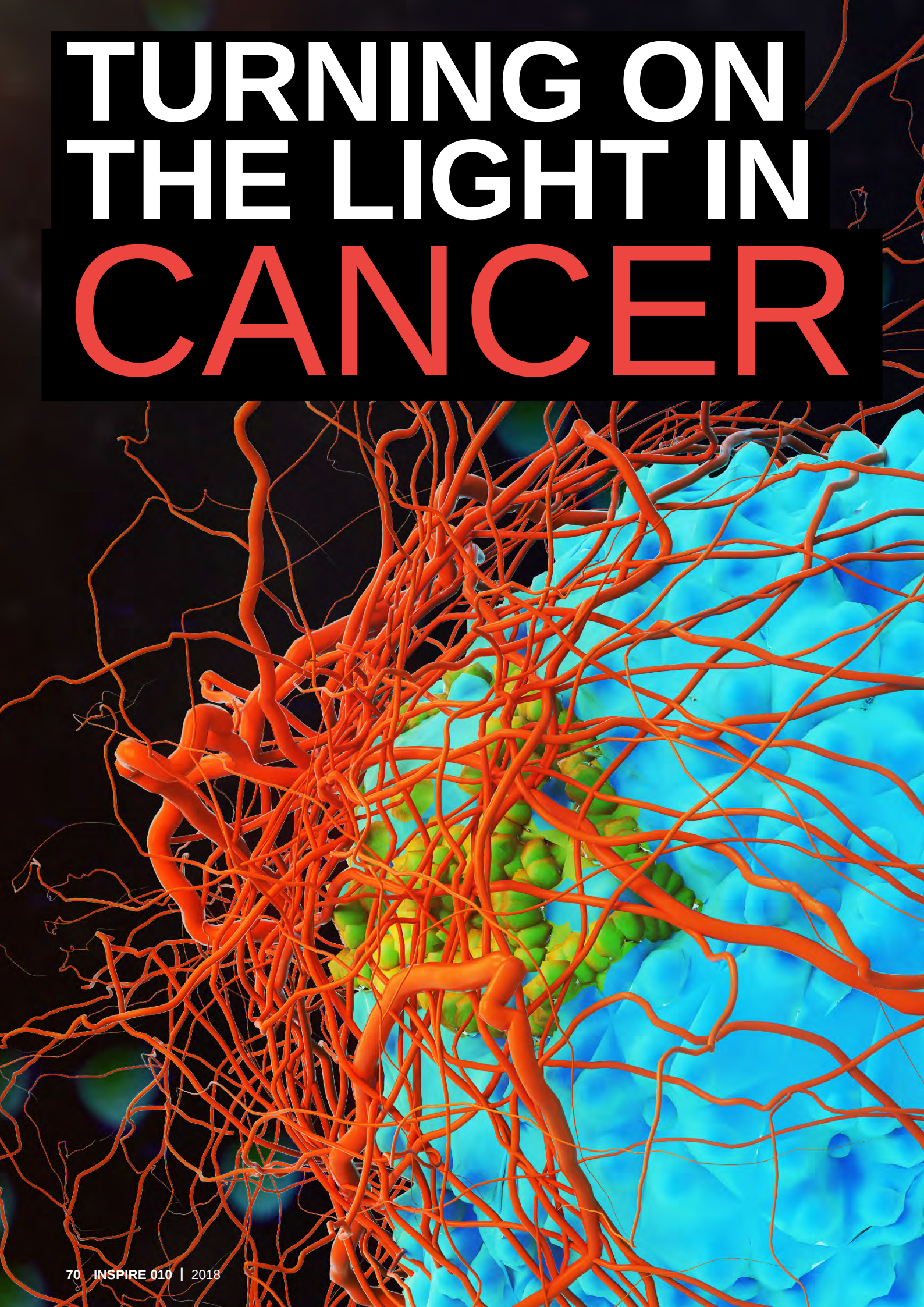
Our research is Australian based and owned. We have an international patent and are negotiating to pass on the IP to an Australian entity. Should our method work on patients in proposed clinical trials, Australia will be at the forefront of mesothelioma treatments to extend quality of life. If early mesothelioma is diagnosed, our treatment has the potential to moderate the onset and severity of the disease.

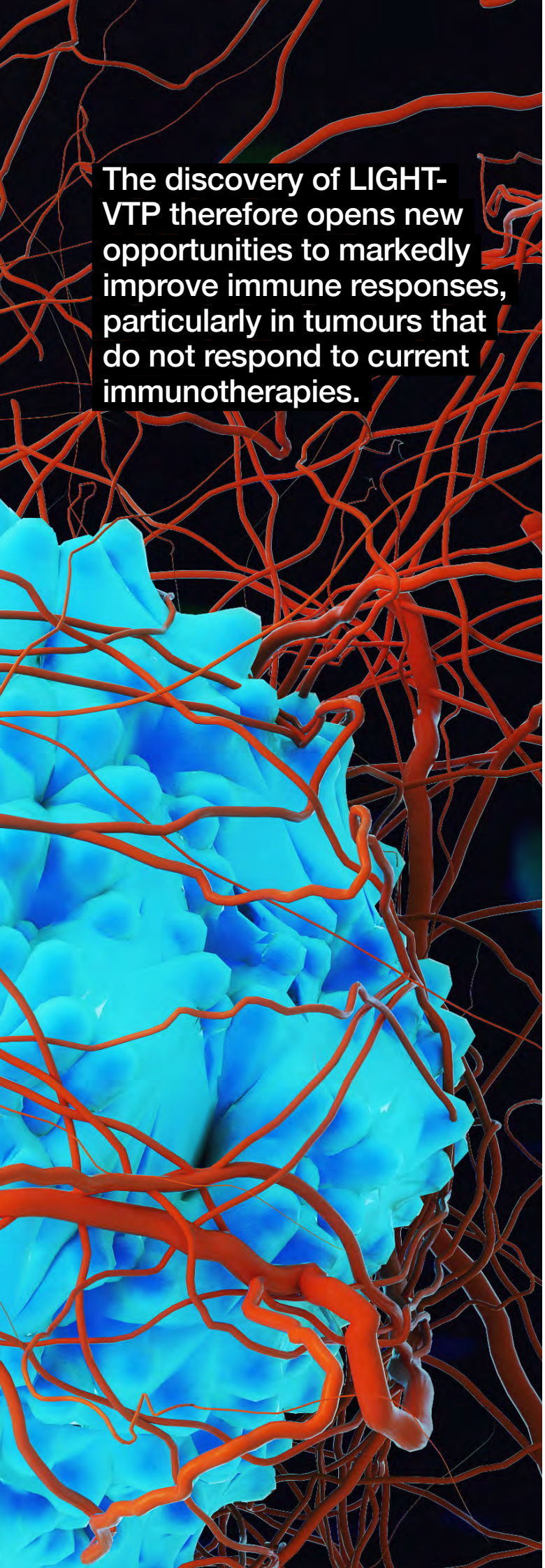
Author: Assoc Prof Anthony M George, School of Life Sciences, Faculty of Science, University of Technology Sydney.



A typical zeolite microporous structure, consisting of a tetrahedral network of oxygen and silicon atoms with aluminium replacing some of the silicon to form an aluminosilicate. The result is an extended honeycomb of channels and cavities through which zeolite can adsorb small molecules, ions, or gas molecules.

TURNING ON THE LIGHT IN CANCER





The discovery of LIGHT-VTP therefore opens new opportunities to markedly improve immune responses, particularly in tumours that do not respond to current immunotherapies.

To use the body's own immune system to fight cancer was a dream that has become reality with the arrival of immunotherapies.

Researchers from the Harry Perkins Institute of Medical Research in Perth have developed a new drug which transforms chaotic cancer blood vessels into a network of more "normal" blood vessels and generates lymph-node-like structures within the cancer, which together enable immune cells to better reach the cancer core. When successful, immune checkpoint inhibitors for example, enable activated T cells to attack cancer.

This kind of immunotherapy has now been approved in Australia for clinical use in advanced melanoma, lung and kidney cancers and provides exciting new treatment opportunities. However, success is not guaranteed. In fact, only 20-30% of patients respond to immunotherapy, raising the question: what else can be done to deliver benefits to more patients? A major focus of current cancer research globally is to discover why immunotherapies work or fail, and how they can be smartly combined with other treatment modalities.

A NEW DRUG TO REMODEL BLOOD VESSELS

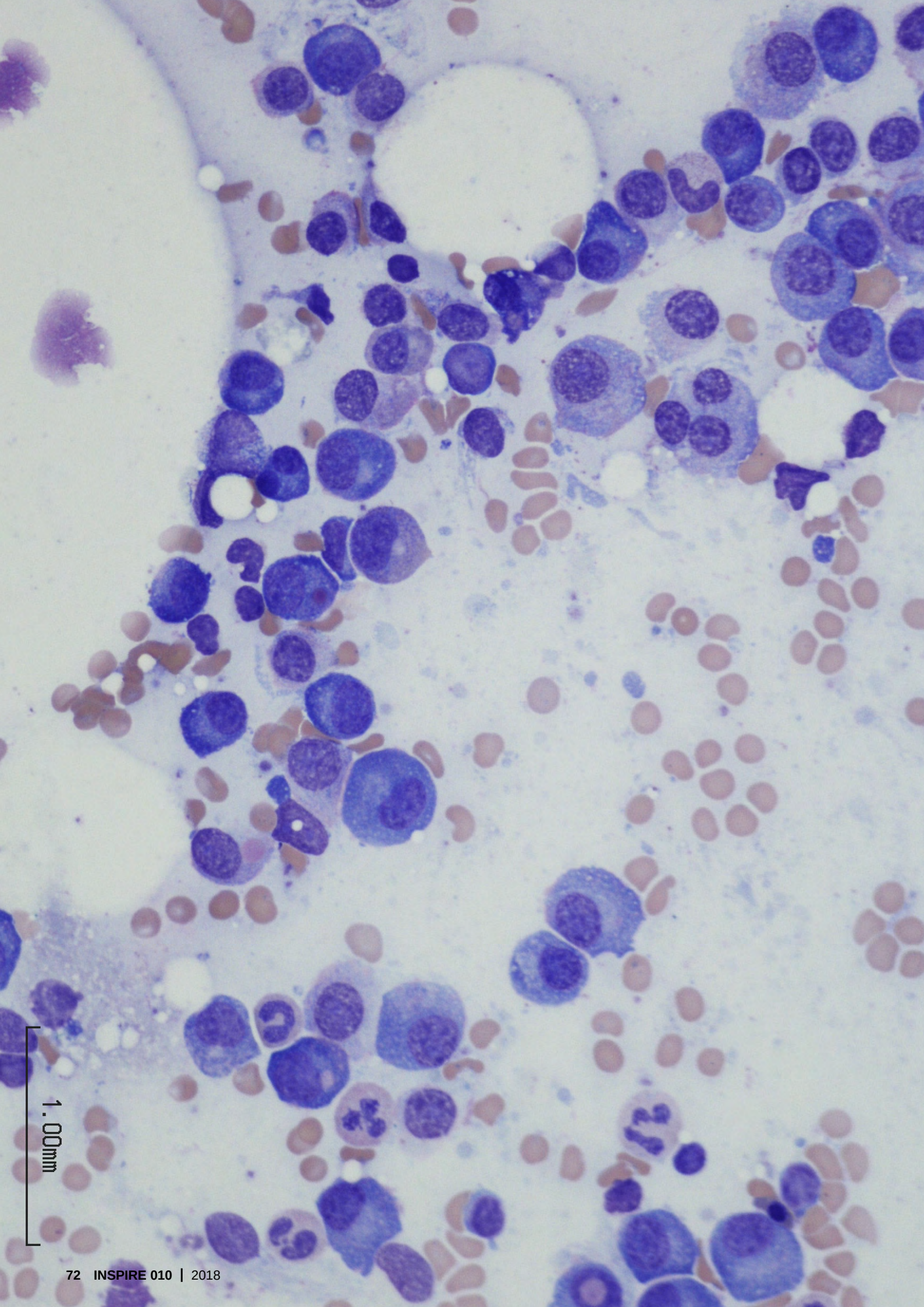
Why immunotherapies work or fail may be linked to the cancer microenvironment. The majority of cancers grow as a solid mass. The tumour cells are surrounded by diverse support cells which together form the cancer microenvironment. These cells nurture the tumour, foster unlimited growth and metastatic spreading, and also protect the tumour from destruction by the patient's own immune system.

> ***"The cancer's unique vasculature (the network of blood vessels that supply the tumour) is a critical part of this tumour microenvironment.***

It is formed in a process called angiogenesis where blood vessels are newly generated to provide nutrients and oxygen to the cancer. In a desperate act to feed the growing cancer, blood vessels form a chaotic, leaky and tangled network which is vastly different to the ordered blood supply in normal organs.

TUMOUR BLOOD VESSELS IN TARGET

Blood vessels are also an integral part of normal tissue immune surveillance and provide immune cells with the means to travel throughout the body and migrate into tissues to fight infections. However, this is not the case in tumours; one of the first hurdles immune cells encounter at the tumour site are the newly formed blood vessels which seem to restrict immune cell access.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These chaotic blood vessels surrounding the tumour block entry by the immune cells. This barrier creates an 'immune desert' in the tumour or a 'cold' tumour environment. 'Cold' tumours harbour fewer T cells compared to 'hot' tumours which are filled with immune cells of all flavours.

'Hot' tumours are often considered to be more sensitive or responsive to immunotherapy treatments because T cells are present within the tumour environment and more easily mobilised against the cancer.

In other words, when the patient's immune system can access the cancer the immunotherapy is more successful. The failure of checkpoint inhibitors to induce long lasting anti-tumour immunity in 80% of patients may therefore well be related to a 'cold' tumour environment and the blood vessels therein.

> ***"This work shows that 'cold' tumours can indeed be transformed into vaccination sites which boost the body's own immune system to fight cancer."***

In proof-of-concept studies, Prof. Ganss' laboratory at the Harry Perkins Institute of Medical Research has shown that 'normalizing' tumour blood vessels helps to bring immune cells or T cells deep into the cancer where they can be stimulated by immunotherapy to kill tumour cells.

Vessel normalisation in this context is the process which reverses angiogenesis and transforms chaotic cancer vessels into more anatomically organised, tighter and functional structures. However, until recently there were no drugs available which could induce long-lasting normalisation of these chaotic blood vessels, exposing a gap for much needed research activity.

A NEW DRUG TO REMODEL BLOOD VESSELS

This research culminated in the development of a new drug (called LIGHT-VTP) which combines the cytokine LIGHT, a member of the tumour necrosis factor (TNF) α cytokine family, with a vascular 'homing address', a short vascular homing peptide (VTP). The VTP part ensures exclusive binding to abnormal tumour vasculature. Once in the tumour, LIGHT induces all the hallmarks of a normalised vasculature in preclinical models of hard-to-treat and immunological 'cold' cancers such as pancreatic and brain cancers.

Following treatment, tumour vessels become tighter, with the added beneficial effect of reducing metastases. On close examination of the normalised vessels, it is evident that part of the tumour vasculature is also remodelled into high endothelial venules (HEVs), a highly specialised form of blood vessel that naturally occurs in lymph nodes where they act as entrance portals for immune cells.

TURNING COLD TUMOURS TO HOT

Excitingly, these HEVs on a background of normalised tumour vessels generate lymph node-like structures in the middle of the cancer. Producing a critical mass of immune cells that infiltrate deep into the cancer creates 'hot' tumours and sets the stage for successful immune checkpoint therapy.

In human cancers, lymph node-like structures can spontaneously arise and have long been reported by pathologists in particular in melanoma, breast, colorectal and lung carcinomas where they are considered to confer a better patient prognosis when compared to cancers lacking such structures. However, until recently these structures could not be induced therapeutically.

The discovery of LIGHT-VTP therefore opens new opportunities to markedly improve immune responses, particularly in tumours that do not respond to current immunotherapies. Angiogenic vessels are a common feature of solid cancers, and VTPs are able to bind to tumour vasculature in all tumours tested thus far including human cancers. Since current anti-cancer interventions are still broad, often systemic and associated with considerable toxicity, precision targeting and 're-educating' the abnormal cancer microenvironment is a promising concept to improve efficacy of anti-cancer therapies.

At the Harry Perkins Institute of Medical Research scientists specifically tackle the current limitations of immunotherapy and LIGHT-VTP is part of a program to develop innovative strategies aimed at converting 'cold' tumours into 'hot' tumours.

Author: Prof. Ruth Ganss, Scientific Head of Cancer Division, Harry Perkins Institute of Medical Research, The University of Western Australia, Perth, WA. This collaborative work has been published in Johansson-Percival et al. *Nature Immunology*, 2017.

THE LAST WORD

MOVING HEALTHCARE TO THE ARTIFICIAL INTELLIGENCE FRONTIER

Welcome to Research Australia's newly dedicated space for Opinion Editorial – a space to share the points of view of members, Research Australia's directors and sector thought leaders on pressing issues.

The English Prime Minister Theresa May has undertaken to use artificial intelligence (AI) technologies to transform the National Health System (NHS). Promising GBP one billion in investment spread across research and implementation, the hope is that AI can be harnessed to diagnose diseases like prostate, lung or bowl cancer at an earlier stage than currently possible. The most ambitious part of this proposed reform is to cut UK cancer deaths by 10%, or about 22,000 lives per year, by 2035.

Australia should take note. We, like the UK, have a health system that is among the global elite in terms of performance and cost-effectiveness. We too are struggling with the inevitable rush of retiring baby boomers and the massive challenge this presents for the sustainability of our health system.

THE CHALLENGE POSED BY OUR FUTURE

Put bluntly, we will soon be faced with proportionally fewer healthcare workers, more patients, and a relatively diminishing tax base. At the same time medical technology and treatments will become more expensive and ever more effective, resulting in patients living longer with multiple conditions. Added to this, the expectations of patients for more personalised healthcare is already on the increase.

Who is going to pay for all this? Who will take care of us? The choices seem stark. The financial calculus suggests that we will have to accept a lower standard of care or take on more of the burden of care ourselves as consumers. Or we could delegate parts of the healthcare process to AI. Indeed, Lord Darzi's recent review estimates that exploiting this untapped potential for automation in the NHS could release about GBP12.5 billion of productivity improvement, equivalent to about 10% of the English NHS budget.

Our national challenge is that we are nowhere near as ready as other nations to compete in or exploit this new AI arms race, and a race it is. Australia has a strong international reputation as a leader in digital health research, and its AI researchers are amongst the world's best. What we lack however, is a concerted effort to invest in this sector, to the benefit of our health system, and to develop our national capacity to compete in this defining 21st century industry.

INTERNATIONAL INVESTMENT IN AI

By comparison, last year the State Council of China announced an ambitious policy for the nation to become "the world's primary AI innovation centre" by 2030. China is for example, building a $2.1 billion AI technology park in Beijing's western suburbs and the country's AI industry is forecast to be worth $150 billion in a decade. The U.S. government's total spending on civilian AI programs in 2016 was about USD1.2 billion and the UK has already invested hundreds of millions of pounds into AI and data analytics as part of more than GBP1.4 billion invested in research and development to support its Cancer Research UK Grand Challenge programme, which includes AI.

WHAT SHOULD AUSTRALIA DO IN RESPONSE?

Firstly, AI needs to be seen as a critical future element of our national healthcare delivery strategy. It is one thing to talk about the power of big data, analytics and precision medicine. It is another to translate the insights from data into actions that save lives. That is where AI comes in. AI is essential, not just to help us discover more about the science of health and illness, but in the

design of intelligent systems that utilise this knowledge to deliver care.

The new Frontiers program within the Medical Research Future Fund provides a key mechanism to begin to fund this urgent national mission.

AN AI ENABLED HEALTH SYSTEM

What will an AI enabled health system look like? No one is surprised today by our ability to ask the digital assistant on our phone to answer straightforward questions, or to go online and get symptoms checked by an app. We might be surprised in a few years to discover how much more of our healthcare these digital assistants can help us with from diagnosis to guiding patients along preventative health pathways. Within a decade, machines are more likely to be diagnosing many of our medical radiological images or images of skin lesions. AI will be used to automatically generate clinical records – releasing clinicians from keyboard slavery so that they can better concentrate on what they do best, making shared decisions with patients.

> ***Perhaps most tantalisingly, AI will assist in tailoring care to individuals. By harnessing machine learning, intelligent agents will help synthesise the evidence from multiple sources including published trial data, personal genetic and biomarker profiles, and the outcomes for similar patients extracted from electronic health records.***

AI is no panacea however, and many are rightly asking that we develop frameworks for the ethical and safe use of AI to ensure it is used in ways that lead to better outcomes, and not create new risks or harms.

AI and machine learning also bring new challenges to our understanding of data governance and privacy, and it is hard to imagine significant technological change in healthcare without appropriate principles and governance structures to support it. There is also much angst about the implications of AI for the future of clinical work and the very existence of some of the professions. If history is any guide, we are more likely to see professional change and opportunity rather than redundancy over the next two decades. For these changes to be successful, there will need to be a concerted effort to fully engage patients as well as clinicians in the design of such transformed health services.

Australia still has a chance to engage in this new industrial revolution, both to make sure we can deliver the healthcare we would hope for over the decades to come, as well as to ensure our nation shares in the economic benefits of competing in this new industry. The pace of what is happening around the globe means however, that this window will not remain open to us for long.

Author: Professor Enrico Coiera is Foundation Professor of Medical Informatics at Macquarie University, and Director of the Australian Institute of Health Innovation's Centre for Health Informatics, a group he co-founded in 2000. He is also the Director of the NHMRC Centre of Research Excellence in Digital Health.

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