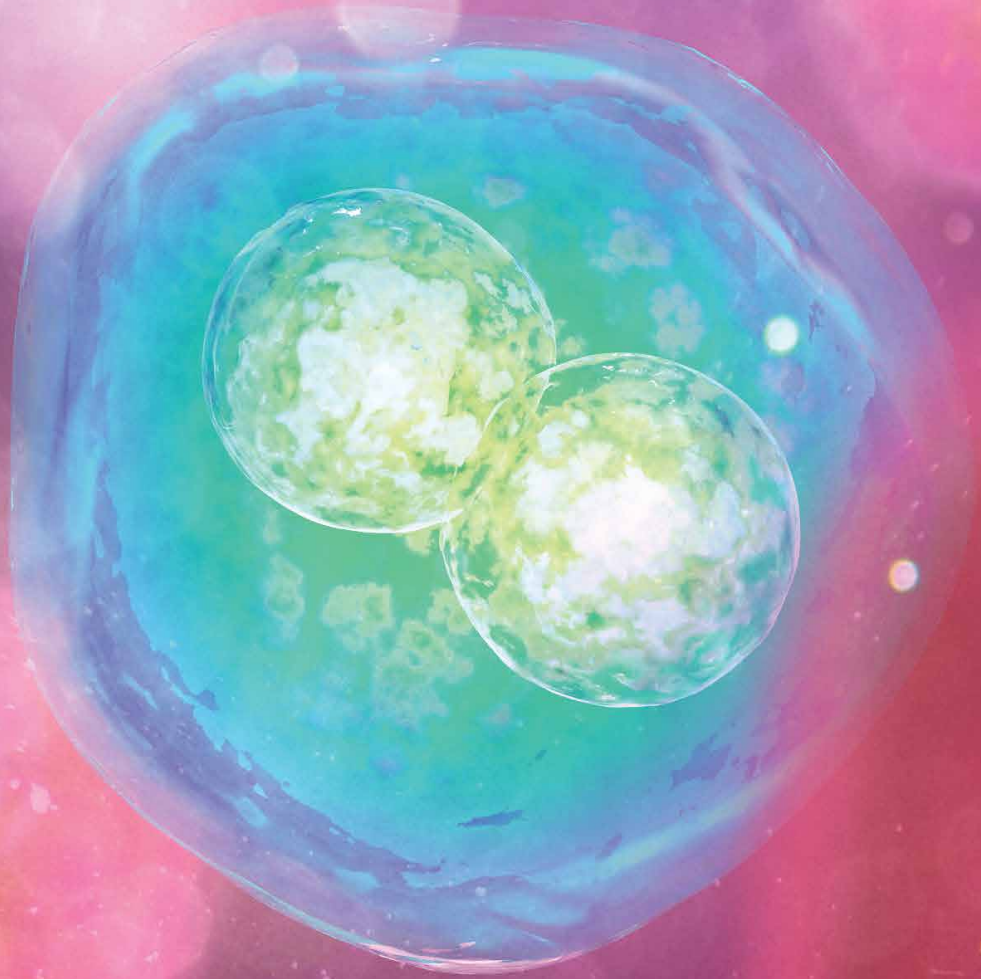
Scientia

HIGHLIGHTS IN HEALTH RESEARCH



EXCLUSIVES:

- National Heart, Lung, and Blood Institute
- Soapbox Science

HIGHLIGHTS:

- Imaging Multiple Sclerosis: Searching for Patterns in the Brain
- Defining Acupuncture's Place in Western Medicine
- Shining Light on Paediatric Cancers
- Do Modern Lifestyles Cause Food Allergies?

Issue: #111

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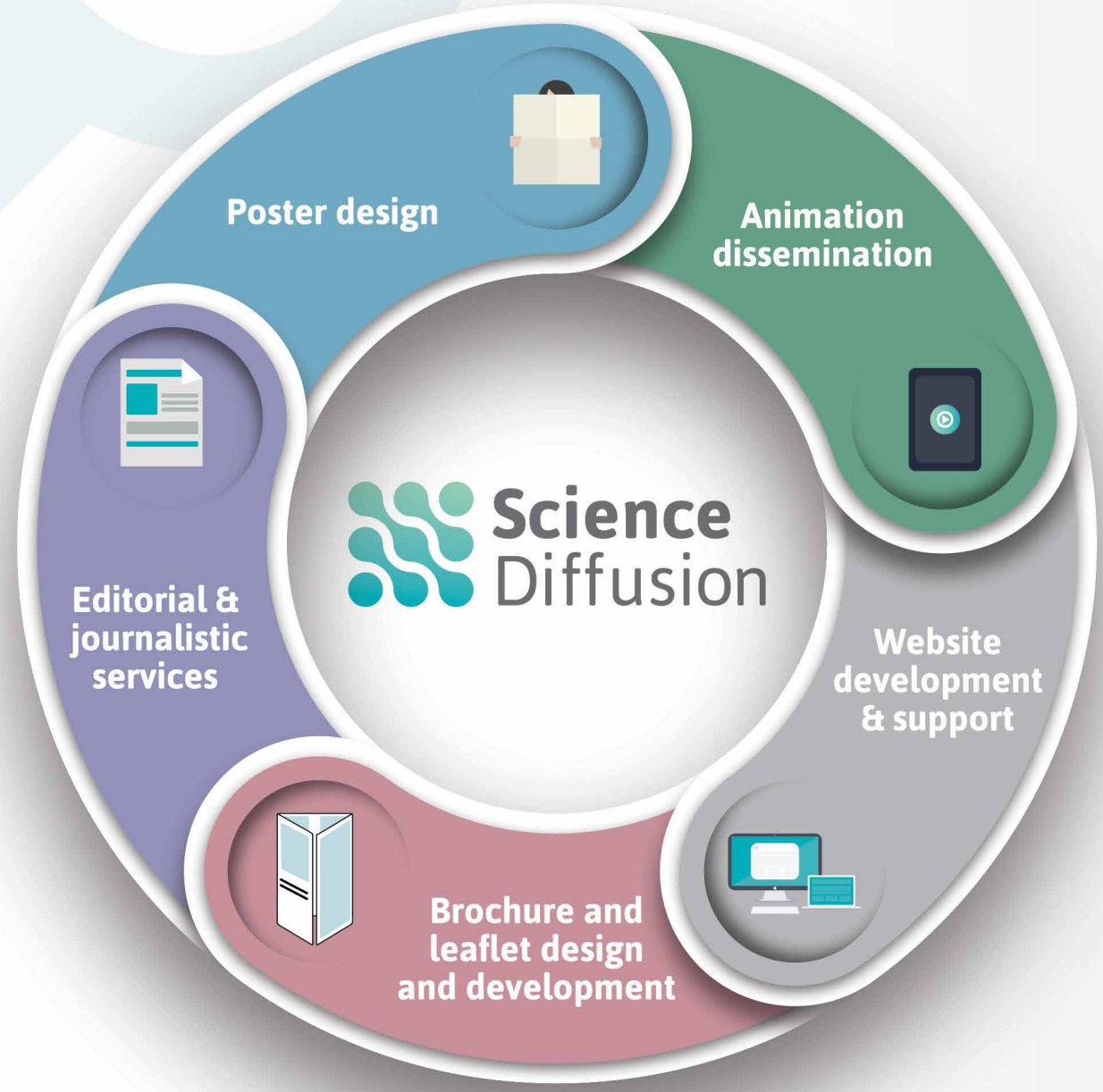

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WELCOME...

Fragility and mortality are inherent traits of every lifeform on Earth, and human beings are no exception. The complexity of biological systems means there are many things that can go wrong – and they frequently do. This vulnerability has driven the healthcare revolution over the last few decades, where modern research techniques and empirical evidence have resulted in our living longer and more comfortably than ever before. In this edition of Scientia, we celebrate some of the many researchers at the forefront of this revolution.

To open the edition, we have had the pleasure of speaking with Dr Seirian Sumner and Dr Nathalie Pettorelli, co-founders of Soapbox Science – a public outreach platform to promote women scientists and their research. In this exclusive interview, the pair tell us about Soapbox Science's work in bringing science to the public, promoting women scientists, and encouraging girls to pursue STEM careers. Immediately following is an introduction to The Sepsis and Critical Illness Research Center at the University of Florida – a new organisation dedicated to tackling sepsis from biological, clinical and translational standpoints.

From here, we become immersed in the world of psychology and neuroscience, where we highlight a diverse array of research projects, ranging from improving refugees' psychological wellbeing to mastering neuronal repair following spinal cord injury. Our next section then showcases the latest in respiratory research, where we introduce the work of four research teams, each dedicated to improving the lives of people with lung conditions. To introduce this section, we had the chance to interview four division directors of the National Heart, Lung, and Blood Institute (NHLBI).

Next up is two research projects that aim to improve lifestyle-related conditions – metabolic disease and food allergies. In this section, Dr Mario Noti and his team aim to investigate if the Western diet causes changes in our gut flora that lead to allergic disorders. From here we move on to highlight the latest in cancer research – from exploring the epigenetic pathways in paediatric cancer to developing new therapeutic strategies for patients with chronic lymphocytic leukaemia.

Not wanting to restrict the edition to human health, our final section features two projects dedicated to improving the health of our equine allies. Here's to future medical breakthroughs and better health for humans, and indeed all inhabitants of our little planet.

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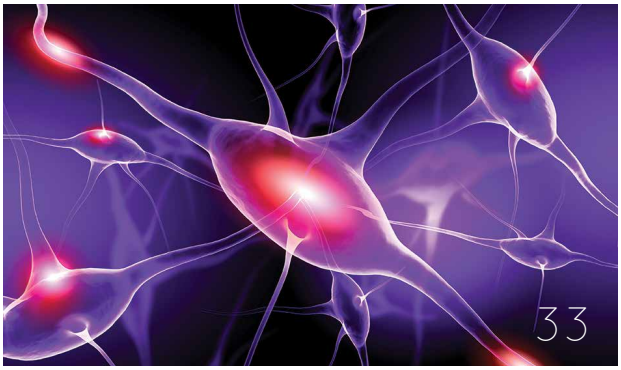

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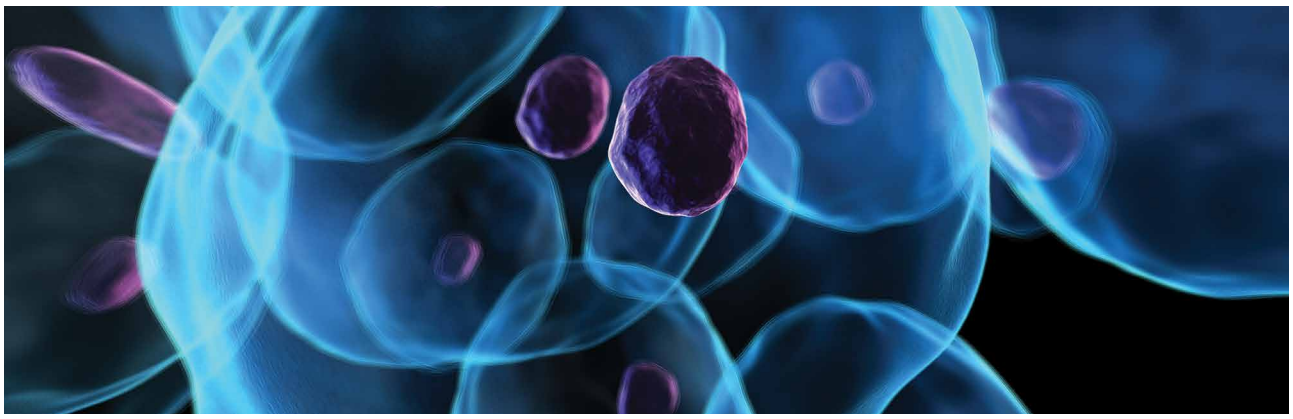

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SOAPBOX SCIENCE

Dr Seirian Sumner and Dr Nathalie Pettorelli

Soapbox Science was founded as a public outreach platform for promoting women scientists and their research. Now in its seventh year, Soapbox Science takes female scientists out of the lab and onto the streets, to talk to the passing, unsuspecting public about science. Using a format inspired by Hyde Park's famous Speaker's Corner in London, the researchers stand on soapboxes (up-turned crates), while enthralling children and adults alike with their latest scientific discoveries.

In this exclusive interview, we have had the pleasure of speaking with the two co-founders of Soapbox Science – Dr Seirian Sumner of University College London and Dr Nathalie Pettorelli of the Institute of Zoology. Here, the pair tell us about Soapbox Science's work in bringing science to the public, promoting women scientists, and encouraging girls to pursue STEM careers.


Alba Maiques-Diaz at Manchester in 2016. CREDIT: Joanne Pennock

‘By giving female scientists a (literal) pedestal from which to talk about their science, they enjoy the exposure, media interest and confidence boost that we hope can make a real difference to their careers’

Dr Veronica Fowler at London in [illegible]
CREDIT: Soapbox Science

To begin, please tell us a bit about Soapbox Science’s mission.

Nathalie: Our initiative has two missions. Firstly, Soapbox Science aims to bring science to the public who would not otherwise seek out, or have the inclination or opportunity, to meet a scientist and learn first-hand about their work. Our format embraces the idea of widening participation in science: influencing not only children, but also families and peers, such that they are encouraged and supported to go on to be a scientist. We particularly hope that our efforts will help generate a new generation of young women who have the courage, confidence and passion to follow science as a career, with no prejudice or bias in their way.

Secondly, it aims to raise the profile of our speakers and contribute to furthering their careers in STEM. It’s early days yet, but we seem to be hitting our goal! Our speakers tell us how taking part in Soapbox has attracted invitations for committee memberships, plenary lecturers, ambassador roles, and promotions within their working environments. By giving female scientists a (literal) pedestal from which to talk about their science, they enjoy the exposure, media interest and confidence boost that we hope can make a real difference to their careers.

Both of you founded Soapbox Science back in 2010 – what gave you the idea to set up such an organisation?

Seirian: We were both sad to see our female peers disappear around us, as we progressed in our careers. As we grew up in the science community, we met fewer and fewer of our female colleagues and friends from our PhD or postdoc days, many of which we know left science altogether. At that point in time, we were lucky enough to be working in a relatively gender-balanced scientific institution (Institute of Zoology, ZSL), but we soon realised that we were in an unusual situation.

This realisation came into sharp focus when we both won L’Oreal For Women in Science Fellowships: these awards marked our achievements as early career women in science, giving us a confidence (and financial!) boost. These awards also made us wake up to the real issue of gender inequality in the science community.

We wanted to make a difference: we knew we couldn’t move mountains. So, we settled for a cheap, no-frills, transportable solution that challenges the public’s perceptions about gender equality issues in science and raises the profile of the female scientists we see around us.

As you mention, there are still much fewer women than men in top academic positions in the UK and internationally – what do you believe are the main reasons behind this?


CREDIT: Soapbox Science

Seirian: A lot of work has been done on exploring reasons for the lack of women in top academic positions. Part of the answer lies in the steadily declining number of women as you progress the career ladder, and part in the gender differences in the likelihood of being promoted. Research has started to focus on factors pushing women out of STEM, and it turns out that many of these factors (namely implicit bias, stereotypes and stereotypes threat) are also the ones driving gender bias in promotions. Ultimately, it's all about perceptions of women's roles and women's skills in the family unit, at work, and in society, and how these perceptions influence external decisions related to professional progression and individual women's confidence. As long as female scientists will be perceived as less competent, less hireable and less reliable than their male counterparts, we will struggle to achieve true parity in STEM.

Does Soapbox Science also engage with policy makers in the hope of increasing gender equality in the STEM workforce?

Nathalie: We are definitively working towards this goal. Last year, we were invited to a UK governmental select committee to provide evidence on science communication. The agenda was not explicitly about Gender, however, ensuring that the genders are equally represented and that the material is presented in a way that is equally appealing to both sexes is necessary when trying to improve the public's understanding of science, and the public's relationships with science and scientists. Our initiative was also mentioned in various governmental reports on gender bias in STEM, and we regularly interact with learned societies and equality charters to share our experience and expertise with them.

Tell us about some of the events that you have planned for 2017, and what you are most excited about.

Nathalie: 2017 is our biggest year so far, with events taking place in Belfast, Newcastle, London, Exeter, Brighton, Hull, Milton-Keynes, Edinburgh, Bristol, Cardiff, Manchester and Swansea. This year we are also launching our Art and Science Soapbox events, which will combine artistic skills and scientific work to explore new ways of enthusing the general public with science. We will have four Art and Science events in the UK this year, including Leeds, London, Lincoln and Oxford. Finally, last year saw our first international event in Brisbane, Australia; this year, we've got new events springing up in Canada, Germany, Italy and Ireland! We are super excited to see Soapbox becoming more and more international every year, but we are similarly really excited to launch our new Art & Science events, which will help demystify the idea that Science and Arts are mutually exclusive. This year, it's difficult for us to know what we are the most excited about!

Finally, what do you see as the biggest challenges facing Soapbox Science's work over the next few years?

Seirian: Our biggest challenge is knowing how we will keep Soapbox going if and when the funding runs out. We've been blown away by the enthusiasm for Soapbox over the last few years. Each new event is born from the motivation and drive of the local organiser, often a previous speaker, who approached us asking if we would support their event. Running a Soapbox event is a lot of work, and we've learned through trial and error what works and what doesn't. We have worked hard to ensure that each Soapbox event is of the very best quality. We encourage all events to conform to our tried and tested format, with appropriate use of branding and sponsor accreditation. So, we put a lot of effort into building capacity at each new location, such that they are equipped to run the best events year after year. To do this, we provide local organisers and speakers with training (in person or online); we make resources including how-to packs available to speakers, local organisers and volunteers; we organise the call for speakers and volunteers centrally, promote all events, speakers and team on our website, advertise each event and speaker via traditional and social media channels; we edit and host blogs written by speakers and local organisers; we produce umbrella press releases for local organisers to adapt; we provide a standardised evaluation procedure and produce event-specific evaluation reports… At the same time, we are full time academics/research scientists, and we are both mums!

We are very lucky at the moment to have secured funding from the Science Technology Research Council (STFC), which pays the salary for a full-time administrator, Isla Watton. She is our life line! Our constant worry is that one day we won't have this support. When Soapbox was just 1–4 events a year, the two of us could just about manage. But the appetite for the expansion of Soapbox, nationally and globally is overwhelming, and we cannot sustain this without administrative help. So, our biggest challenge for the future? Securing long term funding and financial security!

www.soapboxscience.org
@SoapboxScience

THE SEPSIS AND CRITICAL ILLNESS RESEARCH CENTER: FROM PATIENTS TO THE BENCH AND BACK

By taking a complex disease and breaking it down to its basics, The Sepsis and Critical Illness Research Center (SCIRC) has evolved into an organisation with the unique ability to tackle sepsis from biological, clinical and translational standpoints.

What is Sepsis?

Sepsis is a serious complication that arises from the body's adverse response to a prevailing infection. In the past, sepsis often led to multiple organ failure and early death, but due to improvements in treatments and surgical techniques, patient survival has increased. However, long-term mortality and inadequate functional recovery remain a significant burden. Patients – especially the elderly – who survive episodes of sepsis are still discharged to long-term acute care and skilled nursing facilities, and rarely rehabilitate completely. Therefore, although in-hospital mortality has decreased, the burden of care has simply been shifted to other facilities. Many patients in surgical Intensive Care Units (ICU) that are diagnosed with sepsis present symptoms that progress towards morbid long-term outcomes, a phenotype that is now referred to as Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS).

At least a million people in the US are diagnosed with sepsis every year, out of which 30–50% eventually die. To put this into perspective, these figures imply that the mortality rate of sepsis is higher than that of prostate cancer, breast cancer and AIDS combined. Moreover, the Agency for Healthcare Research and Quality has identified sepsis to be the most expensive condition treated in US hospitals. Hence, a full understanding of the causes of sepsis, its clinical presentations and the response to treatment is urgently required.

From Idea to Inception: The Sepsis and Critical Illness Research Center

The Sepsis and Critical Illness Research Center (SCIRC), the first of its kind in the US, was set up in 2014 with the mission to attack sepsis from all angles. The Center aims to do so by undertaking basic research to understand the manifestations of the disease, improving patient care through the use of advanced technology, educating healthcare professionals on best practices, providing community access to relevant information, and finally, by engaging in external fund-raising and advocacy initiatives. The Center's multiple collaborations with universities and healthcare entities, such as UF Health Shands Hospital, combined with a multi-disciplinary approach to research (combining basic, clinical and translational research) offers a unique opportunity to understand and tackle this complex disease.

The SCIRC was conceptualised by Dr Frederick Moore, who was hired in 2011 to head acute care surgery in the University of Florida (UF) Health Shands hospital and by Dr Lyle Moldawer, Professor and Vice-Chair of Research in the Department of Surgery at UF. They received a $12 million, five-year P50 grant from the National Institute of General Medical Sciences (NIGMS), for the purpose of creating a regional and national specialised organisation dedicated to sepsis research and treatment. Dr Moore brought with him expertise in creating translational research

teams studying multiple organ failure, while Dr Moldawer is a world renowned expert in the basic immunological events that occur before, during and after sepsis. Briefly, a severe septic insult simultaneously results in both pro-inflammation (Systemic Inflammatory Response Syndrome) and anti-inflammation (Compensatory Anti-inflammatory Response Syndrome). If this response is not well managed, patients fail to return to immunologic homeostasis and many progress into chronic critical illness. Dr Moore and Dr Moldawer were the first to coin the term PICS to describe the underlying pathophysiology of persistent low grade inflammation, immunosuppression and catabolism that causes the progression of disease into a state that leads to long stays in the ICU, followed by dismal long-term outcomes. By understanding more about the causes of sepsis, its incidence and the progression of PICS, the Center hopes to reduce the burden on the healthcare system and to significantly improve the quality of life and long-term survival outcomes of patients.

The SCIRC's origins date back to 2004, when the UF Health Shands hospital hired Dr Larry Lottenberg to establish a much-needed Level 1 trauma facility for North Central Florida. One year later, a new South Tower was constructed in the Shands hospital with a state-of-the-art trauma and critical facilities. At the same time, over 50% of the Department of Surgery's NIH funding was with Dr Lyle Moldawer, who was already conducting innovative sepsis and trauma basic research. The watershed event happened in 2011, when Dr Frederick Moore was recruited, with the purpose of building a clinical/translational research program dedicated to sepsis and trauma. A multidisciplinary science team was soon put together, which involved collaborations between the Department of Surgery and Anaesthesiology, the Department of Molecular Genetics and Microbiology, the Institute on Aging and the Division of Nephrology. The surgical ICUs were reorganised to perform multidisciplinary translational research. The team went on to establish hospital-wide sepsis surveillance and treatment bundles, and incorporated the use of Computerised Clinical Decision Support (CCDS) systems in the surgical ICUs. They showed that the implementation of sepsis screening and CCDS reduced mortality of severe sepsis from 35% to 14%. In 2013, the Institute on Aging also moved into two new buildings. With over 40,000 square feet of office and clinical space, the institute serves as a perfect base for discharged patients to return for cognitive and functional testing.

Building on Years of Experience and Research

Research related into the dysfunctional inflammatory response that causes multiple organ failure (MOF) led by Drs Moore and Moldawer over the past three decades culminated in the formation of the SCIRC. With advances in ICU care over past decade, far fewer patients are dying early from MOF but many are progressing into chronic critical illness (CCI), defined as > 14 ICU days with persistent organ dysfunction. Based on their understanding, the team coined the term PICS to describe the underlying pathophysiology of the subgroup of CCI patients who go on to experience dismal long-term outcomes. While looking through the University of Florida's clinical databases of patients between 2000 and 2010, it was found that of the 51,577 people who underwent major surgery, 3.8% developed sepsis. 82% of those patients were hospitalised in the ICU for more than 14 days and 62% of these patients died within 2 years. These numbers show that major surgery complicated by sepsis is strongly associated with prolonged stays in the ICU and dismal long-term outcomes. A recent prospective study conducted by Drs Moore and Moldawer confirmed these observations. Of 145 surgical patients who developed

sepsis, in hospital mortality was only 13%, but half of the survivors progressed into CCI, of which only 20% were discharged to home. These CCI patients have biomarkers that are consistent with the chronic low grade inflammation, immunosuppression and catabolism that characterises PICS. They have also documented a persistent expansion of myeloid derived suppressor cells (MDCSs) after sepsis similar to that seen in patients with metastatic cancer who experience a PICS-like phenotype. Interestingly, the increases in MDSCs seen in post-sepsis patients are remarkably similar to those observed in advanced cancer and metastatic disease. It is these similarities that provide a rationale for using therapies successful in reversing cancer immunosuppression in patients with sepsis.

One novel and exciting project that the SCIRC is involved with is based on the hypothesis that even mild kidney injury has a poor prognosis and contributes significantly to the persistent state of inflammation. Towards this, researchers in the Center conducted preliminary analysis on available databases – they identified patients after major blunt trauma or severe sepsis who had no previous history of kidney disease. They found that acute kidney injury (AKI) occurred in a surprisingly high percentage in both groups, and patients with even mild kidney injury were three times more likely to die in hospital compared to patients without kidney injury. Based on this data, the team propose to carry forward this research of the link between AKI and PICS.

An Integrative Approach to Tackle a Complex Disease

The multidisciplinary proposal by the SCIRC to understand and manage sepsis is broadly divided into three projects. The first project led by Dr Moore, along with Dr Scott Brackenridge, Assistant Professor of Surgery and Dr Stephen Anton, Associate Professor and Chief of Clinical Research Department of Aging and Geriatric Research, focuses on understanding the prevalence, prediction and long-term outcomes. In this clinical trial, they plan to enrol 400 surgery and trauma ICU patients who are newly diagnosed with sepsis over a four-year period. The incidence of PICS and patients' long-term survival and functional recovery will be noted, while also measuring quantitative biomarkers in blood, urine and tissue samples to assist in prediction and in understanding the underlying pathophysiology. Outpatient measures such as cognitive and functional performance will also be measured in collaboration with the Institute of Aging.

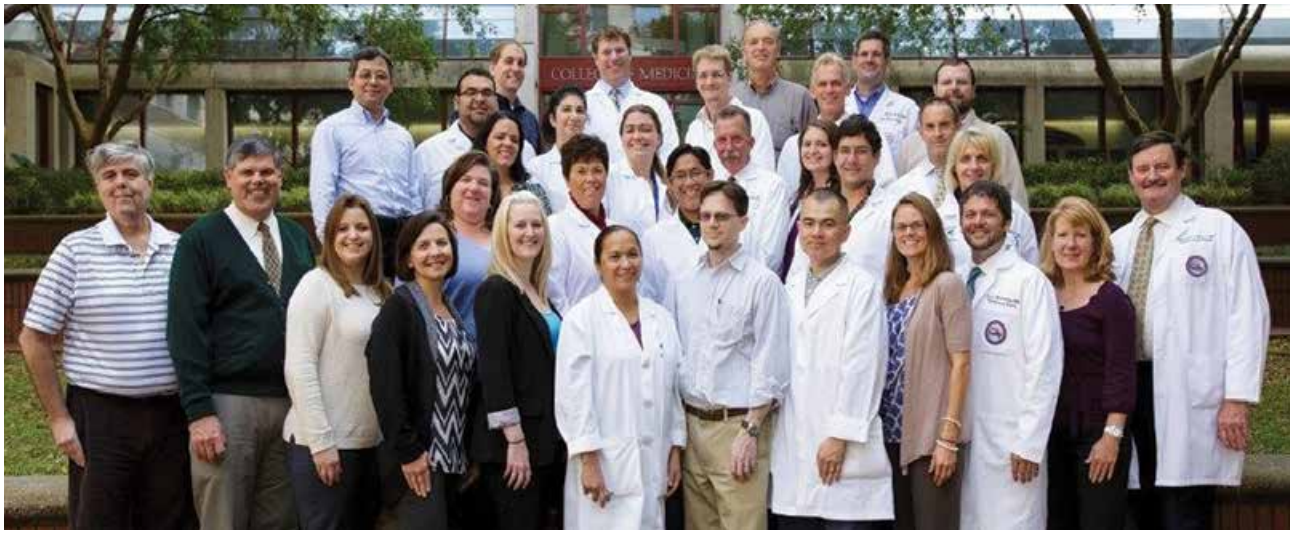
The second project aims to understand the biological basis of the disease, through the study of myeloid derived suppressor cells (MDSCs). These are immature cells derived in the bone marrow, and evidence suggests that sepsis induces rapid and persistent expansion of these cells. This hypothesis will be led by Dr Moldawer along with Dr Philip Efron, Associate Professor of Surgery and Anaesthesiology, and Dr Christiaan Leeuwenburgh, Professor and Chief of the Division of Biology of Aging in the UF Department of Aging and Geriatric Research. The team's work has previously demonstrated that the expansion of these cells is accompanied by a loss of expansion of mature immune cell and stem cell phenotypes in patients presenting with PICS. This hypothesis ties in closely with the third project proposed by the Center, led by Dr Mark Segal, Professor and Chief of the UF Department of Medicine's Division of Nephrology, Hypertension and Renal Transplantation, and Dr Azra Bihorac, Associate Professor of Anaesthesiology, Medicine and Surgery. This strand aims to explore the idea that acute kidney injury results in an imbalance of growth factors, which leads to inhibition kidney repair and drives the expansion of MDSCs. By learning more about the biological events that drive PICS, the Center hopes to pinpoint quantifiable prognostic markers of the disease.

The current program includes faculty from multiple UF colleges with strong interactions with the Institute on Aging, Clinical and Translational Science Institute, Shands UF Health and the Biomedical Engineering Department. SCIRC serves as a tool to promote further collaboration throughout UF Health and with community and corporate partners. This infrastructure has enabled affiliated investigators to garner additional extramural NIH funding. It also plays the unique role of developing young investigators who absorb the cultural and scientific philosophies of team science that cannot be gained by working in a typical RO1 funded investigator lab. Not only are they mentored by older, more established physician-scientists, but they frequently have close interactions with basic health scientists, biomedical engineers, biostatisticians, computational biologists and medical ethicists.

In order to successfully undertake such complex, multi-faceted research, the SCIRC has several support structures in place. In addition to an Administrative Core, a Human Subjects Core is responsible for screening and selecting patients for trials and for obtaining blood and urine samples. These samples will be processed by a Bioanalytics Core that also aims to centralise analysis of tissue samples to reduce costs and improve efficiency of testing. Moreover, a Data Management and Biostatistics Core ensures the digitisation and automatic updating of patient electronic health records. Finally, an Animal Studies Core provides the Center with consistent sepsis mouse models for the study of pre-clinical interventions.

Conclusions

There is a compelling need to better understand the long-term consequences of sepsis in surgical ICU patients and the evolving management of these patients. The current challenge is to return these individuals to a functional life, and to reduce the burden on the healthcare system and society in general. The SCIRC is a unique, one-of-a-kind centre that is built around the hypothesis that the predominant phenotype of critical illness after sepsis is again evolving, and with it, are new challenges diagnostically and therapeutically. Clinical outcomes of patients admitted with sepsis are continually monitored to better understand the disease, and these findings are then taken back into the lab to develop new therapies. Eventually, these therapies find their way back to patients through clinical interventions in what is a successful feedback loop. By taking a complex disease and breaking it down to its basics, the SCIRC has evolved into an organisation with the unique ability to tackle sepsis from biological, clinical and translational standpoints.



Meet the researchers

Dr Lyle Moldawer
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Dr Lyle Moldawer received his PhD in Experimental Medicine in 1986 from the Gothenburg University in Sweden. For the past 30 years, he has conducted inflammation research testing key hypotheses that explore the inflammatory response to trauma and sepsis. Funded continuously by the National Institute of Health (NIH) for over 25 years, Dr Moldawer is a past NIH MERIT Award recipient. His current research at the University of Florida focuses on populations at the highest risk of developing sepsis, the very young (premature infants) and the very old. He has published over 400 peer-reviewed publications and has been cited more than 28,000 times.

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For the past 30 years, Dr Frederick Moore has conducted translational research testing key hypotheses related to the pathogenesis of multiple organ failure (MOF). He earned his medical degree from the University of Pittsburgh in 1979 and completed his general surgery training at the University of Colorado Health Science Center (UCHSC) in Denver. Over the past 30 years, he has participated in three NIGMS P50 sponsored team science grants related to MOF at UCHSC, followed by the University of Texas in Houston and most recently at the University of Florida, where he is now Head of Acute Care Surgery. Over his career, Dr Moore has studied the evolving epidemiology of MOF and its management strategies. He has published over 350 peer-reviewed publications and delivered over 500 invited presentations.

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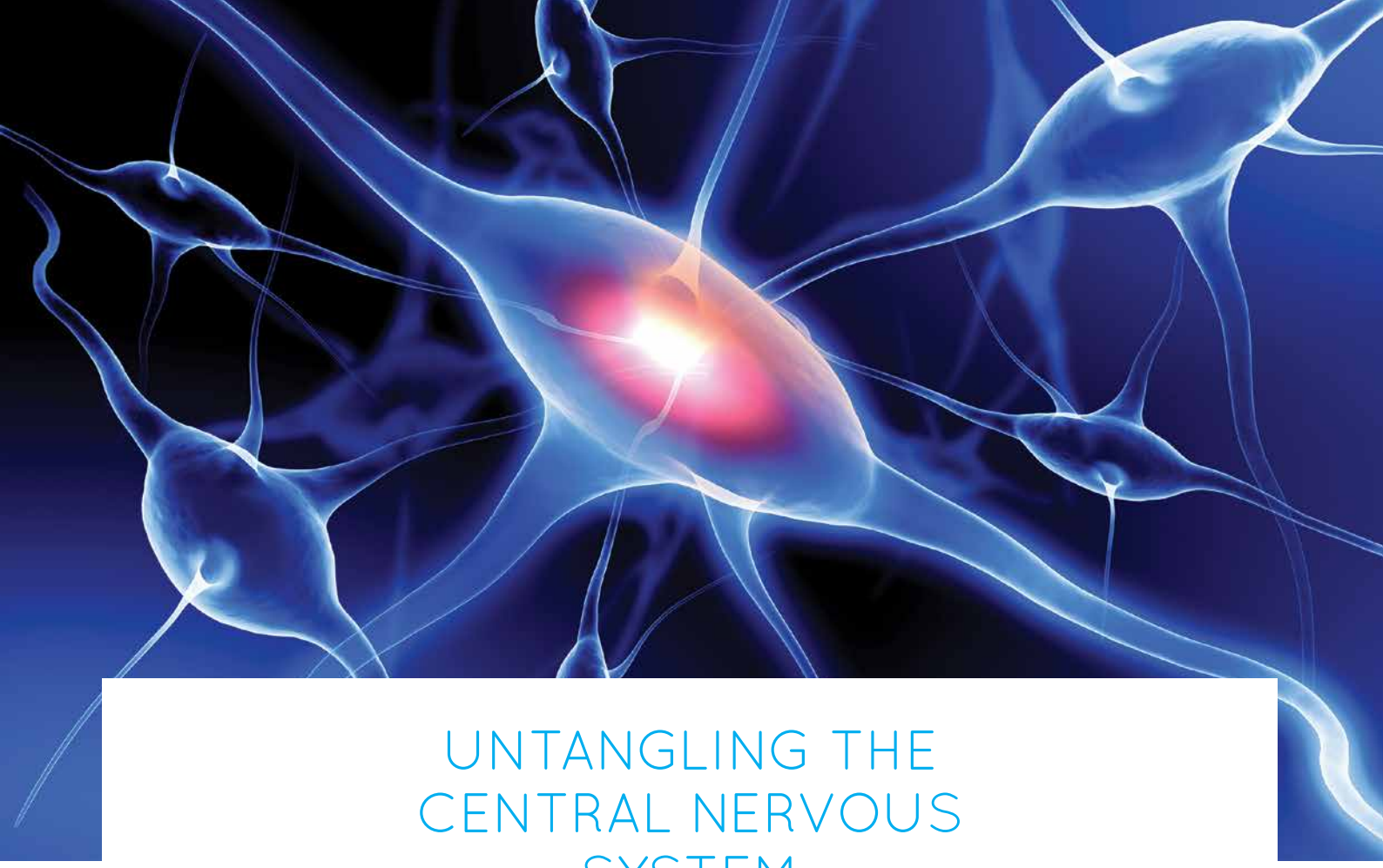


UNTANGLING THE CENTRAL NERVOUS SYSTEM

In this section of the edition, we dive into the complex word of the central nervous system, where we investigate the latest brain and spinal cord research. Starting off in the world of human psychology, we then burrow deep into the brain's biological processes, before finally sliding down the spinal cord.

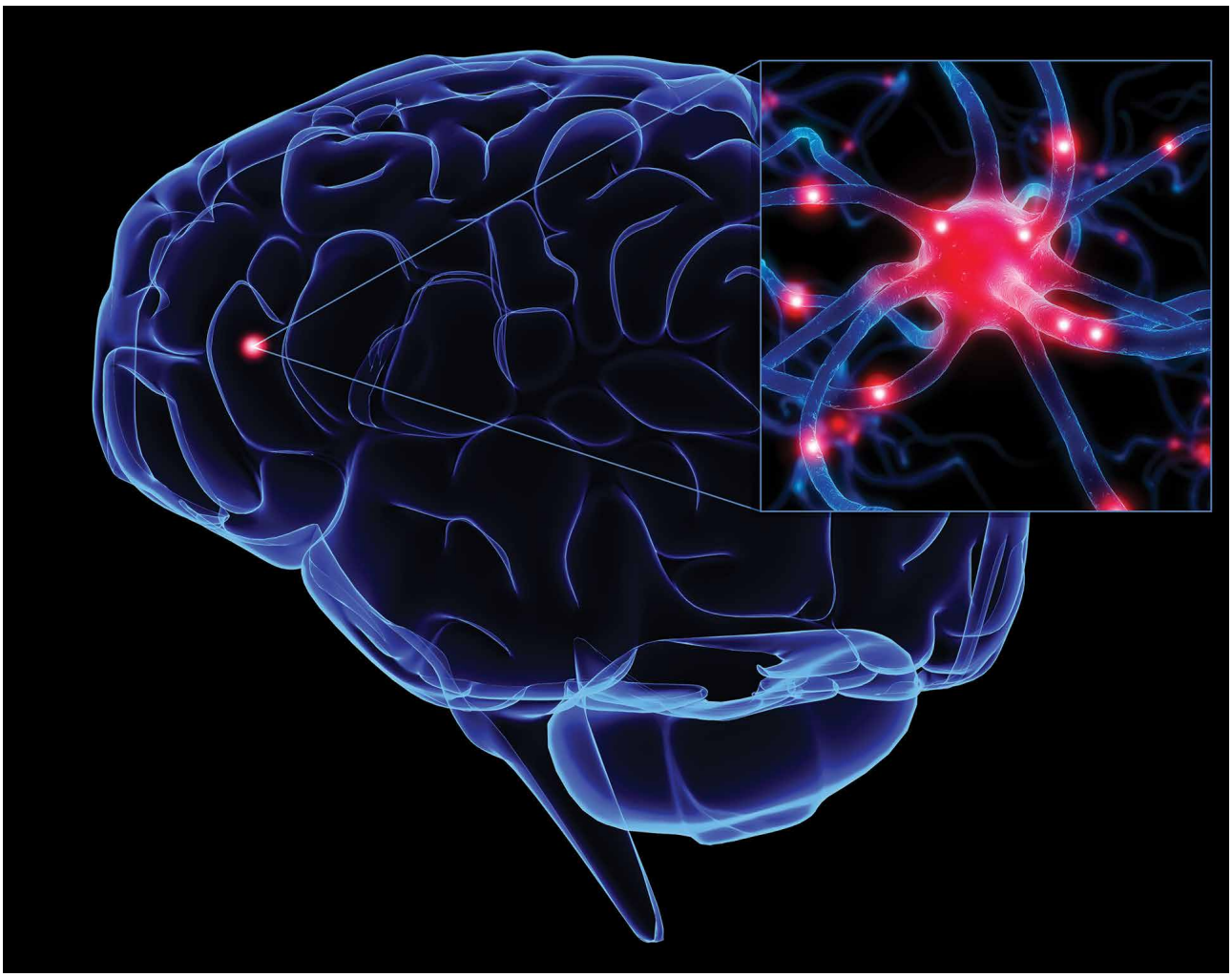
First up is recent research from the University of Zurich in Switzerland. Here we meet Professor Ulrich Schnyder and his team of psychological researchers, who are working to understand the psychological burdens carried by refugees, in the hope of improving their psychological wellbeing. This research has the potential to enhance the mental health of an enormous number of people, as the current number of refugees is estimated to be over 65 million, and continues to rise. Next, we introduce psychologist Dr Jeffry Simpson and his research team at the University of Minnesota. Through studying a participant group of approximately 170 people for over 35 years to date, the team has been investigating how our earliest experiences shape our lives into adulthood. Dr Simpson is now beginning to be able to predict which children will be at the highest risk for both psychological and physical ailments as adults, and is elucidating how children who were raised in stressful environments may be protected.

From here, we become fully immersed in world of neuroscience, where we first explore the neurological processes behind how we perceive the world. Here, we highlight the work of neuroscientist Dr Detlef Wegener and his colleagues at the University of Bremen's Brain Research Institute in Germany. His team investigate the many ways that our brains process the deluge of sensory information that bombards us at each moment. By studying monkeys, the researchers can perform precisely targeted neuronal recordings, pinpointing the distinct neuronal mechanisms that may underlie our perceptual and attentional abilities.

Also unravelling the intricacies of the human brain – the most complex known system in the universe – is computational neuroscientist Professor William (Bill) Lytton. Along with his colleagues at the Neurosimulation Laboratory of the State University of New York in Brooklyn, Professor Lytton uses computer simulations to investigate how the brain functions. The team develops simulation tools and models by working closely with experimentalists who measure activity in both normal and diseased brain tissue. Their research has far-ranging implications in addressing mental and neurological illnesses, such as schizophrenia, stroke, epilepsy, dementia and autism.

Next, we focus specifically on dementia, and introduce the research of Professor Hiroaki Oguro and his colleagues at Shimane University in Japan. Professor Oguro's team explore the effects of plant antioxidants on the cognitive and behavioural symptoms of dementia in humans. Most recently, the research group conducted a clinical trial, in which they investigated the efficacy of ferulic acid (extracted from rice bran and garden angelica) on dementia patients. The initial results were very promising, with the treated group showing significant improvements in memory performance.

Continuing on the theme of neurodegeneration, we move on to investigate the processes behind multiple sclerosis (MS). Here, we showcase recent research by Professor Matilde Inglese and her group at the Neurology Imaging Laboratory in the Icahn School of Medicine at Mount Sinai, who are at the forefront of applying sodium MRI to patients with MS.



After discovering that brain legions in MS patients show increased levels of total sodium, the team are now working towards developing methods to better monitor the disease and improve patient prognoses.

Exploring the mechanisms of both components of the central nervous system – the brain and spinal cord – is a team of three researchers at the University of California, Irvine. In the next article of this section we meet Dr John Longhurst, Dr Stephanie Chee-Yee Tjen-A-Looi and Dr Peng Li, who study the effects of acupuncture on the central nervous system. The team have conducted a large number of clinical studies showing that acupuncture applied at specific points can lower blood pressure elevation through stimulating sensory nerve fibres that underlie the acupuncture points. Their evidence highlights the potential of this traditional Chinese approach for cardiovascular problems.

Finally, we focus our attention exclusively on the spinal cord, where we look at research into mastering the repair of spinal neurons. Here, we introduce Dr Florence Bareyre and her team of neuroscientists at Ludwig-Maximilians Universität München in Germany, who have discovered several new molecules that are important for axonal repair following spinal cord injury. This remarkable insight will hopefully lead to novel therapies for those living with spinal cord injuries, and preclinical therapies are currently on the horizon due to Dr Bareyre's work.

TRANSCENDING TRAUMA: UNDERSTANDING AND HOPE FOR REFUGEES

The present refugee crisis will likely be one of the defining features of the current era. By the end of 2015, worldwide refugee numbers exceeded 65 million and growing, surpassing displacement numbers seen at the end of World War II. At present, nearly one out of every hundred people on earth are refugees; men, women, and children torn from their homes by war and violence. In the course of becoming refugees, many of these people have experienced traumatic events, which may carry heavy psychological consequences. Dr Ulrich Schnyder has devoted his career to understanding the psychological burdens of civilian trauma survivors, with hopes of improving the psychological wellbeing of refugees.

Over the past decade war and terror attacks have loomed over the general consciousness of most of the world. The stress of these events may stretch across nations, but none feel it more acutely than those living in war zones. Researchers, such as Dr Ulrich Schnyder, are working to understand the effects of this severe traumatic stress on the most vulnerable populations, refugees who have fled their violent homelands.

Psychological Consequences of War

Since its addition to the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980, post-traumatic stress disorder (PTSD) has made the journey from a poorly understood phenomenon to household name. In the past decade, public awareness of PTSD has risen dramatically and diagnosis and interventions for this potentially debilitating psychological disorder have improved. PTSD is a mental disorder that may develop following the experience of a highly traumatic event that threatens a person's life or the life of those they care about. Symptoms often include flashbacks, nightmares, distressing memories, strong psychological and physical reactions to things that remind the sufferer of the event, and long-term alterations in thought processes and emotional responses. While PTSD is often associated with soldiers returning from war, civilians can also develop the disorder following traumatic events such as sexual assault, witnessing a murder, terrorist attacks, or natural disasters.

Refugees often experience a multitude of traumatic events while living in and escaping from their violent homelands, placing them at high risk for PTSD and other trauma related mental disorders. Dr Ulrich Schnyder, a professor of psychiatry and psychotherapy at Zurich University, and head of department at the University Hospital Zurich, has been studying traumatic stress for over 25 years. In 2010, he recognised that the unique needs of refugees were poorly understood and often inadequately treated, and embarked on a research program to improve our comprehension of the psychological consequences of war and other state-organised forms of violence such as persecution and torture on civilians. He recalls, 'I realised that there is a need to study this population scientifically in order to better understand their particular situation, to take into account the cultural dimension, and ultimately to develop interventions that

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Refugees are more likely to experience PTSD, along with a host of other mental disorders, including depression, anxiety, obsessive-compulsive disorder, outbursts of anger, and trust issues. The number and severity of traumas experienced are tied to the likelihood of developing a disorder, and many refugees have survived multiple traumas. These experiences are often compounded by the ongoing stress of displacement, due to factors such as homelessness, unemployment, separation from family, insecure visa status, and discrimination against refugees. Dr Schnyder and his colleagues hope that by illuminating the dysfunctional psychological processes caused by these stressors, they can develop effective individual as well as public health interventions that improve the lives of refugees and help them move past the traumas of war and violence to build new lives.

Unique Perspectives on Trauma & PTSD

The DSM is revised roughly every 10 years to accommodate advances in research and understanding of psychological disorders. Original DSM-IV standards for PTSD contained seven diagnostic criteria, generally: exposure to a traumatic event, persistent re-experiencing of the trauma in the form of intrusive thoughts or distress when exposed to reminders of the event, avoidance of things that remind the sufferer of the trauma, and higher reactivity and anxious energy following the event, with all symptoms creating distress, lasting more than a month, and not being due to other causes. When the DSM was revised to the DSM-5 in 2013 it added an additional cluster to the PTSD diagnostic – negative changes in thought patterns (cognitions) and mood following the event. While research in other populations had found relatively little difference in diagnosis levels with the new criteria, Dr Schnyder compared the PTSD diagnostic criteria of the DSM-IV to the DSM-5 in a group of refugees. He found that fewer refugees (49.3% to 60.4%) met the diagnostic criteria for PTSD with the new scale. This was surprising, but may provide important insight into diagnosis and treatment of refugee populations in the future. Negative changes in cognitions and mood could be more predictive of emotional dysregulation and need for treatment in people that have experienced multiple traumatic events, while other PTSD criteria, such as thoughts about the traumas, might be more expected and less indicative of a disorder when a person has been through so much.

Military PTSD treatments focus heavily on reducing the fear related responses typical to PTSD, but Dr Schnyder and his colleagues recognised that the traumas experienced by civilians are often different in nature than those experienced by soldiers. Civilian war survivors certainly experience situations that provoke a life-threatening fear response, but beyond that, refugees often also witness events that run opposite to their deeply held moral principles and beliefs about the world. These types of experiences, such as

witnessing a murder or being forced, under torture, to betray a friend, can cause 'moral injury', a long lasting psychological response to having one's beliefs about humanity and morality shattered during a traumatic experience. Dr Schnyder notes, 'The majority of refugees we are studying had been exposed to torture, and all of them had experienced a multitude of additional traumatic events.' To understand the role of moral injury in the mental disorders that often follow trauma, Dr Schnyder's research group studied a group of refugees seeking asylum in Switzerland, who were suffering from conditions including PTSD, depression, and angry outbursts. After controlling for other factors, such as number of traumas and additional stressors, they found that moral injury largely predicted whether or not a refugee would suffer from PTSD. This holds important implications for treating PTSD in refugees. Rather than focusing on extinguishing fear responses, individuals that have suffered moral injury may benefit more from cognitive therapies that help realign and repair their view of humanity.

Perhaps unsurprising, PTSD is not the only mental disorder likely to plague refugees, and those experiencing PTSD are also more likely to suffer from additional conditions, both psychological and somatic. Studies of refugees across many cultures have indicated that nearly a third may experience PTSD, while over half are likely to suffer from depression. Of those with PTSD, up to 75% have at least one additional psychiatric condition. Dr Schnyder and colleagues have worked to deepen the understanding of conditions that are likely to be comorbid with PTSD in refugees. They found that survivors with more severe PTSD symptoms are more likely to experience obsessive-compulsive disorder, chronic pain, difficulties with anger regulation, and problems adjusting to new living conditions following migration. Surprisingly, the number of traumas experienced was not always predictive of the severity of symptoms and comorbid disorders. In order to understand this, Dr Schnyder and colleagues sought to understand what factors might influence whether or not the experience of a trauma led to a disorder. They found that difficulties with certain aspects of emotion regulation predicted which individuals were more likely to have psychological disorders following a trauma. Specifically, trouble with goal-directed behaviour ('When I'm upset I have difficulty concentrating') and lack of emotional clarity ('I am confused about how I feel') were associated with severity of PTSD symptoms. These findings provide further direction for developing effective psychological interventions for refugees.

Moving Forward in an Uncertain World

Beyond the mental burden of past traumas, refugees often face additional psychological hurdles even after they have managed to escape their dangerous homeland. Those that have resettled in unfamiliar host countries are often expected to integrate quickly, despite language and cultural differences, visa uncertainty, lack of employment, potential discrimination, and possible psychological impairment. Those suffering from a trauma-induced mental disorder may have difficulty finding psychiatric treatment in their language or that is sensitive to their cultural nuances, while those settled in countries with less public health infrastructure may struggle to find treatment at all. To further compound the issue, Dr Schnyder and colleagues have found that survivors of severe traumas, particularly torture, often become distrusting of others and avoidant of forming new interpersonal relationships. These avoidant tendencies may inadvertently work to maintain poor psychological health, as the emotional support, understanding, and stability afforded by close

relationships can be a powerful force for healing in trauma survivors. Cognitive treatments that help to restore trust and support the formation of healthy interpersonal attachments may further benefit refugees attempting to integrate into new societies.

Dr Schnyder and his colleagues are working to understand and address the psychological factors that hinder refugees from integrating their new host countries. In a study of over 100 psychiatric-treatment seeking refugees resettled in Switzerland, they found that difficulties with integration were strongly associated with the number of trauma related symptoms a patient displayed. Factors expected to help with integration, such as high levels of education and stable visa status, made relatively little difference in the face of unresolved psychological trauma, even in individuals that had been residing in Switzerland for over 10 years. This suggests that early and effective psychological treatments for refugees could dramatically improve integration into their host societies, with the long-term effect of increasing their overall wellbeing and contributions to their new communities.

To facilitate integration success for refugees, Dr Schnyder champions the necessity for culturally sensitive treatments for trauma survivors. Psychological healthcare providers can partner with members of the refugee community to gain valuable insights into cultural differences that may present roadblocks to standard treatment strategies. When traditional talk therapy isn't working, patients may benefit from the use of other mediums, such as art or dance, to access and work through traumatic memories. Recognising that not all countries have the public health funding and infrastructure to provide expensive mental health treatment, Dr Schnyder, in collaboration with a large research consortium, is currently embarking on a large-scale study to bring mental health to present victims of the refugee crisis. The EU (Horizon 2020) funded STRENGTHS project aims to provide innovative, low intensity mental health treatment to large numbers of Syrian refugees who had been lucky enough to make it to Europe, as well as in refugee camps in Jordan, and Turkey. These treatments are tailored to the unique needs of refugees, designed to be easy to implement and capable of improving mental health across a wide spectrum of trauma-related disorders. Moreover, the research group in Zurich also hopes to develop new treatment approaches for treatment-seeking, severely traumatised refugees: 'We are currently developing so-called mini-interventions, i.e., short psychotherapeutic interventions that address a specific, circumscribed problem such as the traumatised refugees' lack of perceived self-efficacy,' Dr Schnyder explains.

Meet the researchers

Professor Ulrich Schnyder

Dr Ulrich Schnyder is a professor of psychiatry and psychotherapy at University of Zurich, and head of department at the University Hospital Zurich in Switzerland. His current research revolves around trauma in civilian survivors of war, and he is dedicated to improving the psychological health of these individuals.

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TAKING THE LONG VIEW ON WELLNESS

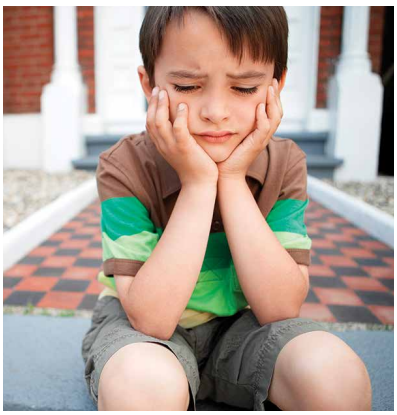
Nature vs. nurture is one of the oldest debates in biology. Are people's lives determined by their genes, their upbringing, or both? Nearly 30 years ago at the onset of the human genome project, scientists believed that once all human genes were known, all of human health would be explained. To the surprise of many, and the vindication of some, this has not been the case. Nurture plays a significant role in shaping the people we become.
Dr Jeffry Simpson and his research team at the University of Minnesota are trying to understand how our earliest experiences shape our lives into adulthood.

One of the greatest revelations of the past decade has been that genetics don't explain as much about human health and behaviour as many scientists once believed they would. A person's genome certainly lays the foundation for their unique traits, but perhaps unsurprisingly, the environment they grow up in still matters. How does early childhood shape our health and wellbeing as adults? Can we predict what a young child's health will be like in adulthood? What can parents do to offset a difficult childhood environment? Dr Simpson's research team is answering these questions.

A Lifelong Approach

'I've always been interested in social development and how it shapes what people are like in adulthood,' Dr Simpson says of his work. Many scientists have wondered how childhood shapes our adult lives, but this process is exceedingly difficult to study in humans. It takes decades for a young child to develop into an adult, during which time the researchers themselves are also aging. Children enrolled in a study before they could talk may not be interested in continuing as adults, and maintaining a group of participants over such a long timeframe is difficult. Many researchers lose participants, lose funding, or lose resolve before enough data can be collected to create a meaningful picture of the effects of early life on adult health.

Dr Simpson's pursuit of this phenomenon has been different. His research team's commitment to pursuing these questions has permitted them to follow the same participant group of approximately 170 people for over 35 years now, and the dedication has paid off. The data from this group – researchers involved in the Minnesota Longitudinal Study of Risk and



Adaptation – is one of the most unique datasets in developmental psychology, as very few scientists have longitudinal data spanning the full lifetime of this many individuals. Dr Simpson and his research team are using this special dataset to observe and test hypotheses about how early life experiences shape adult health. They are beginning to be able to predict

‘A growing body of research suggests that what happens to a person early in life may be systematically associated with the quality of his or her health years later. Very few studies, however, have followed people longitudinally across their lives. Our research team is doing so.’

which children will be at the highest risk for both psychological and physical ailments as adults and are illuminating the factors that may help to protect children who were raised in stressful environments.

Why study early childhood? As Dr Simpson explains, ‘Early in development, our bodies and minds are developing and may be especially sensitive to early environmental events and experiences. This process is called biological programming… If individuals grow up in environments containing high levels of stress, a lot of interpersonal conflict, and fewer resources, the body and the mind must become “prepared” to deal with these environments as best they can.’ Put simply, early childhood prepares the brain and the body for obstacles that will likely be faced later in life. Children growing up in difficult environments are subconsciously being ‘trained’ to deal with difficult environments as adults, which can take a toll on mental and physical health. Later dysfunctional behaviour and thought patterns can also generate distress, which may further elevate stress hormones known to be detrimental to the body and immune system.

Early Relationships Matter

Parents are the centre of a young child’s world and a child’s relationship with his or her parents can be one of the earliest predictors of adult health. Attachment theory is one of the hallmark approaches to human development. Infants who are securely attached to their parents view their parents as a safe, trustworthy, and responsive base from which to confidently explore the world, knowing that they can return to the safety of mom or dad if they get scared. Conversely, infants with insecure attachments view their parents as unreliable, inconsistent, or poor sources of care, and may either anxiously cling to them, desperately demanding attention, or avoid them, apprehensively attempting to rough it on their own. Many psychologists have tied these early attachment patterns to similar patterns in adult relationships, but Dr Simpson and his colleagues were one of the first groups to demonstrate that infant attachment also predicts adult health outcomes. They observed attachment patterns in 163 infants, and predicted that those with insecure attachments to their parents early in life would be less healthy as adults. When they revisited these individuals in their early 30s, they found that, even when factors such as gender and socioeconomic status were controlled for, adults who had been insecurely attached as infants had significantly more health problems, particularly inflammation-related illnesses.

So are parents to completely blame? Not entirely. Dr Simpson and his colleagues predicted that some of the health problems associated with early childhood relationships may be related to overactive stress responses in adults who experienced poor maternal bonds as young children. In particular, they wanted to know whether a child’s early relationship with his or her mother was linked to how she or he handled stress in adult romantic relationships. To find out, they examined a group of adults whose relationship with their mother had been assessed numerous times in early childhood, through repeated direct observations of mother-child interactions. When these people reached their mid-30s, Dr Simpson’s team used an electrodermal activity monitor (a machine that measures physiological indicators of stress in real time) to observe their stress levels during interactions with their adult romantic partners. A clear pattern emerged: individuals whose mothers had been less sensitive and responsive to them as children showed more elevated stress responses during conversations with their partner involving conflict than individuals whose mothers had been more sensitive and responsive. These results held even when factors like relationship quality, gender, and socioeconomic status were accounted for. Less attentive mothers were linked with higher levels of adult stress during relationship conflicts 30 years later.

Unstable Environments & Windows of Influence

One of the patterns also emerging in these data was the influence of unpredictability and lack of consistency early in life. Children are most likely to develop insecure attachment patterns when parental behaviour is inconsistent. Mothers and fathers who are less sensitive to their children’s needs are more likely to provide unpredictable responses. Dr Simpson and his team thus hypothesised that this element of environmental unpredictability may also play an important role in the development of negative health outcomes years later.

To study this, they looked at data from 220 individuals who had been studied from birth. Early life unpredictability, characterised by frequent moves, frequent changes in adults sharing the household, frequent parental job changes, along with overall harshness of the environment were measured when children were between ages of 0 to 16. They found that unpredictability between ages 0 and 5 was the strongest predictor of substance abuse by age 16 and criminal behaviour at age 23. Harshness also led to greater substance use at age 16, and the combination of unpredictability and harshness led to adults being most likely to engage in risky or criminal behaviour. Although these individuals also experienced unstable environments from ages 6 to 16, the impact was not as strong as during the earlier years.

Obviously, childhood stress matters for adult health, but it appears to matter more at an earlier age. Dr Simpson and his team wanted to know more about these windows of influence and were also curious about silver linings. His lab had demonstrated that poor parenting could worsen adult health, but could good parenting be protective in highly stressful and unstable environments? To answer these questions, his team examined 163 individuals on whom there was lifelong data. Participants and/or their parents had been interviewed at 16 different time-points throughout life to assess the overall level of stress in their environment. These measurements were then grouped into early childhood, middle childhood, adolescence, young adulthood, and current stress levels. Maternal sensitivity early in life had also been measured, as in the previous study. Participants' health was evaluated at age 32. An interesting pattern emerged. Viewed individually, stress levels early in life, in adolescence, and in adulthood predicted poorer adult health outcomes. Stress levels in middle childhood and young adulthood were not associated with adult health, nor was general cumulative stress. However, when stress occurred during both early life and adolescence, the worst adult health was observed. These findings indicate that both early childhood and adolescence might be 'sensitive windows' during development in regards to stress and health function.

Fortunately, a silver lining shone through: children living in stressful situations who also had sensitive mothers seemed to be insulated from the effects of stress. Attentive, stable parenting made up for stressful environments at all ages. These findings indicate that stress during periods of major developmental changes, especially early childhood and adolescence, may be the most damaging in terms of predicting adult health outcomes. However, reliable, sensitive parenting in childhood may be a protective factor, even if the overall environment is stressful. Parents can do damage, but they can also provide a safe haven during tough times.

Getting Specific

Dr Simpson's research team is not finished with this long-term study. At this point, many of the participants are in their early 40s and continuing to provide fascinating data. Recently, Dr Simpson received funding from the National Institute on Aging to delve even deeper into the physiology of this unique group of lifelong participants. This has allowed his laboratory to collect more detailed health measures, which has permitted them to examine markers of each participant's health and stress levels, such as levels of inflammation in their blood and their stress hormones. Dr Simpson and his team are combining this data, with the comprehensive information already collected from each individual's early life, in the hope of more clearly identifying windows of stress vulnerability, the specific health problems associated with different kinds and timing of early life stress, and understanding how variations in stress levels at specific life stages interact to create unique adult health profiles. 'Our long-range goal is to determine what kinds of early-life experiences uniquely predict certain kinds of health outcomes,' Dr Simpson summarises.

Scientists are just beginning to uncover relations between early life experiences and adult health outcomes. Research like Dr Simpson's is shaping child care practices and interventions that can have lifelong effects and someday may help us develop treatments to reverse the damaging effects of stressful and unstable childhood environments. As we better understand the interactions between our biology and the environment, it is becoming clear that both nature and nurture have lasting impacts on human health. By appreciating both aspects of our development, researchers will propel medicine forward and improve the quality of life worldwide.

Meet the researcher

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Dr Jeffry A. Simpson graduated Summa Cum Laude with an AB in Political Science and Psychology from the University of Illinois at Urbana-Champaign in 1981. He went on to receive a PhD in Psychology from the University of Minnesota, Twin Cities in 1986. After continuing on to a professorship at Texas A&M University following graduation, he eventually returned to the University of Minnesota, where he currently runs his laboratory and is the Director of Minnesota's Interpersonal Relationships Research Doctoral Minor program. Dr Simpson's research focuses on how early life experiences shape adult health and behaviour across the lifespan. His association with the Minnesota Longitudinal Study of Risk and Adaptation has allowed him and his research team to provide unique insights into the mystery of how our childhood shapes the people we grow up to be.

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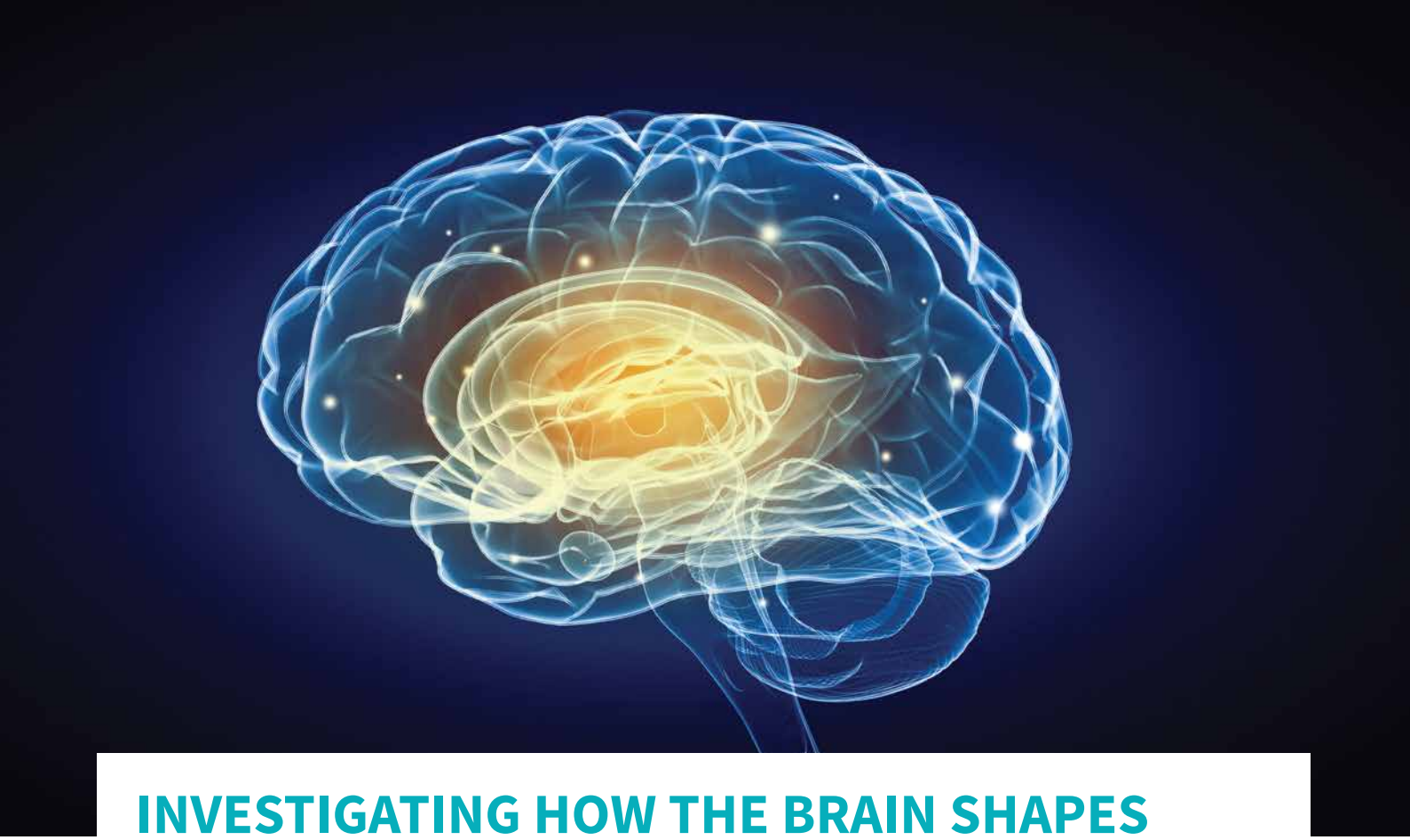
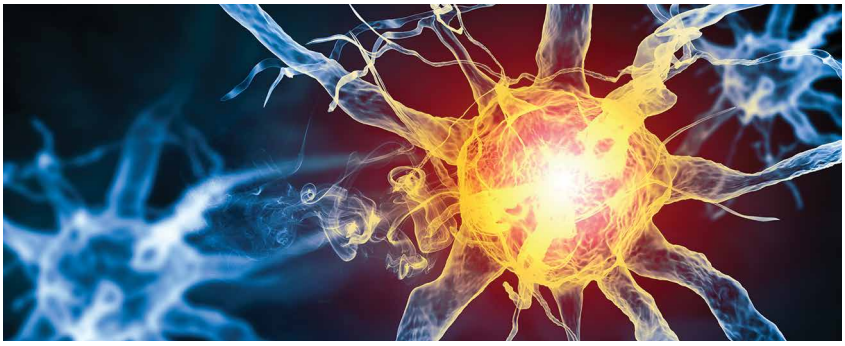


INVESTIGATING HOW THE BRAIN SHAPES PERCEPTION

Neuroscientist **Dr Detlef Wegener** and his colleagues at the University of Bremen's Brain Research Institute in Germany study how cognitive processes influence the way we perceive the world in which we live and act.

How Does the Brain React to Keep Us Alive Minute by Minute?

Everyone has seen him at one time or the other, perhaps portrayed by Johnny Weissmuller in the classic movies or maybe Alexander Skarsgård in a more recent rendition – Tarzan of the Apes. That wonder of a man swinging from tree to tree and leaping from branch to branch. Of course, humans don't do that very well, swinging and leaping through the trees. But monkeys can, and they do it with apparent ease. If you've seen a monkey jumping through the trees, quickly deciding on its next target branch, computing the distance and precise location of its target, programing and executing the movement and landing with precision before leaping off at its next target, it's quite amazing! To do so, the monkey has to precisely select the relevant information and, at the same time, disregard effectively what is not important from the multitude of information reaching its senses in order to avoid errors that might lead to a fall and death on the jungle floor. And all of this must



occur on a very short timescale. The monkey can't stop and pull out a pocket calculator to figure out the next jump – it has to occur almost without thinking. This is the stuff that interests Dr Detlef Wegener and the scientists at the Brain Research Institute at Bremen University.

Maybe humans can't swing through the trees like monkeys, but they do things on a routine basis that are quite similar to the monkey's daunting jungle antics. Humans are continuously faced each day – indeed, each minute – with a huge amount of sensory information. Just think about riding a bicycle through a modern city, swerving in and out of traffic and around pedestrians. Each second there is a huge and fluid amount of data arriving at our senses, like motion patterns, colours, objects, faces, and sounds that are received by the biker's brain. Only some of this information is relevant for successfully managing a path through the traffic, while others are irrelevant and potentially distracting. Our brain provides us with an amazingly rich perception, but assimilating all the incoming information in parallel exceeds the brain's processing capacity by

‘My research interest is to understand how the brain shapes the way we perceive the world’

far. Focussing on the dress of the woman on the sidewalk might have a positive influence on mood, but it may impair the biker from quickly detecting the fast car coming from the side. Hence, moving through the traffic while avoiding other vehicles, people and stationary objects, flying a supersonic jet plane, or playing sports, all relies on the human brain’s ability to select and process the relevant pieces of data in a short period of time to shape our perception in a manner that fits to our current behavioural goals. How does the brain do this?

Small Processes That Generate Complex Results

Dr Wegener carried out his first experiments during his undergraduate education, at Glasgow University in Scotland, where he looked at a particular class of neurons in the nervous system of a leech. Later, during his undergraduate thesis work at Bremen University, he studied a specific class of retinal ganglion cells in a particular species of lungless salamanders. Dr Wegener tells Scientia: ‘Both of these projects had in common that they aimed to understand the specific functional characteristics of a cell class by studying the underlying principles, like the presence of a specific class of genes or the specific arborisation pattern, respectively. More generally, they addressed the question how complexity emerges from simple principles – something that is at the core of brain function and fascinated me as a student, and probably fascinates neuroscientists from all fields.’ When Dr Wegener looked for a doctoral position, he wanted to study these mechanisms in larger brains and with respect to cognitive processes and mechanisms that are closer to human perception and consciousness. What else but monkeys? But how do you get to work with monkeys?

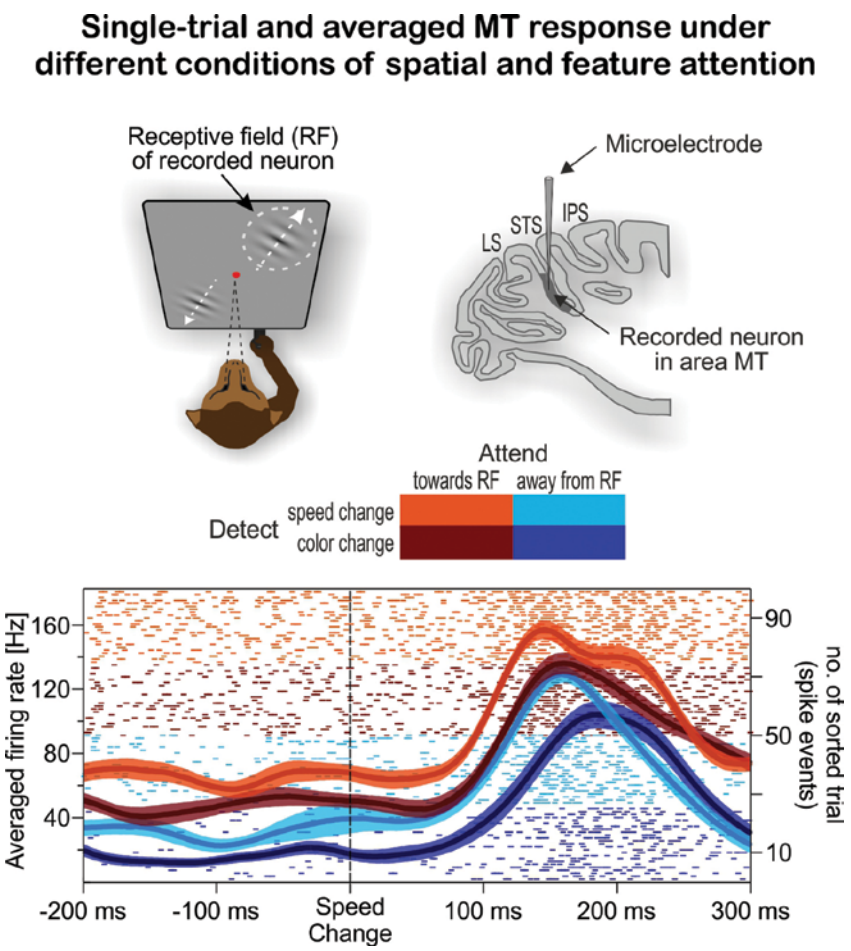
Serendipitously for Dr Wegener, at about the same time he was finishing up his undergraduate work a new institute was founded at Bremen University. It was part of a new collaborative research centre on neurocognition, specifically dealing with the question how cognitive processes like e.g. attention influence the activity of neurons, and how groups of neurons communicate with each other. Dr Wegener applied for a PhD position even though none were advertised at that time and the new institute had not even opened. He secured a position, and then, as he describes it, ‘literally starting with only two pens, we built the lab from scratch within the following two or three years, including all the experimental setups, the laboratories, the animal house, a surgery room, and the hundreds of little things that need to work in order to perform this sort of research.’ He likens it to a jump into the cold water, learning new things every single day.

After finishing his PhD, Dr Wegener received his first German Research Foundation grant, which allowed him to define his own set of experiments, develop new approaches and techniques, and optimise others. He continued with monkey neurophysiological studies, and also added human psychophysical and electroencephalographic experiments. ‘Training monkeys on sophisticated behavioural tasks requires a lot of time,’ Dr Wegener says. ‘Studies in humans allow us to first test and sharpen our hypotheses and then design the specific behavioural tasks for the monkeys. Monkeys can learn demanding cognitive tasks, similar to those we use for humans, and this is why we can then perform precisely targeted neuronal recordings and address the distinct neuronal mechanisms that may underlie ours, and the monkey’s perceptual and attentional abilities.’ With this approach, Dr Wegener and his colleagues at the centre are working on many ongoing projects, which have led to some ground-breaking discoveries to date.

How the Brain Processes Visual Input

Like the monkey in the trees, when we humans ride, drive, fly or otherwise make our way through our world, we are processing the incoming information based on our own intentions and goals. The same sensory information may be processed with high priority in one condition, but gets largely suppressed in another situation, depending on whether it is actually important or not. How does the brain achieve this performance? What are the brain’s signals that determine the degree to which we process the information from our environment? How does this influence our conscious perception, and how does it affect our behavioural performance? In terms of neuronal computation, Dr Wegener thinks this constitutes a huge accomplishment that can teach us a lot about the neuronal mechanisms that are inherent to the vertebrate brain. He also believes that understanding these processes may help us to better understand what is going wrong in the diseased brain.

‘In our lab, we study these cognitive processes by performing experiments that involve some form of change detection, usually a change in the colour or the motion of a visual stimulus,’ he tells us. The



processing of motion signals takes place in a dedicated visual area of the brain – the so-called area MT – where neurons are highly sensitive to the direction and speed of motion. By requiring their monkeys to either attend to the motion or the colour of a stimulus on a computer screen, Dr Wegener and his team investigate the response of the neurons in this specialised area under changing behavioural conditions. 'We found that these neurons are highly affected by the relevance of the motion information,' he says. 'When we investigated their activity, it turned out that many parameters of their response were dependent on the behavioural relevance of motion.'

When under similar experimental conditions, human observers must detect changes in a stimulus as quick as possible, they will be much faster to report a change in the speed or direction of a stimulus when they concentrate on motion as compared to when they are expecting a colour change. 'In line with this, we found that neurons in area MT respond with short-termed but very pronounced changes in their firing rate to these sudden motion changes,' explains Dr Wegener. 'Focussing on the motion of the stimulus caused that these firing rate changes occurred earlier and were stronger.' When analysing the reaction times of the monkeys to report these motion changes, Dr Wegener and his group found that they were closely related to the speed of the firing rate change of these specialised neurons. 'This shows that attention influences the very early stages of visual processing and that those modulations are directly influencing our behavioural performance.' Thus, when the biker is focussing on the motion information he may disregard the woman on the sidewalk, but because his attention is prioritising neurons in the motion-sensitive regions of the brain, he will be faster to react to the sudden appearance of a car from the side.

Dr Wegener and his group obtained more interesting insights into this phenomenon. One of their studies showed that attention modulates the selectivity by which neurons in this visual area of the brain can distinguish between different motion directions, while another showed that these neuronal modulations are reflected directly on the behavioural level. Their results indicate that when the brain is exposed to a lot of visual input, attention allows it to maintain a high selectivity for important information and weed out external 'noise'. The team hypothesise from these findings that the inability to ignore distracting input might be a major cause in some forms of attention-deficit-hyperactivity-disorder and milder forms of attention difficulties in humans. After all, this isn't just about monkeys – it's ultimately about the human brain and how it works in health and illness.

The Work Is Only Just Beginning

Importantly, Dr Wegener and his colleagues can rely on techniques and methods not available one or two decades ago, mainly due to the massive computational power and storage capacities available today. These allow not only the ability to record the activity of a single neuron, but of hundreds of neurons at the same time. They can study populations of neurons in one or several areas and gain access to their dynamic interactions. 'New recording and analysing techniques have to be developed, but colleagues in systems neuroscience and accompanying fields – computational neuroscience, machine learning, neuroengineering, and others – have done great jobs during the last years to achieve this,' Dr Wegener says. In his home university, for example, many people from different institutes have participated in designing, manufacturing, and implementing new high-density multi-electrode arrays that are now used to study distributed brain activity and record signals from the brain's surface. Dr Wegener says such approaches will become very important for future clinical approaches and that they will allow us to study and hopefully also treat neuropsychiatric diseases. Because of the rising number of such illnesses, this will be one of the central challenges neuroscience faces during the next decade or two. 'Any such progress, however, critically depends on the precise understanding of the healthy brain in terms of the neuronal interactions going on during conscious perception and action,' Dr Wegener says. If we can understand how the monkey's brain solves a demanding cognitive task, perhaps we can find ways to cure patients with brains that can't do this anymore.

Meet the researcher

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Dr Detlef Wegener carried out his undergraduate studies in Biology at the Life Sciences Department of Glasgow University in Scotland in the UK and at the University of Bremen, Germany, where he received his degree in 1997. While at Bremen, Dr Wegener worked at the Brain Research Institute and wrote his undergraduate thesis on the identification of morphological specificities of plethodontid salamander retinal ganglion cells according to their projection sites. After that, he joined the newly founded Department of Theoretical Neurobiology of the Brain Research Institute at Bremen and was involved in the development and setup of the department. It was here that Dr Wegener performed his doctoral work, writing his dissertation on the influence of selective visual attention on stimulus selectivity and synchronised, oscillatory activity patterns of single cells in the macaque middle temporal visual area, receiving his PhD in 2003. After receiving his doctorate, Dr Wegener stayed on at the Brain Research Institute where he is currently a Senior Scientist and continues research on the influence of attention on visual processing. He also teaches Bachelors and Masters classes in Neuroscience, and served as lecturer at the University of Applied Sciences in Bremen, teaching Animal Physiology in the Faculty of Biology there.

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Universität Bremen

UNITING BIOLOGY AND MATHS TO UNDERSTAND THE HUMAN BRAIN

Neurologist and computational neuroscientist **Professor Bill Lytton** and his colleagues at the Neurosimulation Laboratory of the State University of New York in Brooklyn are using computer simulation to investigate brain function and disease. Their research has far-ranging implications in addressing human illness.

Bringing Biology and Math Together

'Everyone agrees that we need a paradigm shift – really several – before we can begin to understand the brain, and further understand the mind and brain in disease: for example, schizophrenia, stroke, epilepsy, Alzheimer's and autism,' Professor Lytton tells us. As with prior paradigm shifts, understanding comes from detailed observation using new technologies combined with changes in concepts from models. Think of how Galileo's work with the telescope or Van Leeuwenhoek's microscopy advanced the fields of observational astronomy and microbiology respectively. However, unlike prior shifts, nowadays new models will be based upon complex computer simulation rather than on closed form equations such as those used by Newton or Einstein.

At the end of second world war, three strands of brain and neural modelling emerged. One of these was that of McCulloch, Pitts, Turing and von Neumann, who developed ideas of logical units and extended that to a description of neurons. This field then bifurcated into computer science and artificial neural networks or ANNs – a computational approach based on a large collection of neural units that loosely model how brain solves problems.

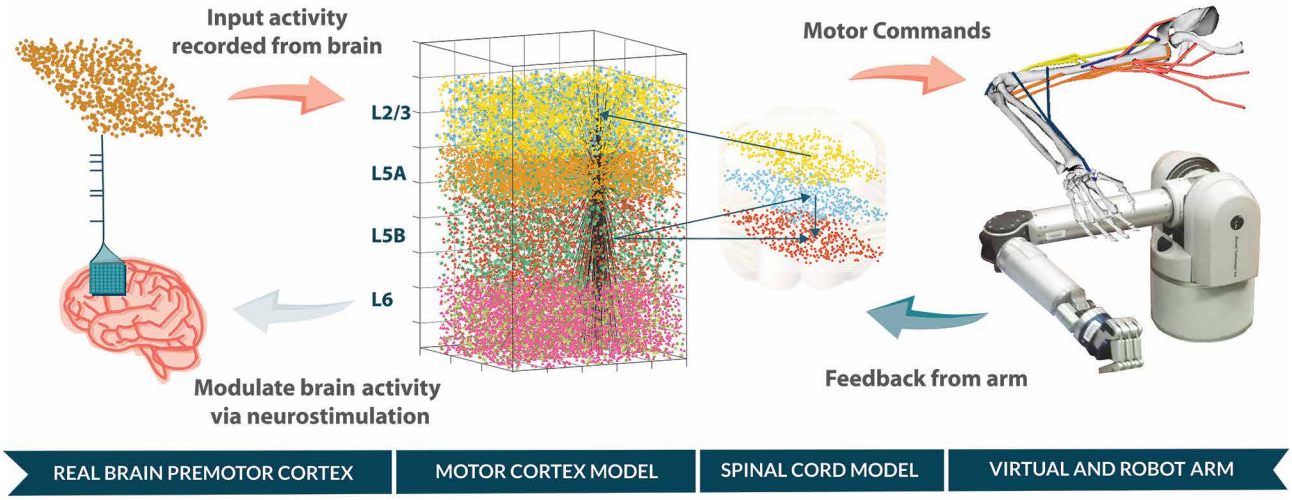
Early on, John von Neumann recognised the limitations of what he called the 'Turing-cum-Pitts-and-McCulloch' approach. Pointing out that the generality of phenomenological laws limited their usefulness for any particular implementation, he noted that 'nothing that we may know or learn about the functioning of the organism can give, without "microscopic" cytological work, any clues regarding the further details of the neural mechanism.' In other words, high-level, 'top-down' models of the brain may be correct, but their generality limits their usefulness for understanding the brain. For example, one large scale theory suggests that a major part of cortical feedback loops across hierarchies of high to lower centres permits the brain to predict the future both for planning, and for producing augmented 'active' perception that depends on knowing what is likely to be seen or heard before it is seen or heard. This is an important brain function, and attributing this function to the cortex seems reasonable. The theory is made more concrete by the fact that it can be identified as Bayes' theorem, which describes the likelihood of an event given prior knowledge. The theory fits performance on a variety of cognitive tasks. However, this is not a mechanistic model – it will not tell us what physiological or neurotransmitter anomalies could cause individuals to show poor prediction, or poor judgment, in certain brain diseases.

The descriptive approach to modelling also stems from the long tradition of mathematical modelling in physics, which is necessarily phenomenological rather than mechanistic. Epistemologically, physics is unique in that it treats the most fundamental levels, which, by virtue of being fundamental, are irreducible to a lower level. The problem with descriptive/phenomenological models of the brain is that they do not give us access to the underlying 'knobs and levers'. Understanding at the knob level will be necessary both intellectually and clinically – it is these knobs and levers that must be turned and pressed to alter the pathologies of damaged brain or disturbed mind. Professor Lytton's work aims to build on the von Neumann observation of a need for microscopic, cytological work by utilising detailed multiscale mechanistic computer models to determine how dynamic and functional phenomenology arises.

Professor Lytton's group strives to bring together math and biology by focusing on the details of biology (bottom-up) at the same time as considering model dynamics in terms of functional attributes (top-down). The team develops simulation tools and models, by collaborating closely

Simulation of a single cortical layer 5 neuron. The apical dendrite (top) extends upwards through many layers, gathering information from as many sources to be conveyed to the soma near the bottom, at the centre of its web. Information then goes out through the axon at the bottom (purple line). The insets show results of parameter explorations and indicate another difficulty of neural simulation: neurons are individuals that themselves learn specific attributes in concert with other neurons.

with experimentalists who measure wiring and activity in both normal and dysfunctional brain tissue. Looking from the bottom up, these simulations themselves become experimental objects: they are so complicated that one has to manipulate them experimentally to understand them. Through this interactive experimentation, the experimental objects (simulations) are repeatedly modified to provide closer representations of the explanandum/simulandum and to seek experimentally-verifiable predictions. Looking from the top down, one is then re-modelling the simulations themselves, using tools to understand how dynamics can be encapsulated and how activity can be understood in terms of information processing and of neural codes. Professor



Design for a future biomimetic brain-machine interface (BMI) model. Left to right: Information about what target to reach can be gathered from electrodes in the brain. This modulates ongoing activity in the biomimetic cortical and spinal cord models which then drives the virtual arm, which is then mirrored by the robot arm. Right to left: haptic feedback (touch sensation) could then be delivered back in the other direction so that the user could feel what is being touched.

Lytton notes that it is great fun mentally to jump back and forth between the abstractions of math and the intricate details of biology.

Computer models are improved over time by additional mathematics, statistics, and computational techniques to incrementally fine-tune them to better fit the biological observations at multiple scales. The more the computer simulations allow scientists to find out about the brain, the more data from the brain they can feed into the simulation to make it more exact, and the more they learn about the brain. It's almost as though Professor Lytton and his fellow researchers are themselves part of an algorithm that investigates the functioning of their own brains' ability to function as an algorithm designed to learn about the brain. Circular investigations, perhaps like being part of the Matrix while trying to find out how the Matrix works. However, whether or not they are themselves part of the system they're trying to study, they have made some real progress.

The Simple is Really Quite Complex

The extraordinary success of artificial neural networks and computer learning in seemingly simulating the human mind – for example, computers playing chess and actually defeating human opponents – are not the things that are really difficult. They are also, of course, largely not the things that evolution has pressured human brains to be able to do. Instead, it's the effortless things that we share with many other animals – acute visual and auditory perception under multiple conditions, control of locomotion across uneven terrain at different speeds – that really bring into play the complex processing for which brain coding is optimised. In fact, the inability to program these complex perceptual and motor skills has been a major impediment to the development of useful robots. News reports are quite glowing when someone exhibits a pondering metal being that can slowly negotiate complex terrain. It's a difficult problem for robots and their programmers, even though human infants can usually walk over uneven ground with ease by the age of two, sometimes even earlier.

Look at the motor system generally. Beyond what other animals can do in terms of locomotion and other muscular activities, we humans have added fine motor control of hands and larynx to the basic mammalian substrate. With these two remarkable innovations in place, humans developed complex capabilities – namely language and tool-making – that made us human. This all took place relatively recently and is quite important to our human existence as we know it. After all, without fine dexterity in our fingers and ability to conceptualise complex language, you wouldn't be reading this article to begin with.

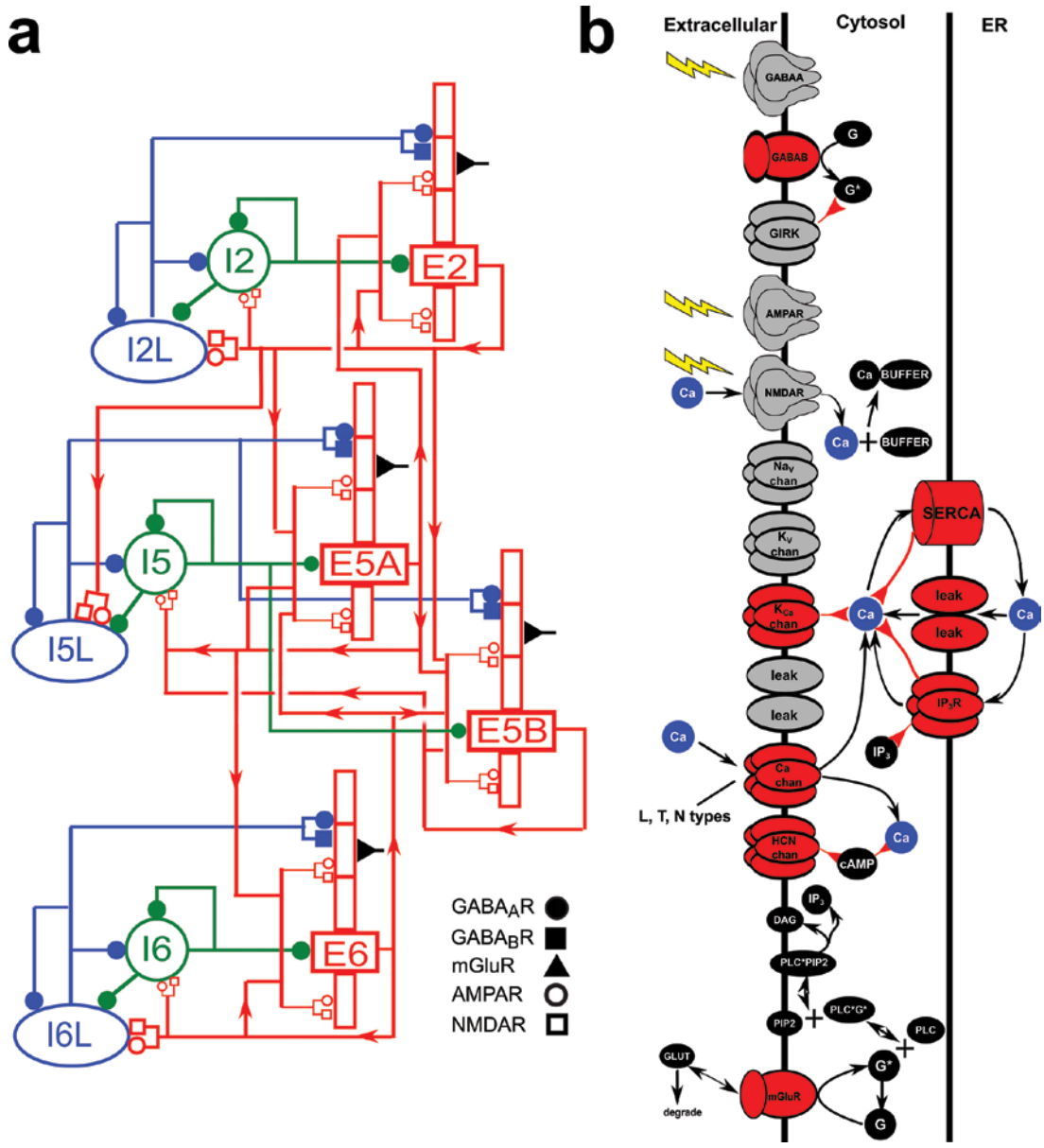
Professor Lytton's interest in the brain's motor cortex is precisely due to this being one of the areas – along with the cerebellum, thalamus, basal ganglia, red nucleus, anterior cord, etc. – that is responsible for the coordinated control of muscles to effect alterations in the environment. To attempt to understand how all of that works, what else would he do but build a cybernetic arm?

Driving an Arm with Multiscale Simulation!

Professor Lytton and his team put together a biomimetic brain area, linked to a virtual arm, both running in computer simulation, finally all harnessed to an actual robotic arm with servos. The model, which can be seen at http://neurosimlab.org/billl/salv_robot.mp4, is trained using a reinforcement learning algorithm.

The biomimetic M1 is programmed as a multiscale simulation. In this version of the model, there are three basic layers in the network that can be grossly mapped onto layers of cortex: a motor layer that outputs muscle excitations; a somatosensory layer that coordinates between the two other layers; and the proprioceptive layer that feeds back muscle lengths, i.e., the size of the virtual muscles as they contract and relax. These three layers are also divided into the various virtual muscles that control the extension and flexion of shoulder and elbow. Left to its own devices – that is, untrained – the virtual arm simply flails around without purpose, causing the same to happen with its robotic alter ego. With training, however, things are much different.

Programming the virtual arm to pick up an object on a table is accomplished by rewarding the arm for getting closer to the object or punishing it for getting farther away. Of course, rewarding or punishing a computer program is obviously analogising to the human experience. In practice, what Professor Lytton's team does is to potentiate or depress synapses based on spike timing depending on whether the arm wanders closer or further from the target. This causes the virtual arm to 'learn' to get closer and closer to the object. When the hand is stabilised over the object, a grasping function, intrinsic to the robot arm, is



Two levels of complexity: network level (a), molecular level (b). Chemicals are believed to be the basic level where memories are stored. Networks are believed to be an important level where memories are accessed and passed on to other networks and to higher levels.

activated and the arm picks up the object.

The purpose of this multiscale model is to incorporate multiple levels of biologic function into a computer model. Here we have cellular dynamics, immediate network interactions, learning, and interactions between arm and brain. In the long run, the ideal would be to include many more parts in the model – cortex, cerebellum, thalamus, basal ganglia, red nucleus, anterior cord and other relevant areas, some modelled in detail, others only at a high scale. Once you can fashion a multiscale model of complex brain pathways, you can start to program it to understand complex brain functioning, both in health and disease.

What's Next in This Research?

There is a great deal of technical work that that Professor Lytton and his colleagues are doing to make massive multiscale simulations and their analysis possible on modern supercomputers. At the same time, they are working to incorporate new streams of data coming in from the US BRAIN project – Brain Research by Advancing Innovative Neurotechnologies – as well as the EU Human Brain Project, the Swiss Blue Brain Project and the Allen Institute brain projects. All of these are collaborative initiatives aimed at understanding brain function.

'In applying our complex simulations to neurological and psychiatric disease, there is always a trade-off about what to include and what to omit in doing any model,' Professor Lytton tells us. 'Models for different purposes – e.g., conceptual versus clinical – need different details, different simulation experiments and different analyses. Schizophrenia is a disease of particular interest to us since it is a brain disease that presents as a disease of the mind. It may, therefore, offer insight into the classical duality of mind and brain.' He and his team are examining the relationships among brain oscillations – popularly called brain waves – and information flow in the brain, their current, weak proxy for the information processing of mind. Just like the virtual computer arm modelling the function of the human arm, they hope to create more complex models for the more complex functions of the brain. In other words, they want to create functional cybernetic androids – brain region by brain region – so they can study biological human beings. Or is it the other way around?

Meet the researcher

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Professor Bill Lytton received his Bachelor's degree in 1978 from Harvard College and his Medical Degree in 1983 from Columbia's College of Physicians and Surgeons, followed by a medicine internship at the University of Alabama Birmingham, and a residency in Neurology from 1984 to 1987 at Columbia University's Neurological Institute in New York. Thereafter, he trained under an NIA fellowship at the Johns Hopkins University in Baltimore, Maryland, and the Salk Institute in La Jolla, California. He was Assistant Professor at the University of Wisconsin, Madison from 1992 to 1998 and became Tenured Associate Professor in 1998. Professor Lytton joined the faculty of the Departments of Physiology & Pharmacology, and Department of Neurology at SUNY Downstate, Brooklyn, in 2000, where he is now Professor.

Professor Lytton's research interest is in Computational Neuroscience, with a focus on the application of Multiscale Modelling to disorders of the brain, including schizophrenia, dystonia, epilepsy, Alzheimer's Disease and stroke. He has authored or co-authored over 70 articles published in peer-reviewed journals, almost all as first or last author. He has also published multiple review chapters and the book 'From Computer to Brain', a basic introduction to the field of Computational Neuroscience. He is licensed to practice medicine in several states, board certified by the American Board of Psychiatry and Neurology and works as a clinical neurologist at Kings County Hospital, seeing patients with a variety of brain ailments.

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THE FUTURE OF DEMENTIA THERAPIES?

Efficacy of Ferulic Acid for the Treatment of Dementia

Associate Professor Hiroaki Oguro and his colleagues at Shimane University study the effects of plant antioxidants on dementia symptoms. Specifically, Professor Oguro is interested in the effect of Ferulic Acid on cognitive and behavioural symptoms of dementia in humans.

Dementia

Dementia is the progressive decline in cognitive abilities. The most common form is brought on by Alzheimer's disease (AD). However, vascular dementia, dementia with Lewy bodies and frontotemporal lobar dementia have also been identified. Cognitive impairments initially occur in one of the following categories: memory, executive functioning (processes related to planning, attention and multitasking), language, visuospatial abilities or personality and behaviour. However, as the disease progresses, impairments may be observed in multiple categories. In addition to difficulties concentrating, focusing and memory loss, dementia may also result in lack of motivation, depression, delusions or hallucinations, sleeping difficulties and muscle weakness. Behavioural and psychological symptoms of dementia may also occur. These include delirium, anxiety, apathy, low activity and agitation. Dementia typically occurs after the age of 65 (although there are cases of early onset), and the risk for dementia increases with age. Life expectancy ranges from 3 to 12 years following the time of onset.

Alzheimer's disease

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder, and the cause behind the majority (75%) of dementia cases. Alzheimer's disease is characterized by the accumulation of senile plaques (deposits of protein fragments called amyloid beta (Aß) in the brain), neurofibrillary tangles (aggregates of phosphorylated tau protein) and nerve cell (neuron) degeneration. The plaques are generated from improper cleavage of a protein known as the Amyloid Precursor Protein (APP). APP is located on the surface of cells. In the healthy brain, APP is cleaved by ß- and y- secretase enzymes, which releases 40 amino acid long protein fragments. However, in the case of Alzheimer's disease, APP is cleaved improperly by ɑ- and y-secretase resulting in 42 amino acid long fragments. These fragments accumulate and form senile plaques. These plaques also make up the Lewy Bodies in dementia with Lewy bodies. Amyloid plaques contribute to neuron degeneration and dementia by disrupting normal cell behaviour and cell signalling and generating oxidative stress – a process resulting from the accumulation of free radicals and other reactive oxygen species resulting in cell damage. Therefore, a treatment that reduces or reverses plaque formation may provide a way to prevent or cure dementia in the future.

Current Therapies for Dementia

Although there is currently no cure for dementia, there are treatments available

‘For dementia there are very few drugs available in the world. Only three cholinesterase inhibitors and memantine are widely used.’

to improve dementia symptoms. Acetylcholinesterase inhibitors (medications that prevents the breakdown of a chemical messenger in the brain involved in cognition) and memantine (a drug used to prevent overstimulation of neurons, a process which can cause cell death) are the only therapies approved by the Federal Drug Administration to treat dementia. A combination of acetylcholinesterase inhibitors is used as a first-line therapy to treat mild and moderate dementia in patients with Alzheimer’s disease. Memantine is only used when patients are not able to tolerate the side effects of inhibitor therapies.

While these treatments moderately improve cognition, they have several drawbacks. One concern is that they are only approved to treat specific forms of dementia. In some cases, these treatments may even worsen symptoms. Potentially severe side effects are also associated with inhibitor therapy. Behavioural and psychological symptoms of dementia can be treated with antipsychotics. However, these treatments also have side effects. Lastly, these treatments can also be very expensive for the patients. The limited options and severe side effects have made the development of new, more effective and safe therapies crucial for the treatment and eventual cure of dementia. It is this lack of adequate, tolerable and affordable therapies that has driven Professor Hiroaki Oguro and his colleagues to explore alternative treatments for dementia. ‘For dementia there are very few drugs available in the world. Only three cholinesterase inhibitors and memantine are widely used.’ he told us. Recently, Professor Oguro and his lab have focused their attention on a plant antioxidant supplement that has several therapeutic benefits.

Oxidative Stress and Antioxidants

Oxygen is the main provider of energy in the body. One of the by-products of its conversion into an energy source is reactive oxygen species (ROS). Related reactions in the body also produce reactive nitrogen species (RNS). In low and moderate amounts, ROS and RNS can have several beneficial effects. They contribute to cell signalling and immune functions. However, in high concentrations, resulting from either an increase in reactive specie production or a decrease in antioxidant concentration, ROS and RNS can cause oxidative stress, a process that has deleterious effects on cell structures and function. This includes DNA and protein damage, formation of tears in the cell surface and even cell death. Several diseases including dementia-related conditions are aggravated or initiated by an accumulation of ROS. In the case of Alzheimer’s disease, the cell damage caused by the reactive species contributes to the deterioration of regions of the brain essential to memory, emotional behaviour and executive functions.

To combat the accumulation of free radicals and other reactive species, antioxidants bind to free radicals to prevent them from interacting with cell structures and causing additional damage to the cell. These are usually obtained from plant-based foods, although meat and minerals can have similar effects on reducing free radicals. Because free radicals play such a basic role in disease onset and progression, Professor Oguro has become increasingly interested in using antioxidants as potential therapeutics for today’s most severe diseases.

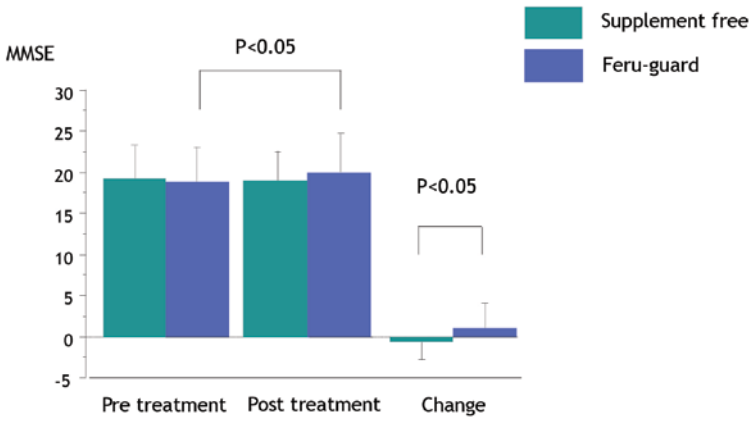
Ferulic Acid

A promising group of antioxidants are phenols. Phenols are organic compounds largely produced by plants

and microorganisms (although, synthetic phenols can also be made). Phenols are best known for their therapeutic effects on a wide range of diseases including neurological, cardiovascular, metabolic, inflammatory and age-related ailments. Because of their abundance, they are a significant part of the human diet. They are not only beneficial in protecting against disease, but also viral and bacterial infections and allergic reactions. Once inside the body, phenols perform many different protective actions such as interact with free radicals to reduce oxidative damage, bind to harmful metals, influence enzyme activity, and even activate gene expression. While synthetic phenols are capable of similar therapeutic functions, naturally occurring phenols are preferred because they contain natural components that are more likely to be compatible with the human body.

Of particular interest to Professor Oguro's research team is the phenol known as 4-hydroxy-3-methoxycinnamic acid, or ferulic acid (FA). Like many phenolics, FA is a naturally occurring antioxidant abundant in plant leaves and seeds of fruits and vegetables. FA has unique properties that make it a particularly potent antioxidant. It has the ability to stop free radical chain reactions that continuously produce new reactive species, and also contains several sites for reactive species to bind to, thus preventing them from attacking host cells. Lastly, FA can attach to the surface of cells and protect them from oxidative damage. FA functions to protect plants from harmful enzymes during germination, regulates plant growth, contributes to mineral and water absorption in the roots and protects the plant from competing plants in its environment. However, its benefits extend past plants. FA's ability to bind to and stabilise free radicals has translated into a wide range of therapeutic effects for humans including anti-diabetic, anti-inflammatory, anti-cancer and neuroprotective effects.

Another beneficial attribute of FA is that it is highly bioavailable, meaning that a high percentage of FA reaches the diseased or injured site after it is administered. Many substances are broken down after administration and so only a small percentage reaches the injured tissue. However, FA is one of the most bioavailable phenols studied. Thus, small doses of FA will have a large medicinal effect. This also minimises the chances of side effects.



The effects of Feru-guard on MMSE in 35 dementia patients. MMSE: Mini-Mental State Examination

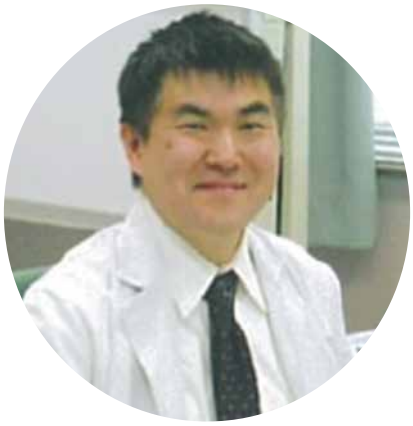
Ferulic Acid and Alzheimer's Disease

There is some evidence suggesting that FA may also be beneficial in treating Alzheimer's disease. A recent study found that treatment with FA blocks amyloid plaque formation, prevents plaque expansion and destabilises plaques that had already formed. Animal models of Alzheimer's disease involving mice with amyloid plaques in their brains also revealed that FA treatment prevented the progression of learning and memory deficits brought on by the disease. It is thought to stave off further deterioration of vital cognition related brain regions by preventing amyloid plaque originating free radical-induced changes in proteins on the cell surface involved in neuron signalling. Long term administration of FA has also been shown to prevent activation of microglia – the nervous system's immune cells. These cells can be activated by amyloid plaques and may contribute to neurofibrillary tangle development in Alzheimer's disease. In addition, FA activates protective genes and proteins in regions of the brain involved in memory.

Ferulic Acid Improves Dementia Symptoms

The multipronged approach of FA in treating symptoms of Alzheimer's disease, as well as its high abundance and inexpensive cost, have driven Professor Hiroaki Oguro and his team to further explore the effect of ferulic acid on dementia. To do this, Professor Oguro launched a clinical study to investigate the effects of a ferulic acid supplement on patients with various types of dementia. Study participants were patients with dementia (Alzheimer's Disease, frontotemporal lobar degeneration, vascular dementia or dementia with Lewy bodies) that experienced progressive cognitive decline and memory impairment. Patients were treated with a supplement known as Feru-Guard® (GLOVIA, Tokyo, Japan). Feru-Guard is a food supplement consisting of FA extracted from rice bran and garden angelica – a biennial plant commonly used as a flavouring or medicinal agent. Feru-Guard was taken twice a day for 6 months. These 6 months were either preceded or followed by another 6 months without treatment. Memory, visual attention and behavioural and psychological symptoms of dementia were assessed after each 6-month period.

The results of the study are very promising. Professor Oguro concluded that treatment with the supplement did in fact improve memory performance, Mini-Mental State Examination (MMSE). And while treatment did not improve visual attention (Trail Making Test-part A: TMT-A), it did prevent further decline in attention (TMT-A). These results suggest that Feru-Guard may have beneficial effects on some of the memory and cognitive impairments resulting from dementia in humans. Based on these findings, Professor Oguro and his lab are now looking at the effect of FA in milder cases of dementia and cognitive impairment in a new clinical trial. Enrolment of new patients is nearly complete.



Meet the researcher

Professor Hiroaki Oguro
Associate Professor
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Professor Hiroaki Oguro is an associate professor in the Department of Neurology at Shimane University. He received his medical degree from Shimane Medical University and subsequently joined their Department of Neurology. In the next two years, he trained as an intern in internal medicine at Shimane Medical University Hospital. He then went on to obtain his PhD in Medical Science from Shimane Medical University. In 2002, he was appointed Assistant Professor. After serving a year as a visiting research fellow at Wales University Bangor in their Cognitive Neuroscience Laboratory, he was appointed to his current position as Associate Professor in 2007.

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IMAGING MULTIPLE SCLEROSIS: SEARCHING FOR PATTERNS IN THE BRAIN

Professor Matilde Inglese, Director of the Neurology Imaging Laboratory in the Icahn School of Medicine at Mount Sinai, is at the forefront of using sodium MRI as a means to better monitor and understand the pathophysiological changes caused during multiple sclerosis.

What is Multiple Sclerosis and How Do We Currently Diagnose it?

Multiple sclerosis (MS) is a debilitating disease of the Central Nervous System (CNS) that affects the brain and the spinal cord. Neurons, which relay signals from the CNS to the rest of the body, can communicate long distances in short periods of time thanks to a protective layer of fatty tissue known as myelin, which aids the efficient and fast transfer of information. In MS, the immune system attacks and destroys the myelin, leading to demyelination and causing significant delays or blockages in the transmission of impulses. This eventually causes damage to the nerves themselves which can sometimes be permanent.

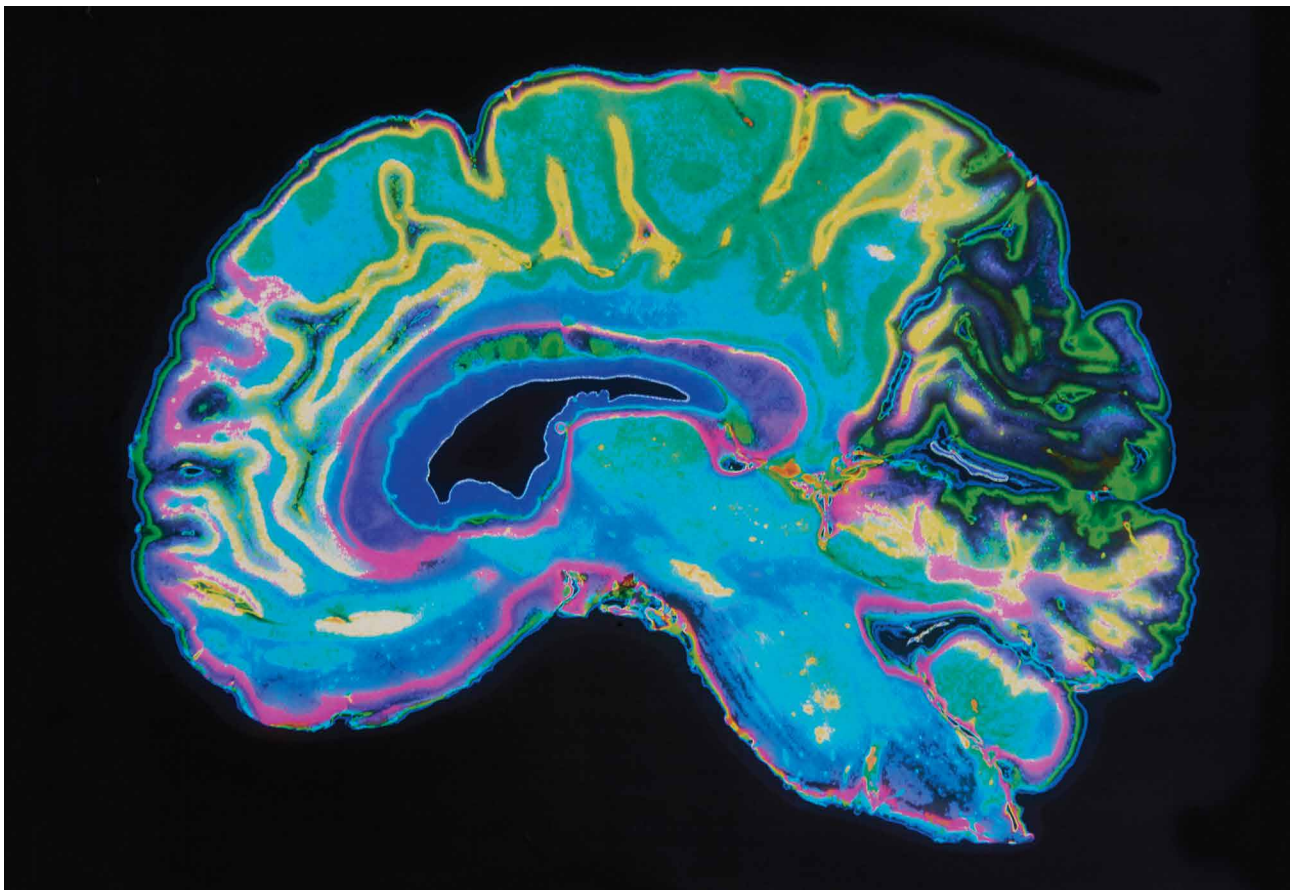
Symptoms of MS can vary widely depending on the location and function of the nerves affected. While early symptoms like numbness, tingling or lack of sensation in a limb can be managed, the unpredictability of the progression of the disease means that these symptoms either disappear or quickly progress into worse outcomes such as difficulty walking, uncontrollable tremors and loss of coherent thoughts.

While there is currently no cure for MS, early diagnosis and treatment can lead to better management of symptoms and significantly improved quality of life. There is no single test to diagnose MS. Instead, a range of clinical tests are often used to eliminate possibilities of other conditions. Blood tests and lumbar punctures are used to rule out infections and other diseases with symptoms similar to MS. Magnetic Resonance Imaging (MRI) is one of the most commonly used methods to confirm an MS diagnosis, or to identify a pre-symptomatic disease known as radiologically isolated syndrome because of its ability to pinpoint the presence of MS lesions in different parts of the brain.

MRI for MS Diagnosis

As a clinician, Professor Matilde Inglese is intimately aware of the situation for patients with MS. In many cases the disease affects young women in their most productive period of life, who become faced with a chronic, elusive and disabling disease with no cure and few reliable techniques for diagnosis. Talking to Scientia, she acknowledges that MS is a very difficult disease to study because of its unpredictability and heterogeneity. No two patients present with the same symptoms of MS. Revealing her motivation to enter the field of neuroimaging, she says: 'Neuroimaging techniques are very attractive in that they provide an array of non-invasive tools to investigate in vivo the pathophysiology of the disease and a set of metrics to help personalise patient treatment.'

MRI, in particular, is a promising tool for diagnosing MS. MRI takes advantage of the huge amount of water molecules found in our body. Each water molecule contains two protons, which have an intrinsic magnetic moment. Under normal conditions, these tiny magnets, or spins, are randomly oriented. However, when a large magnetic field is applied, a considerable amount of protons tend to align their spins in the direction to the magnetic field, which leads to an equilibrium magnetisation proportional to the field strength. To obtain MRI images, a transverse component of this magnetisation is created. The time it takes to return to the equilibrium state, the relaxation time T1, depends on the environment or tissue types.



This time and the interaction of spins can be measured in particular ways and displayed by different shades in the resulting MR image. By additionally using contrast agents like gadolinium that can cross the blood brain barrier, the contrast of MS-associated lesions in the brain can be enhanced. This helps towards a more definite diagnosis.
While over 90% of patients with MS show abnormal lesions in an MRI, the specificity of conventional MRI is still poor. All lesions appear similar on T2-weighted MRI scans regardless of their pathological substrate that ranges from inflammation, demyelination, degeneration, remyelination etc. Hence, there exists an urgent need for better imaging tools to better characterise the severity of the disease and to monitor its progression.

Sodium Imaging as a Predictive Tool for Disease Progression

MS presents with several pathological features in addition to inflammation, such as mutations in mitochondrial DNA, cuts in the axons of the neurons, production of detrimental nitric oxide and accumulation of iron and alteration of sodium homeostasis. Studies in both experimental models of MS and in post-mortem samples of patients with MS have suggested an increase presence and activation of sodium channels in MS plaques. Hence, measuring the level of activation of sodium channels in the brain and non-invasively quantifying the levels of sodium in the brain open up exciting opportunities for improved MS prognosis and monitoring.

Brain sodium MRI is an imaging technique that uses the principles of MRI to measure the sodium signal in different regions of the brain. Since sodium is not as abundant as water, the Signal to Noise Ratio (SNR) is poorer, the spatial resolution is lower than proton MRI and the technique requires longer acquisition times. Sodium MRI has been around for more than 20 years, but because of these disadvantages, the technique has not become widely used as a diagnostic tool. However, with recent technological advancements in both hardware and software, and with the advent of ultra-high field magnets, it is now possible to explore the use of sodium MRI as a tool for studying the pathophysiology and progression of disease. As new therapies for treating the neurodegenerative aspect of MS evolve, there is an unmet clinical need for better imaging techniques to non-invasively monitor response to such treatments.

The Sodium Concentration Puzzle

Neuro-axonal degeneration is highly correlated with permanent disability in MS patients. However, the pathophysiological process that leads to neuronal injury is not well understood and there are no effective treatments to prevent or slow down the progression of disability. Several studies suggest that an increased influx of sodium ions into demyelinated axons leads to delayed axonal injury and associated symptoms. Furthermore, using therapeutic agents to partially block sodium from influxing into demyelinated axons protects against axonal degeneration in experimental models. Hence, measuring sodium concentration represents an important step in understanding the pathophysiological basis of the disease.

The first study implementing the use of sodium MRI on patients with MS was carried out by Professor Inglese and her colleagues in the Department of Radiology, New York University School of Medicine, where she was initially a postdoctoral fellow in 2001 then became an Associate Professor in 2007 in the Departments of Radiology and Neurology. The study, published in 2010 in the journal Brain, reported an increase in

total sodium concentration (TSC) in the lesions of MS patients. More importantly, the researchers showed increases even in the apparently normal white and grey matter of MS patients compared to healthy controls. They also found a weak inverse correlation between sodium concentration in grey matter and the volume of grey matter – the higher the sodium concentration, the lower the volume of grey matter. The same correlation was not found for white matter, suggesting that the sodium concentration in grey matter could be used as a measure of earlier tissue injury.

Although measuring TSC in MS patients is promising, one of its main limitations is its inability to accurately pinpoint differences in intracellular and extracellular sodium. While extracellular sodium is more abundant (140 mmol/L), intracellular levels are low (10–15 mmol/L). This difference in concentration is physiologically essential for axonal impulses to propagate and for basic cellular functions to be maintained. TSC only measures a weighted average of extracellular and intracellular sodium concentrations and can either result from neuro-axonal metabolic dysfunction or from the expansion of the extracellular space. An increase in TSC in brain tissues is not just attributed to tissue loss and expansion of the extracellular space – high TSC could also be a consequence of inflammatory-related hyper-cellularity and increased intracellular sodium in neuronal and astroglial cells. Thus, in addition to calculating TSC, it is also necessary to differentiate between intracellular and extracellular sodium concentrations (ISC and ESC respectively) to understand the relationship between MS and these compartments, and their contribution to the progression of the disease.

In order to measure and distinguish between sodium levels of the two compartments, Professor Inglese's group implemented a magnetic resonance 12 step phase-cycling pulse sequence in order to acquire a triple-quantum filtered sodium MRI, which offered an increase in the signal to noise ratio by 40% compared to previous methods. They also implemented and developed a technique using high field magnets (7 Tesla) to quantify ISC and intracellular sodium volume fraction (ISVF), which is an indirect measure of ESC. A decrease in ISVF implies a decrease in intracellular volume, which reflects an increase in extracellular space and consequently ESC. In a recent study reported in Brain, Professor Inglese and her colleagues used the above-mentioned techniques to measure both ISC and ISVF in 19 MS patients and 17 healthy controls. They sought to identify the relationship between intracellular and extracellular sodium with measures of lesion and brain volume, and to evaluate the clinical significance of abnormal sodium distribution.

In the study, they showed that ISC and ISVF values can complement TSC values to provide a clearer picture of the pathophysiology of the disease. While ISC values reflect changes in cellular metabolism related to mitochondrial and ion channel dysfunction, ISVF values reflect expansion of the extracellular volume related to cellular loss and development of tissue atrophy. It is known that abnormal cellular metabolism can either lead to cellular death or could even reverse back to physiological conditions. This suggests that increases in TSC and ISC may be useful in predicting and selecting patients who will particularly benefit from neuroprotective therapy even before structural damage occurs.

Future Work

While these studies report very promising findings on the relationship between sodium concentration and disease progression, there is a need for these results to be confirmed in a larger cohort of patients and in longitudinal studies. Technical advances in the field should particularly focus on clearer distinctions between intracellular and extracellular sodium levels. Clinically, the field is moving towards combining sodium MRI with different conventional MRI modalities that are sensitive to neuro-axonal loss. Professor Inglese is optimistic about the future: 'The next step is to extend far beyond the lab to understand the dynamics of changes in brain sodium concentration in relation to the progression of the disease'. With such advances, we hope this research will lead to better prognostic and monitoring tools that will not only help in understanding this complex disease, but also immensely improve quality of life for patients with MS.

Meet the researchers

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Dr Lazar Fleysher, an Instructor in the Department of Radiology at Mount Sinai, has a broad background in physics and mathematics, with practical experience in the fields of data acquisition, image reconstruction, experiment design, protocol optimisation, post-processing, and statistical data analysis. He has contributed to the development of a quantitative sodium MRI technique which allows non-invasive quantification of intracellular sodium concentration and cell-volume fraction in the human brain. He has authored and co-authored more than 40 publications in peer-reviewed journals.

Professor Matilde Inglese is an Associate Professor of Neurology, Radiology and Neuroscience at the Icahn Mount Sinai School of Medicine, New York. She received her medical degree magna cum laude from the University of Genoa, Italy in 1992 and earned a PhD degree in 2004 from the same university after her formal training in neurology. After completing post-doctoral training in neuroimaging at San Raffaele Hospital, Milan, and in the Department of Radiology in New York University, she went on to become a fellow and subsequently an Associate Professor in the same department. Here, she started delving into sodium MRI and its applications in multiple sclerosis. Professor Inglese has authored and co-authored more than 150 publications in peer-reviewed journals, is on the editorial board of several journals and has served on grant advisory panels for the National Institute of Health, the National Multiple Sclerosis Society and for several international funding agencies.

Her current research in Mount Sinai is funded by the National Institute for Neurological Disorders and Stroke, the National Multiple Sclerosis Society and by the Congressionally Directed Medical Research Program in Multiple Sclerosis. Her focus is to identify mechanisms of degeneration that lead to clinical disability in order to provide markers to monitor the effect of neuroprotective treatments in patients.

Dr Niels Oesingmann, a MR physicist in the UK Biobank, has extensive expertise in development of cardiac, body and brain applications. A former member of the Siemens R&D group, in the last 15 years he has managed collaborations for Ultra High-Field and Multinuclear Imaging at major university hospitals worldwide. He has contributed to the development of the triple-quantum MR sequence for the acquisition of sodium imaging at 7 Tesla. He has authored and co-authored several peer-reviewed publications and application manuals.

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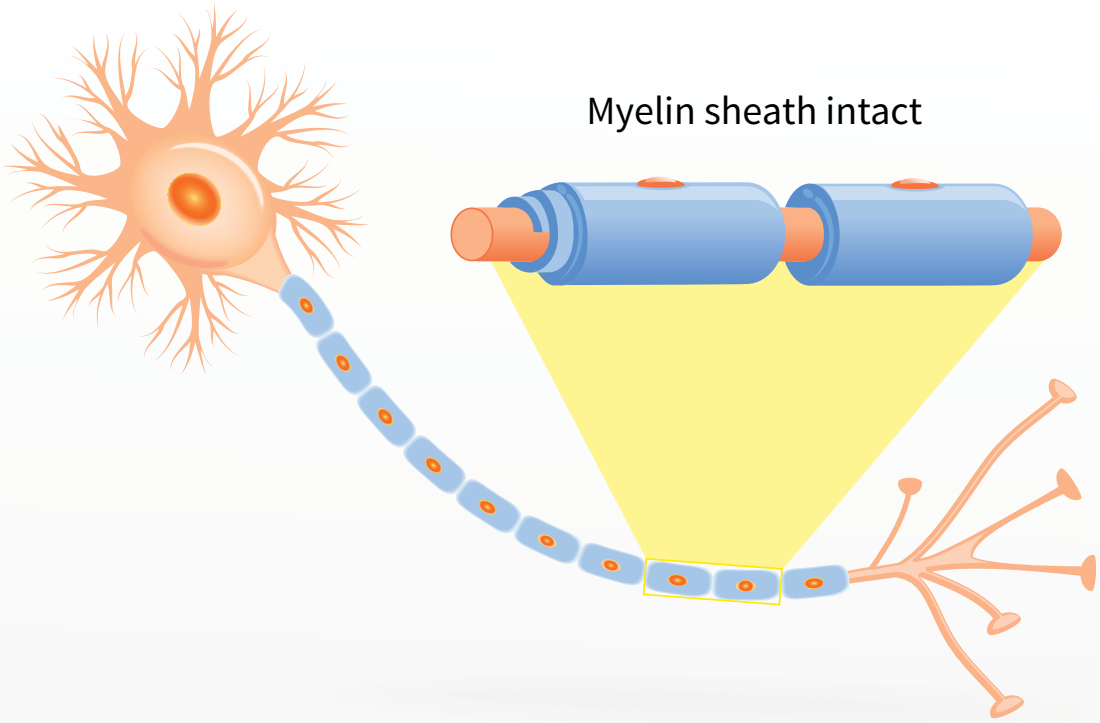
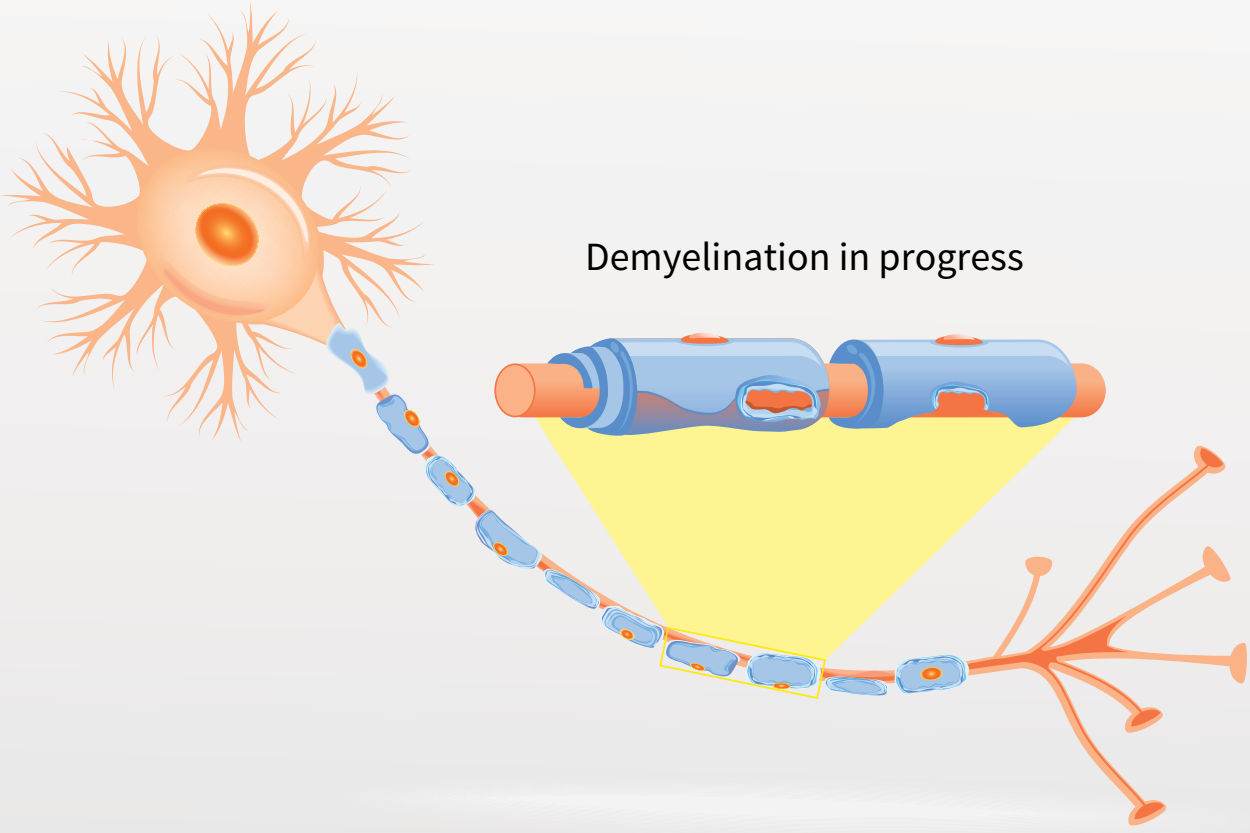
Icahn School of Medicine at Mount Sinai

Healthy Nerve



Nerve affected by multiple sclerosis



DEFINING ACUPUNCTURE'S PLACE IN WESTERN MEDICINE

Acupuncture may not be a treatment one associates with cardiovascular health, but **Drs John Longhurst, Stephanie Tjen-A-Looi and Peng Li** have spent the last two decades gathering evidence as to why this traditional Chinese approach should not be overlooked.

Effective Treatments from Ancient Practices

Acupuncture is one aspect of Traditional Chinese Medicine (TCM), the practice of which began over two millennia ago. This ancient practice involves the insertion of fine needles into the skin at specific points along the body. These points are known as acupoints, located along pathways called meridians. According to TCM, meridians are routes through the body along which energy, or Qi, flows. Although acupuncture has been practiced for thousands of years, it is only in recent decades that it has been tested from an evidence based approach.

Western medical practitioners have often approached acupuncture with scepticism. There are a number of reasons behind this, including a lack of verification of the underlying concepts such as Qi and meridians, and the overall absence of the scientific method. Clinical trials have produced mixed results and are open to bias and the placebo effect. It should also be noted that around one third of patients do not respond well to treatment.

Upon observing acupuncture in practice for the first time in the early 90s, Dr John Longhurst was similarly sceptical, due to an insufficiency of scientific evidence. 'I was asked to consider collaborative research in acupuncture. My initial reaction was no, but my future collaborator, Dr Peng Li, then Professor and Chair of the Department of Physiology at Shanghai Medical University, showed me his curriculum vitae containing publications in respected western journals on the central neural mechanisms underlying acupuncture's cardiovascular actions,' Dr Longhurst tells us. This led to a long-term collaboration between the two scientists, exploring the neural mechanisms underlying the actions of acupuncture on cardiovascular function. Dr Stephanie Tjen-A-Looi soon joined them, and the team went on to carry out over 40 experimental and clinical studies on the effects of acupuncture on myocardial ischaemia (reduced blood flow to the heart), reflex induced hypertension (high blood pressure), sustained hypertension and reflex hypotension (low blood pressure), as well as identifying mechanisms that underlie the physiological effects of acupuncture.

One of the most significant areas of study in acupuncture has been the role of the nervous system. Multiple studies suggest that meridians are in fact neural pathways along which nerve bundles are located. 'We have conducted a large number of studies – over 40 in total – showing that electro- and manual acupuncture applied at specific acupuncture points lowers short-term elevations (by about 50%) and long-term elevations in blood pressure through stimulation of sensory nerve fibres underlying the acupuncture points,' Dr Longhurst explains. A 2005 study by the team showed that the transection (cutting) of sensory nerve fibres eliminated the modulatory effect of acupuncture on cardiovascular responses. They did not observe similar outcomes with eliminating the actions of motor nerve fibres, suggesting an important role for sensory neural pathways in acupuncture.

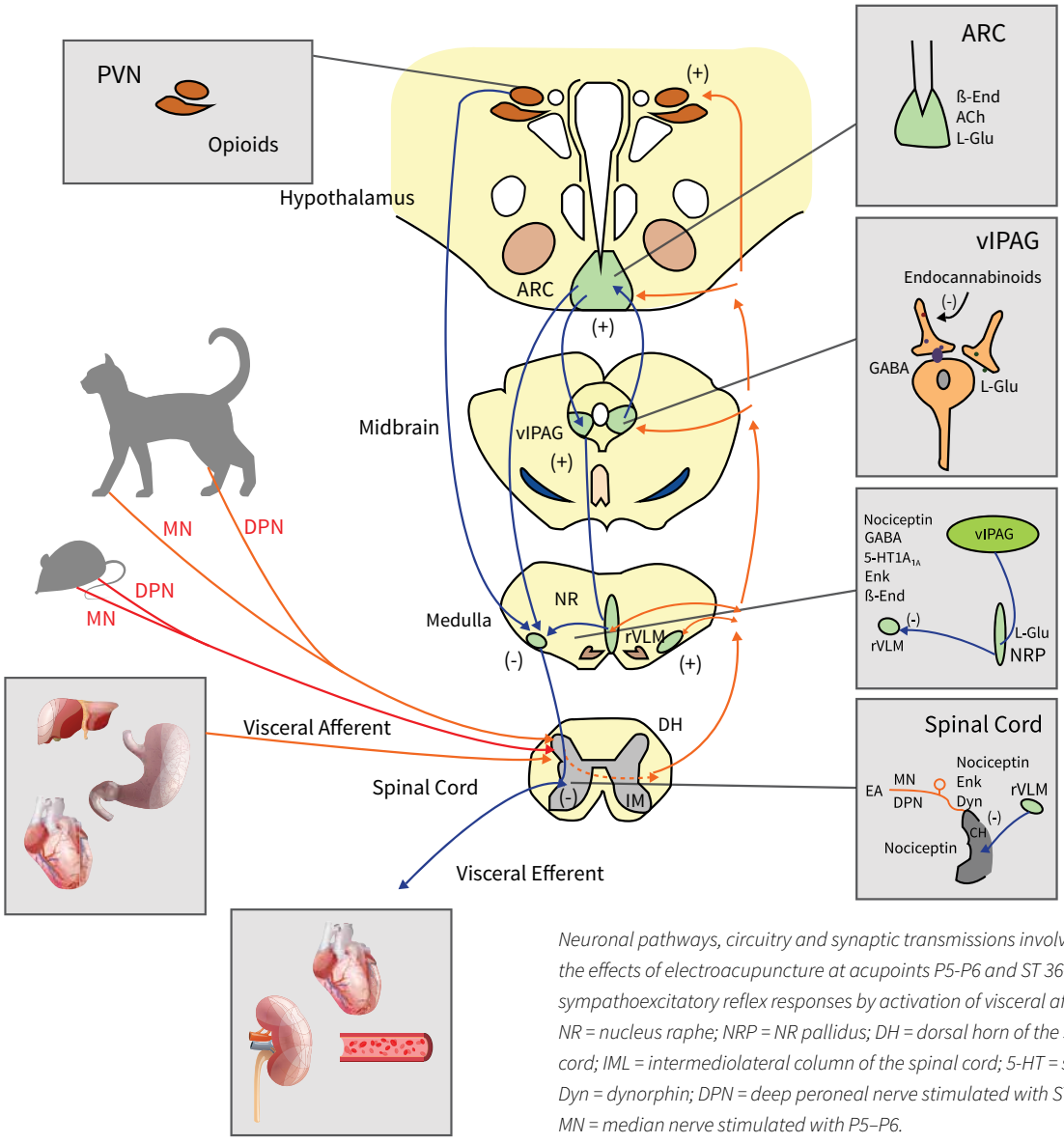
Acupuncture and Mechanisms of Action

Over the last two decades, many mechanisms of action on cardiovascular function have been identified. These mechanistic studies are significant, as they help to guide clinical studies. The central nervous system (CNS) plays a key role in mediating the physiological responses of the cardiovascular system. Contained within the CNS are centres that regulate the function of autonomic nerves – important regulatory nerves that control different aspects of cardiovascular function such as heart rate, blood pressure, cardiac output and peripheral blood flow.

Electroacupuncture's modulation of reflex increases in blood pressure is based on a long-loop pathway involving at least three areas of the brain: the hypothalamus, midbrain and medulla. These areas are relevant to the autonomic nervous system (which functions to regulate the body's unconscious actions). The autonomic nervous system can be divided into two branches: the sympathetic nervous system (which stimulates 'fight or flight') and the parasympathetic nervous system (which stimulates 'rest and digest'). Under different conditions acupuncture acts on these two branches of the autonomic nervous system to produce effects on the cardiovascular system.

Several of the relevant neurotransmitter systems involved in these actions are located in the rostral ventrolateral medulla (rVLM), which is responsible for the control of sympathetic outflow associated with

‘We began with a study of myocardial ischemia… but quickly realised that acupuncture’s ability to lower elevated blood pressure was one of its principal actions. To put it into lay terms, our interest has been to provide evidence from a mechanistic perspective of how acupuncture regulates cardiovascular function, with a focus on elevated blood pressure or hypertension.’

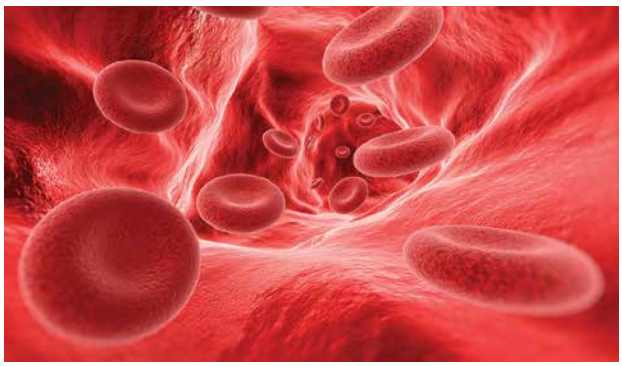


Neuronal pathways, circuitry and synaptic transmissions involved in the effects of electroacupuncture at acupoints P5-P6 and ST 36-ST37 on sympathoexcitatory reflex responses by activation of visceral afferents. NR = nucleus raphe; NRP = NR pallidus; DH = dorsal horn of the spinal cord; IML = intermediolateral column of the spinal cord; 5-HT = serotonin; Dyn = dynorphin; DPN = deep peroneal nerve stimulated with ST36-ST37; MN = median nerve stimulated with P5–P6.

cardiovascular function. Electroacupuncture stimulation applied for 15 to 30 minutes activates a long-loop pathway, leading to the opioid (Beta-endorphin (ß-End) and Enkephalin (Enk)) mediated regulation of rVLM neurons through the inhibition of the excitatory neurotransmitter glutamate (L-Glu). Other neurotransmitter systems in the rVLM (namely GABA released from the rostral and caudal ventrolateral medulla and serotonin released from the nucleus raphé pallidus) also participate in the regulation of hypertension.

The long-loop pathway also involves the arcuate nucleus (ARC) and paraventricular nucleus (PVN) – located in the hypothalamus – and the ventrolateral periaqueductal grey (vlPAG) – located in the midbrain. A reciprocal excitatory pathway between the two areas reinforces and prolongs the actions of electroacupuncture. This excitatory connection between the ARC and vlPAG is due to two neurotransmitters – L-Glu and acetylcholine (ACh). In addition to this, endocannabinoids, the endogenous marijuana-like system, in the vlPAG reduce the release of GABA during acupuncture.

Spinal pathways are also involved in acupuncture’s modulation of cardiovascular function. Electroacupuncture reduces reflex hypertension through both opioid and non-opioid mechanisms in different areas of the spinal cord. The action of electroacupuncture in these areas implies inhibition of sensory inflow during reflex stimulation and modulation of sympathetic outflow in the spinal cord.



Promoting Homeostasis and Heart Health

Cardiovascular disease and its associated symptoms – such as hypertension and angina pectoris – are new areas where there is mounting evidence for using acupuncture as a treatment component. For instance, accumulating data in patients and animal models shows that acupuncture decreases sympathetic outflow, including reducing renal sympathetic activity and attendant decreases in plasma hormones renin, angiotensin and aldosterone, leading to a long-lasting lowering of blood pressure. Dr Longhurst emphasises however that such hormonal changes that likely underlie acupuncture's cardiovascular actions in hypertension require confirmation and further investigation. This increasing evidence provides a strong rationale for achieving a greater understanding of the clinical actions of acupuncture at organ, cellular and subcellular levels.

Experimental studies by Drs Longhurst, Tjen-A-Looi and Li suggest that stimulation of certain acupoints located on the arm and the leg can lower systolic blood pressure by 8 to 12 mmHg and diastolic pressure by 3 to 5 mmHg in 70% of patients. Although the reduction in blood pressure is slow in onset (a course of treatment over several weeks was required), the duration of the effect extended for as long as one month after treatment had ended. Therefore, it is likely that acupuncture can be safely used to treat patients with mild to moderate hypertension and it may be especially useful in patients with sustained vascular constriction – the excessive contraction of smooth muscle in arterial walls that can elevate blood pressure.

Another study by the team looked at the effect of acupuncture on myocardial ischaemia. A feline model of demand-induced myocardial ischaemia was induced by partially ligating a coronary artery, resulting in insufficient blood flow and transient ischaemia. They found that a course of acupuncture lowered elevated blood pressure and also reduced the rate-pressure product during exercise. The rate-pressure product is a measure of the energy demand in the heart. Together this indicated lower myocardial oxygen demand, thus reducing ischaemia. A follow-up study showed these outcomes could be reversed with naloxone (an opiate blocking drug), implicating the endogenous opioid system as the underlying mechanism for acupuncture's action.

Further Studies into Blood Pressure

The team are also exploring the effect of acupuncture on hypotension and bradycardia (low heart rate). In experimental studies, the team found that electroacupuncture significantly reversed bradycardia and hypotension. They used two models to investigate brain regions and neurotransmitter systems involved in acupuncture's capability to raise blood pressure. In the first model, researchers used an IV infusion of a chemical to evoke bradycardia and hypotension in order to mimic vasovagal syncope – a sudden drop in heart rate and blood pressure, often leading to fainting. They found that the preganglionic cholinergic neurons in the nucleus ambiguous in the brain stem – part of the parasympathetic nervous system – were located in close proximity to axons containing enkephalin – an opioid neurotransmitter that modulates or reduces parasympathetic neural outflow from the brain to the heart. These neurons were activated by 30 minutes of electroacupuncture, during which both enkephalin and GABA modulated the vasovagal reaction.

The second model of reflex hypertension involved gastric distension in hypercapnia induced acidosis, which involves increased acidity in the blood and body tissue triggered by elevated carbon dioxide levels. Spinal and vagal pathways are stimulated by gastric distension to lower blood pressure through a combination of sympathetic withdrawal and increased parasympathetic outflow. The team found that electroacupuncture inhibited this increase in parasympathetic outflow and limited sympathetic withdrawal, thus reducing reflex hypotension and bradycardia.

Expanding the Evidence Base

In a recent review of the evidence, Dr Longhurst confirmed the need for further research in this area. If acupuncture is to take a place within conventional western medicine, more well designed unbiased prospective studies are required. Experimental animal models can provide additional clues about how best to apply acupuncture clinically and properly constructed clinical trials on acupuncture's effects on smoking, cholesterol reduction and weight loss are needed. Further investigation into how acupuncture can modulate cardiovascular risk is also warranted. For example, recent experimental studies examining the potential for electroacupuncture to be used in treating myocardial infarction, arrhythmias, heart failure, stroke and peripheral vascular disease either have shown mixed results or have not been conducted at all, so further experimental and clinical studies will be needed to determine acupuncture's role in treating these diseases.

Another area of importance is research into how acupuncture effectiveness can be improved. A number of studies have indicated that only 70% of patients respond to acupuncture. Recent investigations by the team suggest that non-responders can be converted to responders by administering into the hypothalamus an antagonist to the octapeptide (a protein molecule that consists of eight amino acids linked in a chain) of the hormone cholecystokinin. This octapeptide exerts an anti-opioid effect in the brain, leading to opioid tolerance. Initial research suggests that the octapeptide in the rVLM contributes to the absence of electroacupuncture actions on hypertension in rats. This may be the beginnings of how to convert non-responders.

Finally, more experimental and clinical studies are needed to determine how acupuncture treatment can be reinforced to provide prolonged suppression of hypertension. Although a single 30-minute application of acupuncture stimulates an enkephalin response lasting 90 minutes, repeated acupuncture over several days leads to longer elevations of neurotransmitter messenger RNA, called preproenkephalin and the protein neurotransmitter enkephalin expression, which can last hours and days after acupuncture treatment is terminated. Repeated acupuncture can therefore exert a very prolonged action on blood pressure, but further research is required to guide physicians on how to best incorporate this into a care plan.

Meet the researchers

Dr John Longhurst, MD, PhD is Professor Emeritus in the Departments of Medicine, Physiology and Biophysics and Pharmacology in the University of California, Irvine. After completing an undergraduate degree in Zoology from the University of California, Davis, Dr Longhurst went on to receive his MD and PhD in cardiovascular-pulmonary physiology. Dr Longhurst's research focuses on cardiovascular neural reflex control mechanisms originating from somatic and visceral regions and integrative cardiovascular neurobiology with reference to mechanisms of cardiovascular regulation by acupuncture.

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Dr Peng Li, MD is Project Scientist and Allied Health Professional in the Department of Medicine at the University of California, Irvine. After graduating from Shanghai First Medical College, Dr Li went on to complete postdoctoral training in the Department of Acupuncture and Traditional Chinese Medicine in Hua San Hospital, in the Department of Physiology in the University of Birmingham, and later, served as the chair in the Department of Physiology in the Shanghai first Medical College. His research interests include the effects and mechanisms of acupuncture on cardiovascular function and the central nervous system.

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A CHORDATE WITH DESTINY

Spinal cord injuries have garnered the dedication of countless researchers. Nevertheless, the path towards understanding and mastering neuronal repair in the central nervous system (CNS) remains more tortuous than even the tangled nerves themselves. It therefore seems apposite that **Dr Florence Bareyre's** journey in neuroscience research began with one or two detours of its own.

Few phenomena outline human physiology's limits more starkly and infamously than spinal cord injuries. Whether caused by local ischemia or inflammation, or the split-second result of trauma, a fully severed spinal cord is exceptional for its permanence, notorious for its evasion of successful treatments, and alarming in its implications for the remainder of a person's life.

The spinal cord, a delicate bundle of neural cells and circuits, originates from the medulla oblongata in the brainstem and terminates near the top of the lumbar vertebral levels. It houses the neuronal circuitry involved in various reflexes, and links its companion in the CNS – the brain – to the peripheral nervous system (PNS). In its pivotal latter role, it serves as the envoy for signals from the brain to the muscles, and carries sensory signals in the opposite direction.

Its critical functions earn the spinal cord a reasonable degree of physical protection, including vertebral bone and three meningeal membranes that support the tubular structure and enclose it in adipose tissue and cerebrospinal fluid. Despite this protection, between 250,000 and 500,000 people suffer a spinal cord injury each year worldwide, and for many the prognosis is poor. Most spinal cord injury victims suffer lasting sensory or motor function loss and chronic pain, and many must live with paraplegia or quadriplegia and damage to the systems that regulate, for example, their bladder control, breathing or heart rate.

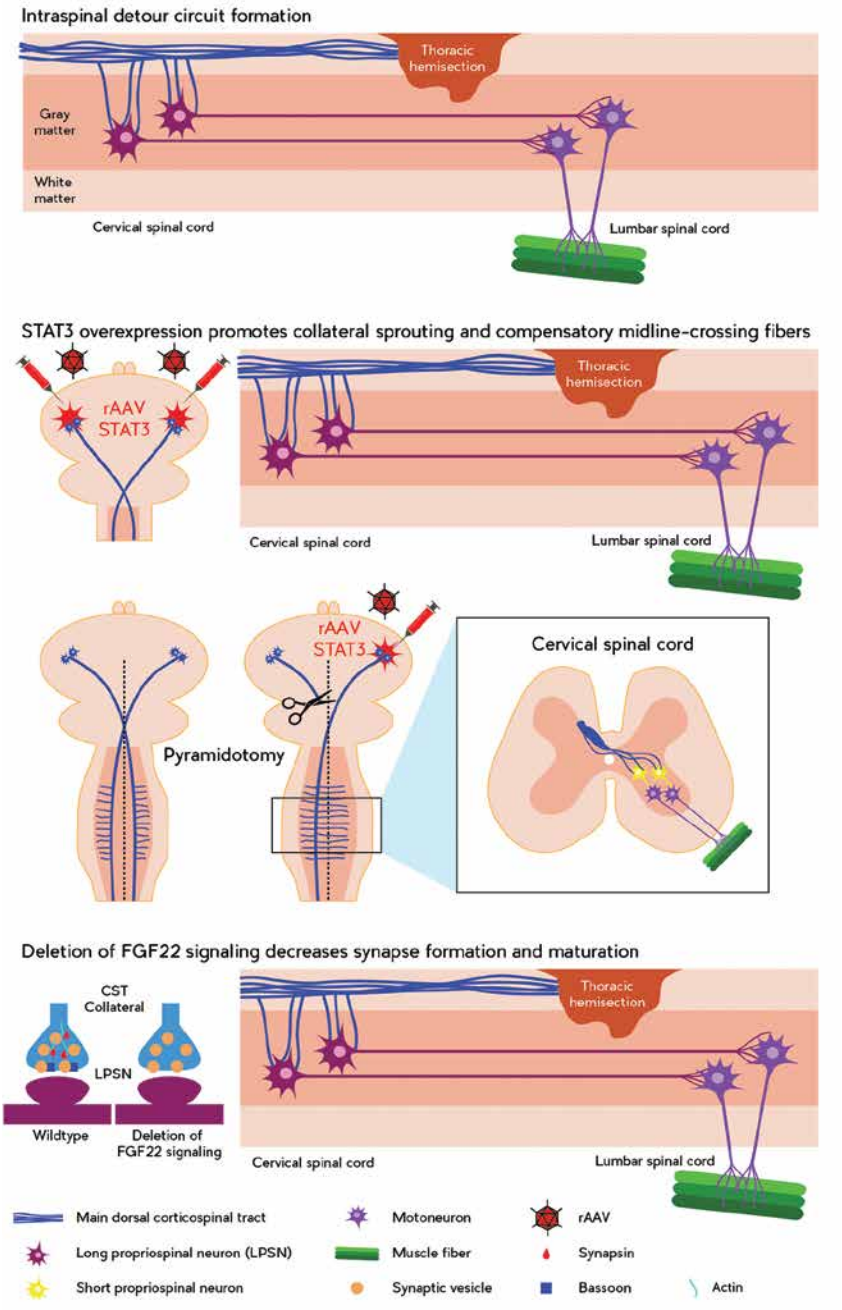
In contrast to the CNS, the PNS is known for its ability to regenerate and return function to damaged neurons. Researchers excitedly demonstrated in the 1980s that a permissive peripheral nerve graft could even allow certain mature CNS axons to regenerate. With the lack of intrinsic plasticity in the CNS taken as dogma, the subsequent discovery by Dr Florence Bareyre and colleagues that following partial lesions in the spinal cord axonal tracts could spontaneously sprout and restore function was spectacular.

Detour de Force

'Since the beginning of my scientific training in 1996, I have always been attracted to understanding how nerve cells respond to CNS damage,' says Dr Bareyre, who currently heads up her own laboratory at Ludwig-Maximilians Universität München, Germany, and has used her score of years in research to elucidate CNS remodelling mechanisms in some of the world's most accomplished laboratories. Throughout her career, she has primarily used the rodent corticospinal tract (CST) to study how axonal connections rewire in response to injury.

She began her research career at University

‘In our laboratory, we are trying to understand the molecules important for axonal outgrowth, axonal guidance and synapse formation in order to design new therapeutic strategies to foster axonal remodelling and improve functional recovery after central nervous system injuries.’



of Pennsylvania, investigating how therapeutic strategies limit neuronal cell death following experimental brain injury. Following a string of publications, she moved to Professor Martin Schwab’s laboratory at ETH Zurich to complete her PhD thesis. ‘To further understand how spontaneous recovery of function is achieved, I studied the reorganisation of the CST after spinal cord injury or inflammatory lesions. For this purpose, I combined advanced tracing techniques to follow the reorganisation of hindlimb corticospinal connections on multiple anatomical levels.’

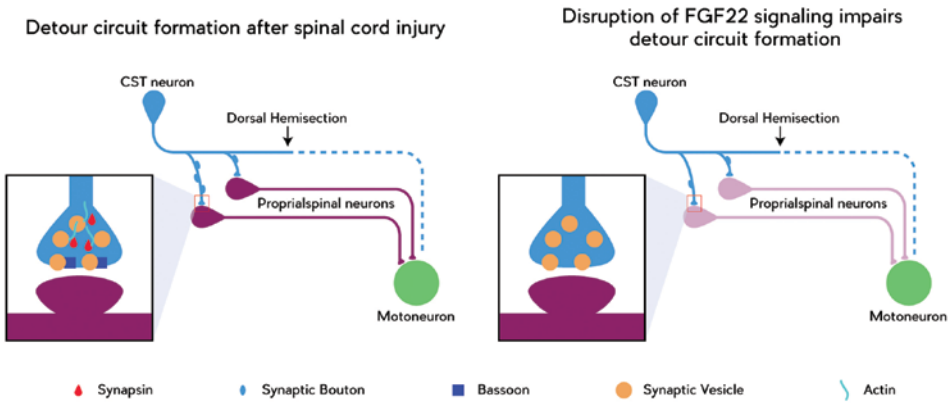
Dr Bareyre’s first great breakthrough arrived when she and co-workers at ETH Zurich definitively demonstrated that partial spinal cord lesions in mice can be bridged by so-called intraspinal ‘detour’ circuits, restoring the function of severed spinal cord pathways. The group showed that transected hindlimb CST axons sprouted neuronal offshoots, known as collaterals, that contacted functioning long propriospinal neurons rostrally to the site of the lesion. Dr Bareyre explains that they not only observed signs of plasticity in the spinal cord, but also found that the reorganisation of intraspinal connections was paralleled by remodelling of the cortical motor representation. Researchers had previously noted motor cortex reorganisation after neuronal damage, but these authors were rewarded for providing solid evidence for the basis of ‘detour’ circuit formation and its direct role in functional recovery and wider neurological impact with a place for their work in the prestigious journal *Nature Neuroscience.*

A follow-up study corroborated these findings in an animal model of multiple sclerosis. Rather than inducing traumatic lesions, the group instead targeted the CST with an inflammatory lesion that severely damaged the nerves. Despite the differing causes of the lesions, the findings were similar: local interneurons exhibited sprouting; CST axons above the lesion extended collaterals, forming a detour circuit; spared CST axons below the lesion increased their terminal branching; and the motor cortex was again remodelled.

‘The following important questions arose from these studies,’ recounts Dr Bareyre. ‘How do the growing axons find the appropriate path to their intraspinal targets and how do they form and stabilise synapses onto these targets?’ To gain insight into the principles that can regulate axonal pathfinding and synapse formation, Dr Bareyre joined the laboratory of Joshua Sanes at Harvard, one of the leading experts studying circuit formation in the developing nervous system.

Striking a Cord with Technicolour

At Harvard, Dr Bareyre bolstered her biological imaging toolkit by developing methods of visualising synapses using tagged peptides, a technique that proved very useful for monitoring synapse formation. She put this experience towards her next significant achievement, which she reported in *Nature Medicine* in 2005. In this work the authors gathered expertise in transgenic technology and generated a new transgenic mouse model in which the corticospinal tract is labelled with a fluorescent protein. Dr Bareyre envisioned that the CST-YFP mice would be useful for evaluating strategies designed to maximise remodelling and promote regeneration. To learn emerging *in*



vivo imaging techniques that allow the direct visualisation of regrowing spinal axons and their path to the target cells in vivo, Dr Bareyre joined the Institute of Clinical Neuroimmunology at the LMU Munich.

Chasing the Peripheral Vision

There are clearly differences in the CNS and PNS that explain why the former lacks the latter's knack for regrowth. Researchers have previously identified growth-inhibiting factors in the CNS and growth-promoting factors in the PNS. For example, particular proteins in CNS myelin and other molecules associated with astroglial scars are known to inhibit axon growth and plasticity. At the same time, the down-regulated expression of growth-promoting genes, which are highly expressed in damaged PNS neurons, also limits brain and spinal cord repair in the CNS. Contrasting the natural strategies adopted by the PNS and CNS after injury has therefore been a pivotal way for Dr Bareyre and other researchers to locate and exploit the factors involved in neuronal growth and plasticity. As you might expect, however, this is not a simple task.

In 2011, Dr Bareyre and colleagues employed *in vivo* time-lapse fluorescence microscopy, genetic modification and viral gene transfer to uncover the key molecular players in PNS plasticity that are lacking in the CNS. Lesions were introduced to the peripheral or central axon branches of the dorsal root ganglia, as they extend branches to both nervous systems. The group discovered that the transcription factor STAT3 plays a key role in initiating neuronal regeneration, with its absence limiting PNS outgrowth and overexpression greatly enhancing terminal branching and collateral sprouting after a CNS lesion.

Based on these promising findings, the group explored the potential of STAT3 in CNS plasticity further in 2013. They found that, although STAT3's artificially sustained expression did enhance lesioned CST neuron sprouting, it unfortunately did not seem to influence the formation of intraspinal detour circuits. In a ground-breaking discovery, however, the group found that after a unilateral pyramidotomy (which interrupts the corticopsinal tract on one side of the body rostral to the pyramidal decussation), sustained STAT3 expression led to a 4- to 10-fold increase in the number of collaterals crossing from the functioning side of the body to contact short propriospinal neurons and spinal motoneurons of the side affected by the unilateral pyramidotomy. Additionally, these connections led to some functional recovery, with cortical stimulation creating an EMG signal in the previously disconnected muscles – revealing the potential for extraordinary plasticity in the CNS.

Continuing Off the Beaten Pathways

Since this important observation, Dr Bareyre has enthusiastically continued her research into the processes underlying neuronal plasticity. For instance, her group at Ludwig-Maximilians Universität München also recently identified the first key regulator of synaptic formation in adults following injury: FGF22. Dr Bareyre found that the fibroblast growth factor FGF22 and its receptors are respectively expressed in spinal relay neurons and cortical projection neurons, and that blocking their expression hinders the functional recovery of mice with spinal cord injuries.

Dr Bareyre's research group has been supported for 6 years by the German Federal Ministry for Research and Education, through a competitive national award aimed at supporting outstanding young female neuroscientists, 1 of 5 grantees over more than 70 applications. Her group is currently part of various research consortia funded by the German National Science Foundation and further supported by the wings for life spinal cord research foundation. Funding from these sources acts in much the same way as an action potential – it is the stimulus that triggers the group's cascade of vital research activities and yields results far in excess of its face value. Some of the ongoing activities in Dr Bareyre's laboratory include investigating the biochemical events underlying the improved outcomes during physical rehabilitation, and further delving into the nature of intraspinal detour circuits.

Dr Bareyre asserts that her laboratory will keep working along the previously described lines in order to keep discovering new molecules that are important for axonal remodelling following spinal cord injury. Lines of work currently followed by Dr Bareyre include, for example, investigating how overexpression of FGF22 can further promote post-injury axonal remodelling, understanding the how rehabilitation and voluntary training do impact functional recovery. 'We then hope to be able to manipulate these molecules – also using combinatorial therapies – in order to improve functional recovery following spinal cord injury,' she says.

The global scale of research into spinal cord injuries is reassuring, and important results and promising preclinical therapies are on the horizon due to Dr Bareyre's group and others like it. Nonetheless, for those afflicted with CNS injuries, the next paradigm shift in spinal cord injury treatment surely cannot come soon enough. With luck, the label 'permanent' will soon acquire plasticity of its own.

Meet the researcher

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Dr Florence Bareyre obtained her PhD at the Brain Research Institute, ETH Zurich in 2003, after which she pursued postdoctoral research at Washington University, Harvard University and LMU Munich. She became a Group Leader at the Institute of Clinical Neuroimmunology, LMU Munich in 2008 and then also at the Biomedical Center, LMU Munich in 2015. She is a member of the Munich Centers for Neurosciences and a principal investigator in the Collaborative Research Center 870, the graduate school for neuroscience and the excellence cluster syNergy. Since 2014 she has served as a board member in the Collaborative Research Center 870. She has received several awards, among them the medal of excellence from the ETH Zürich, the SOBEK junior price for multiple sclerosis and an independent group leader award from the Federal Ministry of Education and Research. She studies spinal cord injuries and the mechanisms underlying the recovery process to develop new therapeutic strategies that can support spinal cord repair in neurological disease. She is married and has four children.

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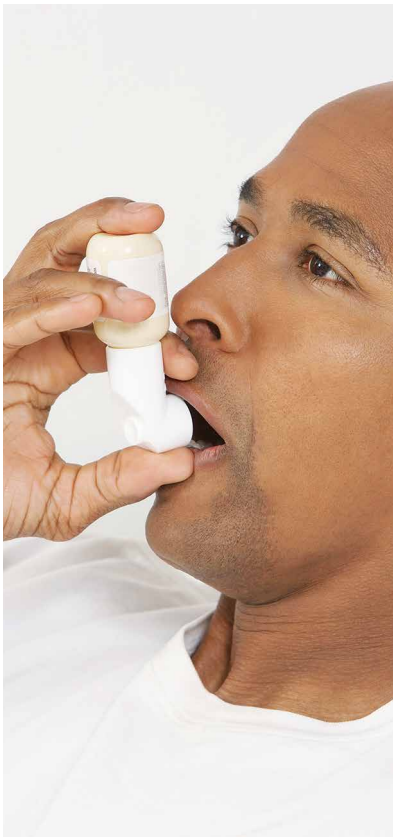
BREATHING NEW LIFE INTO LUNG RESEARCH

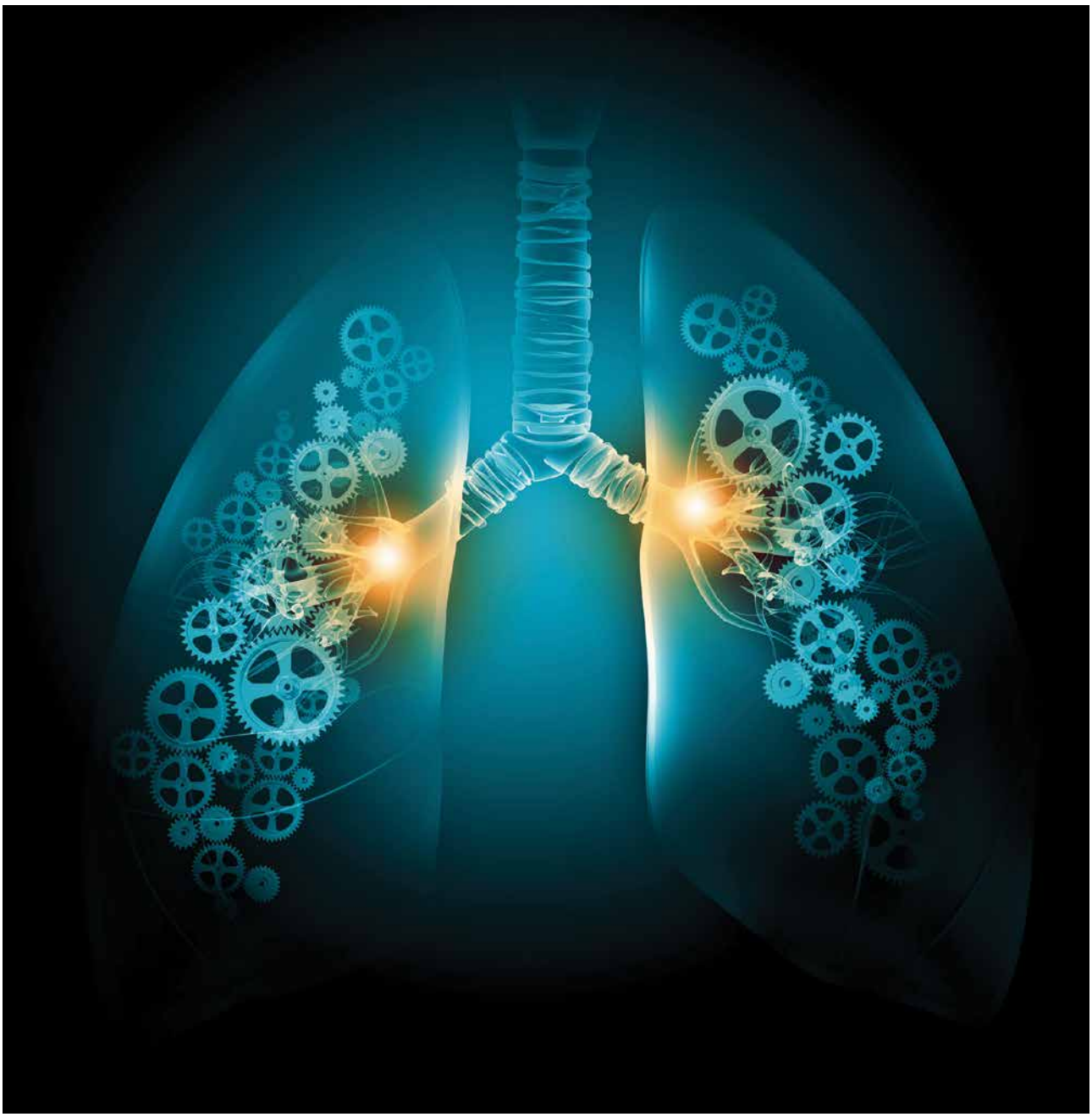
Over the course of a normal day, the average person inhales and exhales nearly 25,000 times. This vital process replenishes our bodies' oxygen levels and eliminates the carbon dioxide produced as a by-product of our metabolism. Without breathing, we would survive mere minutes before sustaining irreversible brain damage and dying.

Due to their complexity, there are a myriad of ways that our lungs can begin to stop working properly. Problems can arise in the airways, the alveoli (where gas exchange takes place), the blood vessels, the pleura (a thin lining surrounding the lung) and even the nerves and muscles required for breathing. Airway problems constitute the vast majority of lung conditions, including asthma, which affects a whopping 8% of the global population, and chronic obstructive pulmonary disease, or COPD. Rather than being a single disease, COPD actually refers to a group of diseases that cause airflow restriction and breathing-related problems, responsible for around 6% of all deaths globally.

Living with a chronic lung condition such as severe asthma or COPD can mean constantly battling for oxygen, even when performing the simplest of tasks. Everyday activities that most of us take for granted, like hanging out the laundry or climbing up the stairs, can be enormously challenging for individuals with these conditions.

In this section of the magazine, we feature a number of research projects, each dedicated to improving the lives of people living with lung disease. To introduce the section, we have had the pleasure of speaking with four division directors of the National Heart, Lung, and Blood Institute (NHLBI). In one part of this exclusive interview, Dr James Kiley, Director of the Division of Lung Diseases, tells us about the NHLBI's commitment to tackling respiratory disease in the US and further afield. One team of researchers who has received enormous support from NHLBI over the years is the Spirometry 360 group, led by Dr Jim Stout at the University of Washington. Our next article in the section details this team's work in improving asthma care through innovative training schemes, quality improvement methods and research into health disparities.





Also on a mission to alleviate the suffering of the 234 million people living with asthma globally is Professor Michael Roth, head of the Pulmonary Cell Research unit at University Hospital Basel in Switzerland. Although current treatments for asthma can effectively relax the airways and reduce symptom severity, they are unable to improve the structural problems present in the walls of the airways that cause airflow restriction. To address this issue, Professor Roth's research team has been investigating the pathologic causative mechanisms that give rise to these structural problems, with the aim of developing novel treatments. In addition to asthma, the team are also investigating the mechanisms behind the pathogenesis of COPD.

This leads us on to the work of Dr Yoshiaki Minakata and his colleagues at the Wakayama Hospital in Japan, who are also working hard to improve the outlook for patients with COPD. Although physical activity is known to improve COPD outcomes, patients find exercise extremely difficult as they are unable to breathe properly. However, the results of a recent study carried out by Dr Minakata and his colleagues have shown that patients can increase their physical activity through the simple use of a bronchodilator.

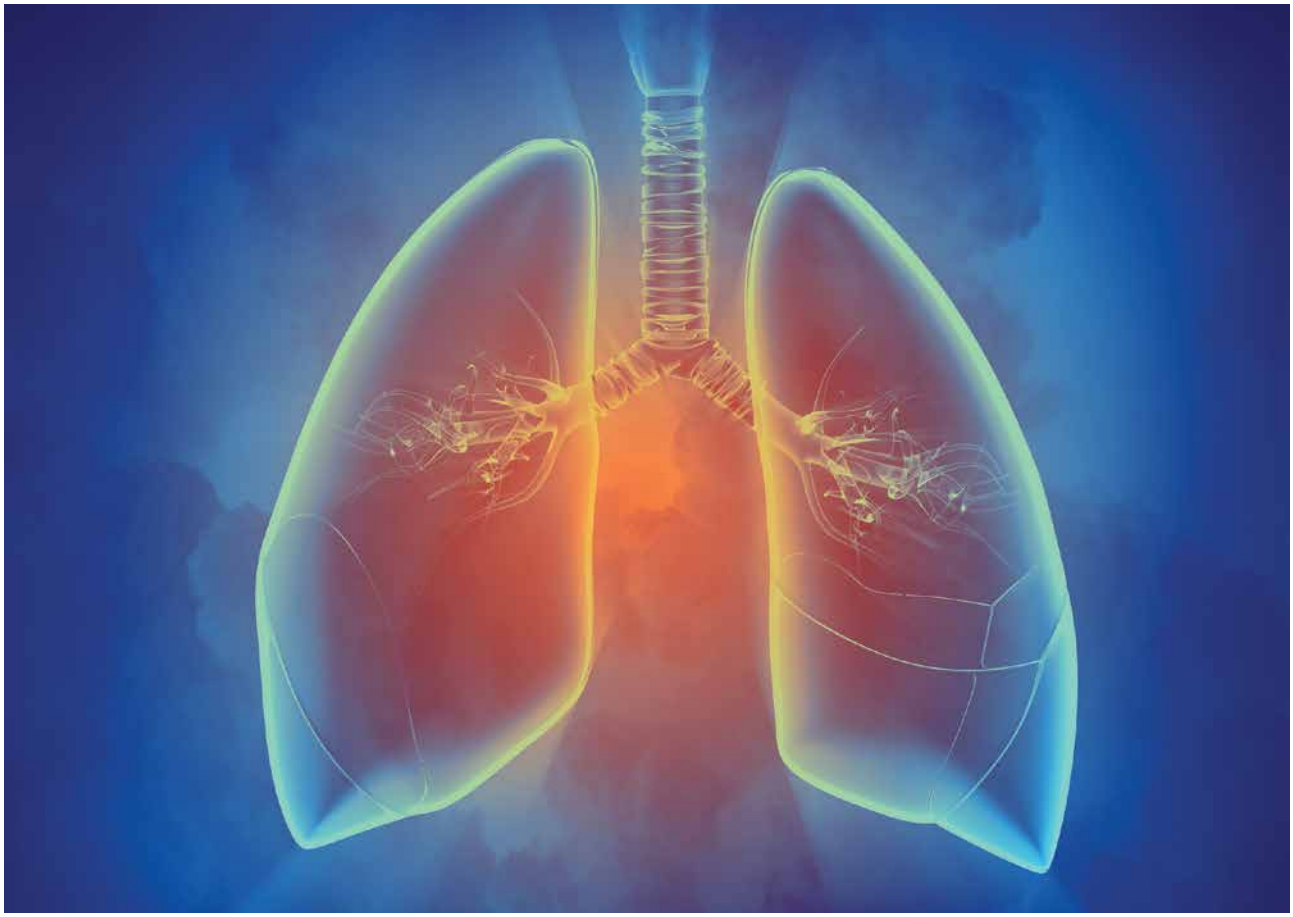
Our final article in this section details the research of Professor Tom Royston at the University of Illinois at Chicago. His team have developed the Audible Human Project, which aims to use sound to detect disease and injury within the body, particularly in the complex structure of the lungs. It can be extremely challenging to gather accurate diagnostic information from the lungs, and Professor Royston hopes his team's new acoustic and computational technique will improve the detection and diagnosis of many respiratory diseases, such as COPD, collapsed lung and cancer.

THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) is one of 27 Centers, Institutes, and Offices within the National Institutes of Health (NIH). It was established originally as the National Heart Institute in 1948 with a mission to support research and research training in the prevention, detection, and treatment of diseases of the heart and blood vessels. In 1972, the National Heart Institute was renamed the NHLBI and given a mandate to expand its mission to include lung and blood diseases. Since that time, NHLBI has further expanded its activities to include research on sleep disorders. In all of these areas, the NHLBI maintains a strategic desire to understand and promote health and resilience, stimulate discoveries in the causes of disease, enable the translation of discoveries from basic research into clinical practice, and foster training and mentoring of emerging scientists and physicians.

In this exclusive interview, we have had the opportunity to speak with four representatives of the NHLBI. Dr George A. Mensah, MD, FACC, is Director of the Center for Translation Research and Implementation Science, Dr James Kiley, PhD, is Director of the Division of Lung Diseases, Dr W. Keith Hoots, MD, is Director of the Division of Blood Diseases and Resources, and Dr David Goff, MD, PhD, is the Director of the Division of Cardiovascular Sciences. Together, these four division directors discuss the NHLBI's commitment to tackling heart, lung and blood diseases, which include many of the leading causes of death worldwide. Here, they share some of the NHLBI's achievements, and discuss the challenges that lie ahead for these fields of research.

‘The conditions that fall within NHLBI’s research portfolio include some of the most common diseases and risk factors as well as some of the leading causes of death in men and women in the United States and worldwide.’



Please describe some of the most common conditions that fall under the categories of heart, lung and blood diseases, and give us an idea of their prevalence and severity.

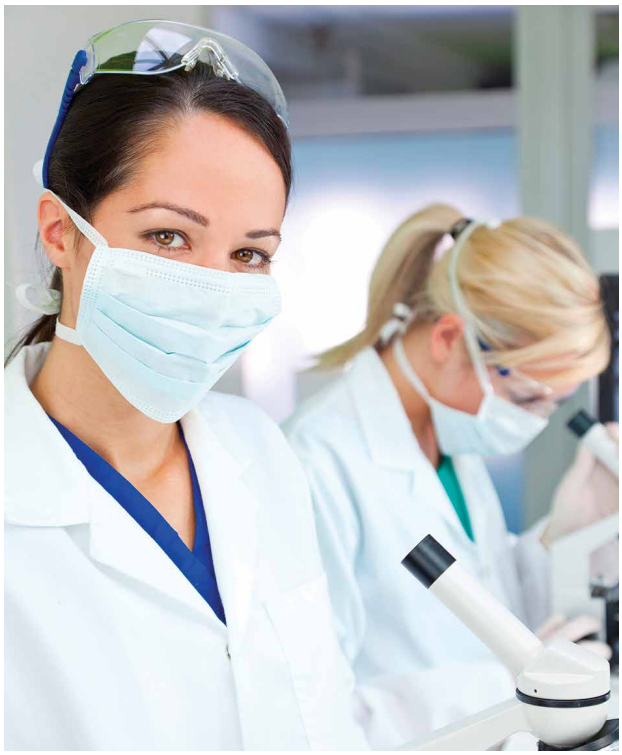
Dr George A. Mensah: The conditions that fall within NHLBI’s research portfolio include some of the most common diseases and risk factors as well as some of the leading causes of death in men and women in the United States and worldwide. For example, diseases of the heart such as heart attack, sudden cardiac arrest, heart failure, hypertension, and atrial fibrillation, remain the number one cause of death in the United States. An estimated 85.6 million American adults (more than one in three) have at least one or more of these heart diseases. High blood pressure alone affects more than 80 million American adults. Diseases of the lung such as asthma, emphysema, and chronic obstructive pulmonary disease (COPD) also cause substantial death and disability and remain the third leading cause of death in the United States and accounted for nearly 150,000 deaths in 2014 alone. Some of the common blood diseases addressed by NHLBI include sickle cell disease, chronic anaemias, thalassemia, haemophilia, and other bleeding disorders.

NHLBI plays a huge role in supporting COPD research in the US – what causes this condition and why is it so common in western countries?

Dr James Kiley: Cigarette smoking is the major culprit for COPD. While smoking rates have declined in the US, there are currently up to 100 million adults that are smokers or ex-smokers. Second hand smoke remains an issue as smoking is not universally banned in public places. Although more data is needed, there is some evidence that other environmental and occupational exposures, such as airborne particulates, can increase COPD prevalence. Genetic factors also play a role. One genetic condition, alpha-1-antitrypsin deficiency, is known to lead to COPD. Additional genetic factors, which we are still learning about, also contribute to a predisposition to COPD, particularly when they are combined with a history of smoking. The role of non-optimal lung development during the early stages of life is currently under investigation as a possible predisposing factor to COPD. Finally, COPD is a disease commonly found in older individuals, and we are still trying to understand what role aging may play in the disease course.

Despite the ubiquity of asthma worldwide, current drugs primarily work by dampening inflammation in the lungs, rather than also treating the structural problems, or remodelling, present in the lung tissue of asthma patients. What promising projects is the NHLBI currently involved with to address this deficit?

Dr James Kiley: The question raises a larger question of whether the inflammation observed in patients with asthma results in



remodelling or remodelling occurs as a 'primary process' independent of inflammation. Inflammation is likely the precursor of remodelling, and, therefore, managing the inflammation is expected to prevent remodelling. Evidence is accumulating, in pre-clinical models, that downstream effects of inflammation can include activation of cell signalling pathways that affect the integrity of the airway epithelium and vasculature as well as resulting in proliferation of smooth muscle cells and mucus cell hypertrophy and mucus hypersecretion. It's also been shown (in preclinical models) that several targeted therapeutics currently being evaluated for the treatment of asthma, can abrogate some of the downstream pathophysiology associated with inflammation. Thus, it's vital that we continue to probe the pathophysiologic consequences of inflammation as well as the molecular and cellular effects, in addition to clinical outcomes, of therapeutic interventions. In this way, we can increase our understanding of the entire therapeutic range of a particular intervention, and, through comprehensive patient phenotyping, tailor therapy to the appropriate patient strata. It is also possible that rather than remodelling, there are structural differences in the airways of people who develop asthma and the inflammation that is characteristic of asthma makes the anatomic changes manifest. NHLBI has numerous supported research activities to understand what occurs in patients with severe disease and the relative contributions of inflammation and other biologic processes to asthma.

What do you believe are the biggest challenges facing lung research in the US?

Dr James Kiley: Personalised or precision medicine is a huge challenge to address in lung research, whether it is at the point of primary prevention (or maintaining 'resilience' or lung health) or management of existing lung disease. Most of the diseases we study are 'complex diseases' and the interplay between multiple etiologic factors (including genetics or inter-individual variability) and time presents a challenge to understand the best approach for each patient throughout the lifespan. The major challenges to address in lung research include identifying better 'markers' of health and disease throughout development, and across the lifespan to enable the development of disease-modifying interventions and primary prevention strategies. We also need to leverage the vast amounts of existing data and the potential for future data collection to its maximum advantage.

One major challenge for moving theory into practice is developing better models of lung diseases. This means better models of human cells and tissues that we can manipulate in the lab as well as better animal models that really recapitulate the important aspects of the human disease. Without these models, it is difficult to understand on a molecular and cellular level what is going wrong in disease and it is also difficult to pre-clinically test possible therapeutics. With the recent advances in stem cell technologies and CRISPR gene editing, these challenges might be met in the next several years. The areas of regeneration, precision medicine, implementation, and primary prevention of lung diseases are major challenges, but offer great promise for new strategies to advance lung biology and disease research.

Another huge area of NHLBI's focus is Sickle Cell Disease. In the 1970s, the average life expectancy in the US was 14 years for people living with the disease, and this has now risen to about 40 to 60 years. What has been the NHLBI's role in improving the outcomes of individuals with this genetic condition?

Dr W. Keith Hoots: The NHLBI has a long history of working to improve the outcomes for individuals with Sickle Cell Disease. And given that the life expectancy for people living with SCD has increased, NHLBI has begun to fund research focused on the care of adolescents and adults. Adolescents and adults with SCD experience difficulties in accessing high quality longitudinal medical care from qualified providers and are unable to benefit from evidence-based therapies that may reduce morbidity and mortality during the third and fourth decades of life. NHLBI recently funded the Sickle Cell Disease Implementation Consortium (SCDIC), which is currently supporting eight regional centres to undertake the analyses of barriers to care in defined geographical areas (urban, suburban, and rural) as well as develop interventions to remedy these barriers and allow access to health

care. In addition, the project will create implementation protocols that compare novel strategies to improve care with standard management. NHLBI has funded eight geographic areas, and has committed $33,000,000 over a six-year period to this program.

NHLBI has also been funding STRIDE, a multi-centred study to investigate the safety and feasibility of performing stem cell transplantation in subject with sickle cell disease over the age of 18. Previously the vast majority of stem cell transplants have been performed in children. However, many adults suffer from a chronic disease burden of pain, renal, cardiac, pulmonary and neurological disease. The STRIDE study will conduct HLA-identical transplantation in 60 adult subjects, and compare the clinical course to 60 adults with SCD who do not have HLA-identical donors. This study, which is just starting, has the potential to change the natural history of SCD in older subjects, in whom the effects of current therapeutic efforts have been minimal.

Finally, NHLBI is currently funding a major program to promote innovative basic and translational research in the hemoglobinopathies. The Excellence in Hemoglobinopathies Research Awards (EHRA) funded eight groups of investigators to develop multidisciplinary projects that will lead to new therapeutic and diagnostic modalities for SCD and thalassemia. The funded projects include new therapeutics to elevate the foetal haemoglobin level (the most powerful known modifier of the severity of SCD); new therapeutics for sickle cell pain; novel modulators of inflammation; and treatments for SCD-associated kidney disease.

Although prevalence is low in the US, Sickle Cell Disease and other blood disorders such as thalassemia are far more common in sub-Saharan Africa and in Southeast Asia. Does NHLBI collaborate with other countries so that the benefits of research conducted in the US are extended to helping people in developing countries?

Dr W. Keith Hoots: The worldwide burden of SCD is rising. Between 2010 and 2050, it is expected that about 14.2 million affected babies will be born worldwide. More than 75% of SCD births occur in sub-Saharan Africa. In sharp contrast to children with SCD in the US, 50–80% of affected Africans now die before the age of five years, often as a consequence of limited health resources and infrastructure. While high regional disease prevalence would be expected to facilitate epidemiologic, translational, and clinical research, most sub-Saharan African nations lack the means and capacity required to pursue such investigations. Two related Funding Opportunity Announcements (FOAs) were published by the NHLBI in January, 2016 and responsive applications were reviewed in July of 2016. The first award will support the development of a Sub-Saharan African (SSA) Collaborative Consortium, which will engage in capacity building activities and develop an infrastructure upon which a future SCD in Sub-Saharan Africa Research Network can be built. The second award will support an African based Data Coordinating Center (DCC) that will work closely with the Collaborative Consortium.

The NHLBI also funded a Sickle Cell Disease Ontology Workshop that was convened in Cape Town South Africa in February 2016. The meeting's objective was to develop and standardise a sickle cell disease specific ontology appropriate to the African region. The intent was to harmonise definitions of phenotypes, diagnostics, therapeutics, quality of life, as well as disease modifiers and stage. This standardisation will expedite

future African SCD research. Thirty-seven experts participated, and the workshop proceedings and results were published in Applied and Translational Genomics in March, 2016.

As a new division director, coming in as NHLBI embarks in the implementation of its new strategic plan, what are your scientific priorities to have the biggest impact on the Nation's health?

Dr David Goff: It is an exciting time to join the leadership team at NHLBI. As a new division director, one of my top priorities will be to listen to smart scientists inside and outside of NHLBI to help identify new strategic initiatives that hold the greatest promise for making progress. While I have much to learn in that process, several areas of focus are already clear.

Research on the preservation of heart health in childhood through early adulthood holds great promise for improving the Nation's health. Most of our children are born with ideal, or nearly ideal, heart health, but far too many of our children find that health frittered away by early adulthood, by which time, far too many Americans smoke cigarettes, eat an unhealthy diet, and are inactive. The consequences include obesity, high blood pressure, high cholesterol, diabetes, and preventable heart disease. Discovering how to preserve the heart health most of our children are born with could lead to the elimination of epidemic heart disease. We should also not lose sight of the great advances our scientists are making understanding the causes of birth defects that affect the heart. Heart defects are among the most common birth defects in the US. Research on the causes, prevention, and treatment of birth defects will make a big difference for these families!

Heart diseases, and many other health problems, occur much more often among the poor than among the wealthy. The identification of programs and policies that work to address these inequities could make major contributions to our Nation's health. NHLBI-funded research is already making progress in this effort. For example, Dr Lisa Cooper and her colleagues have identified ways to improve treatment and control of high blood pressure in a low-income population in Baltimore. Discovering effective ways to promote heart health equity and eliminate heart health disparities would help reduce the life expectancy gaps between wealthier and poorer Americans.

The revolution in omic technologies offers unprecedented opportunities for gaining insights into the biological continuum from the genotype to the expressed phenotype. Interrogation of the different omic domains including the genome, epigenome, transcriptome, proteome, metabolome, and microbiome can now help us understand the functional consequences of an individual's interaction with the environment and subsequently also help identify the molecular determinants that (a) predispose some to adverse heart health or (b) confer protection in others. More importantly, by generating functional information at a much more granular level than possible before, omics can help identify subtle biological changes that are predictive of future clinical manifestation of a disease (dilated cardiomyopathy as an example. Such information can also help distinguish between similarly appearing but different disease conditions facilitating the tailoring of treatment strategies.

Research on how to improve the implementation and dissemination of proven prevention and treatment strategies into clinical and public health practice is needed. We know much of what we should do to improve heart health and prevent heart disease. We need to learn how to do a better job of accomplishing those goals. For example, we have known for many years that smoking is harmful, and smoking cessation

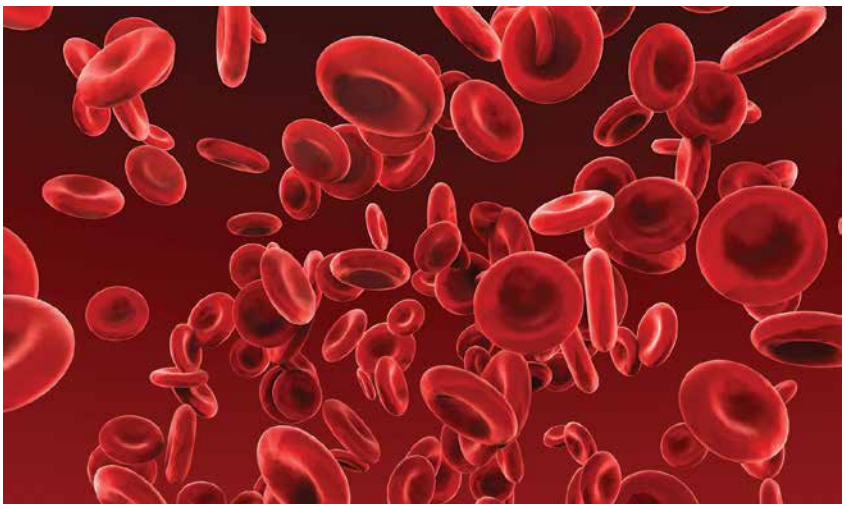
is beneficial. We need more effective smoking cessation programs and more effective ways for delivery of those programs to people addicted to tobacco products. Likewise, we need better ways of preventing and controlling high blood pressure and cholesterol.

Can you please offer some insight on what the future may hold for cardiovascular disease research in the US, and the challenges you may meet?

Dr David Goff: The past 50 years have seen tremendous progress in research on heart health and heart disease. Due to this research death rates from heart diseases have declined by about two-thirds in the US. Put another way, if we had the same death rates from heart disease today that we had in the mid-1960s, three times as many Americans would die each year of heart disease. We've come a long way, yet heart disease remains our leading cause of death. While much work remains to be done, it may now be reasonable to consider the elimination of heart disease. At one point, elimination of small pox seemed impossible. I believe we can eliminate most forms of heart disease through continued research and implementation of that knowledge. Our biggest challenge may well be complacency bred from decades of uninterrupted progress. Recent evidence that the decline in heart disease death rates has ended should serve as a wake-up call to redouble our efforts to support research and to implement what we already know.

The high cost of technology-intensive research represents another challenge. The cost of cutting edge research has increased more rapidly than other parts of our economy, putting strain on funding agencies and research institutions.

At the more basic research end of the scientific spectrum, a number of technological developments are poised to make an impact on health. The development of induced pluripotent stem cells and their differentiation to cardiomyocytes is poised to impact cardiovascular research in a number of ways, from enabling drug discovery to disease modelling to cell therapy and tissue engineering of blood vessels and cardiac patches. Genome editing with CRISPR/Cas 9 also has enormous potential, raising the possibility that monogeneic diseases could one day be treated by gene correction, although many challenges remain to be



overcome. Nanotechnology offers a range of options for imaging disease processes and for targeted delivery of therapeutics such as siRNA, for example to modulate inflammatory processes. The challenge will be to move these technologies towards translation into clinically useful entities.

Finally, assuring a strong supply of talented and well-prepared scientists is an ongoing challenge. Twenty-first century science is so complex that the educational process has become demanding in terms of both time and financial resources. To become a competitive scientist often means putting other life decisions, such as starting a family, on hold until education is completed, educational loans are paid off, and careers are established. We need to address this issue in the very near future to avoid losing to other career options many of the bright young people, especially those from under-represented populations, who could discover new treatments or cures for heart disease.

Despite these challenges, I remain very optimistic about the opportunities we face to substantially reduce, and perhaps even eliminate, epidemic heart disease this century. Accomplishing this goal will require a redoubling of our efforts to train new scientists, support critical research, and translate knowledge into heart health through clinical and public health practice.

Finally, Dr Mensah, would you like to share your thoughts on the future of all heart, lung and blood research, and the biggest challenges you expect to encounter?

Dr George A. Mensah: In addition to the challenges mentioned specifically for heart, lung, and blood diseases and sleep disorders, we also have the overarching challenge of translating research discoveries into routine clinical and public health practice in order to maximise the return on NHLBI's research investments. This additional challenge falls under the rubric of dissemination and implementation gaps. For example, although we have very compelling research evidence of the safety and efficacy of interventions for high blood pressure and numerous guidelines for the prevention, treatment, and control of this important condition, only about half of Americans with high blood pressure have it under control. In fact, in African American men, fewer than half of those with hypertension have it under treatment and control at a time when successful blood pressure control in African Americans has been demonstrated in clinical trials and routine clinical practices. For example, in the Kaiser Permanente Southern California health system, control of high blood pressure was achieved in more than 80% of African Americans and baseline racial and ethnic disparities in blood pressure control were eliminated. The primary drivers of successful high blood pressure control are now better understood and include important systems-level changes such as those instituted in in the Kaiser Permanente study. The NHLBI remains committed to advancing research that seeks to understand the strategies needed to ensure rapid adoption and sustained use of proven effective interventions so that, as a nation, we can successfully turn research discoveries into health.

NIH National Heart, Lung, and Blood Institute

www.nhlbi.nih.gov/

The EasyOne Spirometer, manufactured by ndd Medical Technologies and used by the Spirometry 360 team.

SPIROMETRY 360: ASTHMA MANAGEMENT GETS AN UPGRADE

Dr Jim Stout and his multidisciplinary team at the University of Washington are on a mission to improve asthma care. Through novel training schemes, quality improvement methods and research into health disparities, these researchers are determined to reduce undertreatment and morbidity associated with asthma and lung obstruction.

Asthma affects approximately one in twelve individuals and most of us have someone in our lives who lives with the condition. Although common, it is important not to underestimate the impact that asthma can have on an individual's life. So, what exactly is asthma? Asthma is a disease of the lungs in which the airways become irritated and inflamed causing them to tighten and contract. This leads to coughing, wheezing and breathlessness which vary in severity from person to person.

According to US guidelines, asthma can be categorised into four levels of severity: intermittent, mild persistent, moderate persistent and severe persistent. It is essential that individuals be correctly diagnosed, as choice of treatment will depend on the determination of severity. Underestimation leads to undertreatment, higher healthcare costs and increased morbidity and mortality. Severity is determined on the basis of symptom frequency and pulmonary function. In the past, pulmonary function was measured through peak expiratory flow (which measured how well your lungs could push out air) but the medical field has now moved away from peak flow meters as diagnostic devices. Compared to spirometry, peak flow provides far less accuracy and sensitivity in determining pulmonary function. Spirometry measures how much air your lungs push out and how quickly they do it. Studies have shown that spirometry is more reliable and has a higher correlation with the degree of airway obstruction than peak expiratory flow.

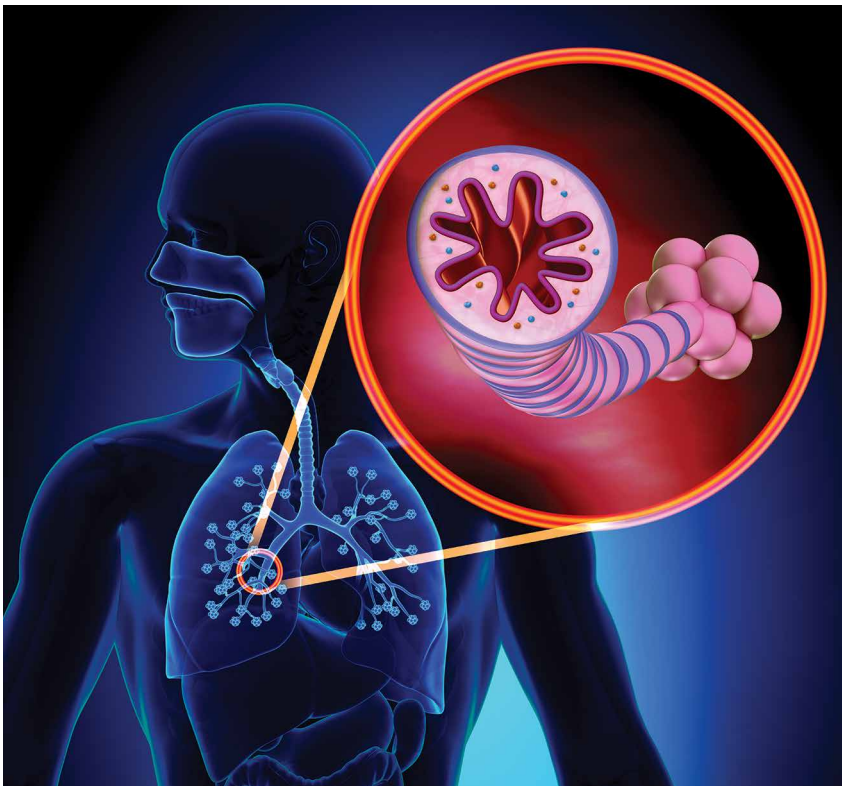
So how well do healthcare providers use these tools in the diagnosis and treatment of asthma in children? In a 2006 study, Dr Jim Stout and his colleagues aimed to find out. Their objective was to determine if adding these lung function measurements to clinical history substantially changed severity classification and treatment decisions. Although clinicians are recommended to use a combination of objective measurements and clinical findings, many rely more on the presentation of symptoms than the use of spirometry. The team measured what proportion of children in two cohorts were reclassified from less severe classifications to more severe classifications when lung function measurements were taken into account. They found that 22.8% and 27.7% of children in the mild intermittent category of each respective cohort would be reclassified to either moderate or severe persistent asthma when lung function was accounted for. Additionally, in both cohorts, approximately one third of children with mild persistent asthma would be similarly reclassified.

Several other studies have also reported that doctors systematically underestimate asthma severity, in part because they do not carry out spirometry tests with patients. 'Although a recommended component of asthma care, spirometry is not routinely used in most primary care offices, and test quality and interpretation often leave room for improvement,' Dr Stout states. Why is this happening? Many physicians cited a lack of time and training as the primary barriers. Faced with this problem, Dr Stout and his colleagues took action and began developing a quality improvement tool that would improve the overall diagnosis and management of asthma.

Developing Spirometry 360: An Online Training Program

Over time, Dr Stout gathered a multifaceted team to tackle the problem. Dr Karen Smith, Dennis Burges, Ben Hendrick, Sharon Kiche, Drew Martenson, Bonnie Rains and Louise Warren all contributed to the development of Dr Stout's novel spirometry training program. Spirometry 360 offers a number of online courses and webinars that aim to improve the quality and frequency of spirometry testing in primary care practices. But given that it is delivered through an online platform, how well does such a program work?

‘Our first trial of Spirometry Fundamentals taught us we needed a more comprehensive solution… from which we created Spirometry 360. We’ve trained about 300 practices domestically, and dozens of clinicians and support staff internationally.’



In a study published in 2012, Dr Stout and his team (led by Dr Rita Mangione-Smith) evaluated the effectiveness of a virtually delivered quality improvement program for enhancing primary care management of children with asthma. They hoped that the program would lead to increased frequency and quality of testing, better documentation of asthma severity and improved prescription of controller medications. Participants received a CD-ROM on spirometry fundamentals, access to interactive webinars and feedback on spirometry quality. Feedback is the essential second prong of the program. The system allows the team to review and analyse spirometry tests from point of care and give appropriate technique feedback to the practitioner.

The results showed a significantly greater percentage of high quality tests in the group that participated in the program when compared to a control group. They were also 2.9 times more likely to document the severity of asthma, which had high concordance with appropriate treatment. This shows that successful quality improvement can occur through distance learning.
‘Since 2009, Spirometry 360 has been licensed to over 300 practices domestically and internationally,’ says Dr Stout. ‘Spirometry Fundamentals, our first training tool, is a compulsory part of a comprehensive spirometry training program in The Netherlands.’ With over 25,000 graded spirometry tests stored in the system, the team are now working towards developing a more sophisticated grading system based on machine learning techniques. The Spirometry 360 Feedback Reporting System has also been successfully integrated with SpiroSmart, a smartphone-based spirometer app in development, allowing for remote training and feedback.

Dr GM Monsur Habib, Paediatrician & Primary Care Respiratory Physician, Khulna, Bangladesh

Dr Stout is keen to acknowledge support for Spirometry 360 from the National Heart, Lung, and Blood Institute (NHLBI) over the years. ‘NHLBI has funded us three times – initially through two funded projects from the National Asthma Control Initiative (NACI), to initially deliver Spirometry 360 to “safety net” practices, and then to deliver a “train the trainer” Spirometry 360 program to four sites around the US,’ he explains. ‘NHLBI also funded an R-01 led by Dr Mangione-Smith, a controlled trial of the effect of Spirometry 360 on health outcomes among children and teens with asthma.’

Going International

Dr Stout is also a long-standing member of the International Primary Care Respiratory Group who are responsible for enabling numerous training relationships for Stout and his colleagues. In one such example, he and his team carried out a study between the University of Washington (where the researchers are based) and an outpatient clinic in Bangladesh. International collaborations such as these are made possible by grants from projects such as Horizon 2020 FRESH AIR, which aims to improve health outcomes associated with non-communicable lung diseases in low resource settings.

Spirometry is available in some low resource settings but there is limited training available on the use and interpretation of these measures. This is where Spirometry 360 comes in. Over the course of five months, the comprehensive online training and feedback program was used to improve the quality of spirometry in the Bangladeshi clinic. Facilitated by site leader Dr Monsur Habib, seven physicians and a medical assistant were trained with an online primer known as ‘Spirometry Fundamentals’, engaged in self-paced learning labs and received feedback from the reporting system. Upon completion of their training, the results were significant. The useful test rate jumped from 85% to 91% and the ratio of grade A tests jumped from 66% to 77%.

Reducing Health Disparities Through Guideline Implementation

However, there is more to improving asthma management than just training physicians. In order to instigate true change, Dr Stout and his team at Seattle/King County Health Department are supporting practitioners and patients alike in implementing best

Safia Mohamed, Asthma Community Health Worker, holding a spirometer she was trained to use through the Spirometry 360 program

practice guidelines for asthma management. This approach to asthma care is based on the results of several studies showing poor adherence to recommended guidelines and the influence of environmental and social factors, such as poverty, housing supply, race and geographical location, on asthma management.

Asthma can be controlled and guidelines for optimal care are available, but care often doesn't live up to these standards. Poor adherence is a major problem amongst patients – only one third are compliant with their asthma controller medication, while only two thirds follow advice on reducing environmental asthma triggers. This particularly affects minority populations (such as ethnic minorities and low income individuals), because of substandard housing and indoor air quality, and because health education may not be culturally relevant or account for lower levels of literacy. There is also variable adherence to guidelines amongst providers, especially in terms of carrying out allergy testing and developing asthma action plans. A lack of patient centeredness and poor communication between patient and provider also contribute to low adherence and health inequities.

Dr Stout and the Guidelines to Practice (G2P) group are addressing these issues through a community based participatory research project. The study was designed with input from a consortium of patients, public health organisations and experts in health information and quality improvement. The concept behind this project came from an earlier demonstration project funded initially by the American Lung Association of Washington in 1995, in which the team developed an Asthma Outreach Project at Odessa Brown Children's Clinic, involving home visits and planned clinic visits using an asthma Community Health Worker model. The Asthma Outreach Project at Odessa Brown was a proof of concept, further developed, refined and evaluated through a series of studies, conducted primarily by researchers led by Dr Jim Krieger at Seattle/ King Country Health Department over two decades.

Firstly, the G2P project aimed to improve the implementation of asthma guidelines through integrated multicomponent interventions. Key recommendations of these guidelines include making a correct diagnosis, assessing asthma severity and control, integrating spirometry testing and allergy skin prick testing into usual work flow for planned asthma visits, appropriately prescribing medications and providing and using an Asthma Action Plan. During the study, participants were randomly assigned into four groups: with or without the services of a Community Health Worker (CHW), and with or without services at a practice receiving specialised training in delivering preventive asthma care. The group that the G2P team were most interested in focusing on was the one where CHW services were being integrated with the trained 'intervention' practices. For this group, the team built a preventive asthma template used as a communication portal between the CHW and the practice team, to integrate the work of each. Results of this trial will soon be available. 'The real "innovation" of this trial was the development of this EHR portal, and its use by both CHWs and the practice,' says Dr Stout.

So what do each of these interventions involve? The health plan enhancement intervention comprises case management, increased passive guideline dissemination, medication fill monitoring and provider education. Case managers received training from asthma experts, while healthcare providers are notified of any hospitalisations or emergency department visits involving their patients within 24 hours of discharge.

The enhanced clinic intervention implements multiple components of decision support, audit and feedback, staff education and electronic health record (EHR) enhancements. Team based care is encouraged through integrated communication platforms and system redesign. Asthma champions helped to redesign the clinic team and system, while the Chronic Care Model Framework and continuous quality improvement activities are employed to provide enhanced pre-visit assessment, focused clinical encounters and expanded post-visit options.

Finally, community health worker home visits provide patients with tailored self-management plans to control their asthma. This allows the community health workers to work with patients and learn about their challenges and concerns, provide targeted education and referrals to resources and implement an individualised management plan. Trigger reduction in the home is supported through the provision of education and additional resources (such as allergen impermeable bedding and low emission vacuum cleaners).

The community health workers also have access to the integrated EHR platform in order to share information with the rest of the team. The G2P project is innovative in its development of a multicomponent, multi-level systems approach to asthma management. As well as the benefits to patients (better health and quality of life, better self-management skills and improved communication with health care providers), clinicians have gained tools to enhance their skills and patient relationships as well as a CHW serving as their 'eyes and ears' into the patient's home environment. The G2P team also hope that the project will lead to improved quality metrics, decreased healthcare costs, and reduced health inequities. The potential of this project to improve asthma management is great and, if proven models like this are widely adapted, the future is bright for asthma sufferers worldwide.

Meet the Spirometry 360 Team

Dr Jim Stout

Dr Jim Stout is Professor of Paediatrics and Adjunct Professor of Health Services in the University of Washington. He is Founder and Director of Interactive Medical Training Resources (iMTR), whose 'flagship' program is Spirometry 360, at the Child Health Institute in Seattle. After completing his MD at the Bowman Gray School of Medicine, he went on to receive his paediatric residency training at University of Washington, and his MPH from the University of Washington School of Public Health. He served as Director of the Asthma Clinic in the Odessa Brown Children's Clinic for over two decades. His research interests include asthma and office-based diagnostic spirometry, quality improvement and the development of remote physiological monitoring applications deployed through smartphones.

Dennis Burges

Dennis Burges is a software engineer who develops remote training web applications and produces audio-visual resources for distance learning platforms on a variety of health care topics.

Ben Hedrick

Ben Hedrick manages enrolment and the day-to-day operations of Spirometry 360. He also designs, implements, and monitors updates to course websites and online advertising and co-develops new online training programs.

Sharon Kiche

Sharon Kiche works on international projects where she tracks and manages communications and produces progress reports for member countries.

Drew Martenson RRT

Drew Martenson is a respiratory therapist and Chief Over-Reader for Spirometry 360. His central focus is the reading, grading, and education of Spirometric testing, and providing coaching insights and quality feedback to the practices that participate in the Spirometry 360 program.

Bonnie Rains

Bonnie Rains manages clinical and quality improvement projects and related activities.

Louise C. N. Warren MPH

Louise C. N. Warren provides research and program coordination, financial management, and organisational support for Dr Jim Stout and team.

Maria Hamilton

Maria Hamilton provides fiscal management support for Dr Jim Stout's grants and other projects.

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SPIROMETRY 360

UNCOVERING NEW PATHOLOGIC MECHANISMS OF ASTHMA

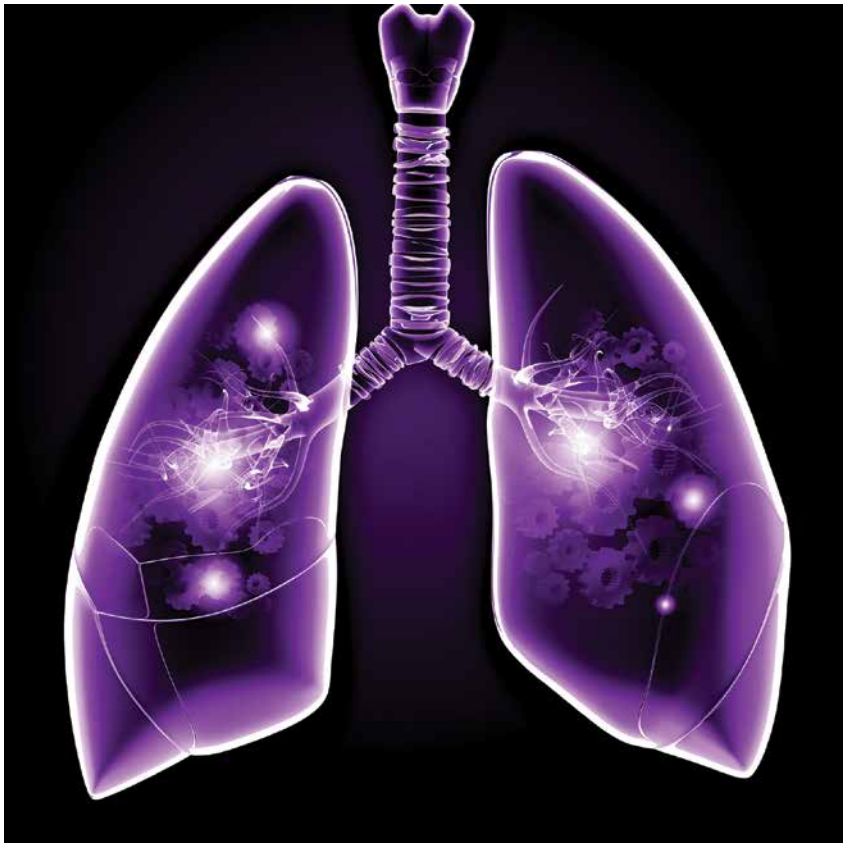
Professor Michael Roth, Head of the Pulmonary Cell Research unit at the University Hospital Basel, Switzerland, has been investigating the pathologic causative mechanisms behind asthma and COPD for the last 30 years, with the aim of developing novel treatments for these ailments.

The incidence of respiratory conditions such as asthma has been on the rise over the past 40 years, potentially due to factors including air pollution and smoking. Out of the global population, 234 million people suffer from asthma, thus making it the most common chronic inflammatory lung disease. Half of all sufferers are children, and unfortunately, no cure is currently available. Because of the large number of children with asthma, the condition is the most frequent cause of absence from school, and has a significant negative impact on children's quality of life. Adult asthma can be caused by working conditions (baker, miller, construction and metal dust) or can be initiated by hormonal changes after menopause in women. Thus, asthma significantly affects social and working life and patients need to adapt their daily life to their condition.

Although many different types of asthma medications exist, they are only palliative and don't actually cure the disease. Their mechanism of action allows the symptoms of the condition to be alleviated, by reducing inflammation and relaxing the tightened airways so that normal airflow can resume. Although current treatments can effectively relax the airways, they lack the capacity to improve the structural modification present in the walls of the airways – known as remodelling – that causes thickening of the airway walls resulting in permanent airflow restriction. At this point, a major factor standing in the way of a cure is our insufficient understanding of the interaction between the airway structure and the inflammatory processes in the lung. Instead of resulting from chronic inflammation, the remodelling of airways in asthma patients often appears before inflammation, and in fact can trigger inflammatory processes. Consequently, researchers have concluded that our only hope for curing asthma lies in understanding the pathology behind this initial airway remodelling. However, animal models that help scientists understand the phenomenon are extremely limited, as only certain aspects of the disease can be simulated, rather than the entire set of causes and symptoms.

The knowledge we currently possess stems from this line of research. In this vein, a significant discovery came from Professor Michael Roth (University Hospital Basel, Switzerland) and his collaborators from the University of Sydney (Australia), University of Manitoba (Canada) and Jiaotong University (Xi'an, China). By comparing cells from healthy and diseased airways, they found that the most important contribution to the pathogenesis of asthma comes from the interaction of airway epithelial cells, fibroblasts and smooth muscle cells.

‘Our research has opened new targets for curative therapeutic strategies for asthma’



A Protein Puzzle

A crucial finding made by Professor Roth’s group was that the transcription factor and differentiation factor C/EBP-α was lacking in asthmatic airway smooth muscle cells. Moreover, the absence of the C/EBP-α transcription factor is not detectable by transcriptomic analysis, because it results from the faulty translation of RNA into the corresponding proteins. The background of this research was based on the premise that asthmatic patients often have increased muscle mass in their upper airways due to a proliferation of bronchial smooth-muscle cells. The smooth muscle cells of people without asthma are kept in check in terms of numbers by cortisone, an effect which is mediated by an interaction between the glucocorticoid receptor and C/EBP-α. To test this premise, Professor Roth looked into the signalling pathway that controls the anti-proliferative effect that glucocorticoids have on smooth muscle cells and the synthesis of interleukin-6, which indicates inflammation, in bronchial smooth muscle cells in asthmatic patients and controls. The test compared isolated primary smooth muscle cells from 20 asthma patients, 8 patients suffering of emphysema and a control group of 26 people, to verify smooth muscle cell proliferation. During this experiment, the researchers found that the glucocorticoids only inhibited proliferation of smooth muscle cells in subjects without asthma and confirmed that the inhibition mechanism malfunctions in asthmatic patients. The C/EBP-α protein was found in all bronchial smooth-muscle cells from subjects without asthma but not in those with asthma, whereas the protein was expressed in the lymphocytes of both subject groups. Mifepristone, an inhibitor of glucocorticoid receptors, reversed the anti-proliferative effect of glucocorticoids in bronchial smooth muscle cells from subjects without asthma. When smooth muscle cells of asthmatic patients were transfected with an expression vector for human C/EBP-α, the administration of glucocorticoids inhibited cell proliferation. Therefore, the researchers proposed that the cell-specific absence of C/EBP-α causes the airways to produce increased numbers of smooth muscle cells. Moreover, this would explain why glucocorticoids administered in vitro fail to inhibit abnormal cell proliferation.

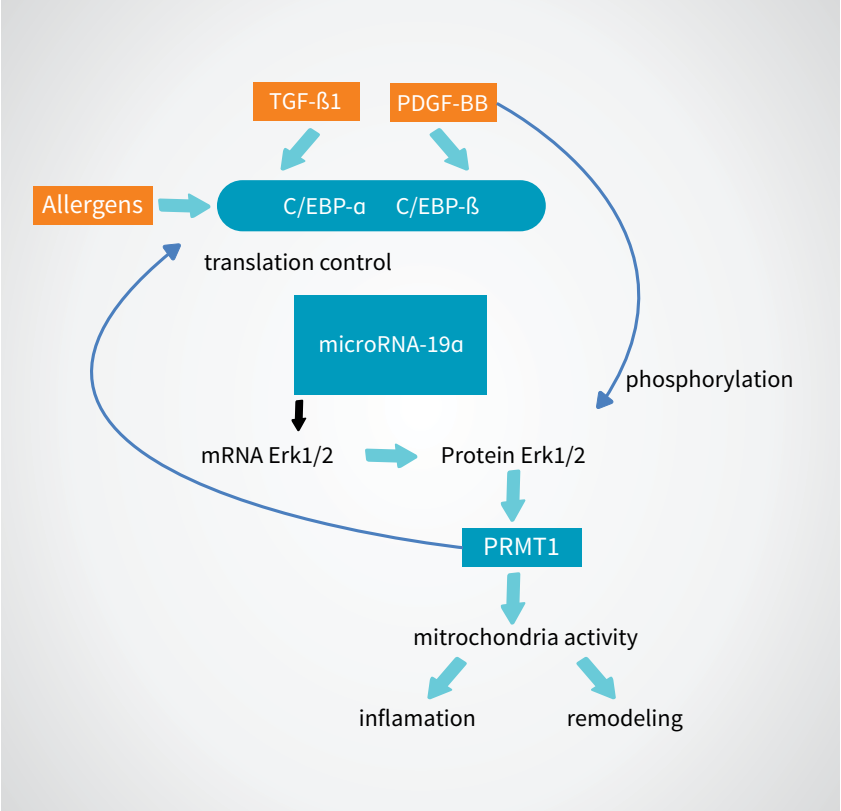
Although Professor Roth and his collaborators found clear evidence that the factors triggering asthma reduce the translation of C/EBP-α, the lasting effect only in the cells of asthma patients is still not well understood today.

Advances in the Biochemistry of Breathing

Professor Roth’s activity stretches back to 1998, when he was studying the signal transduction proteins isolated in human smooth muscle airway cells. His research attracted a flourishing collaboration with the Institute for Medical Research of the University of Sydney, Australia, where he was the first to identify the biomolecular basis of the improved action of inhaled combined steroids and long acting ß2 adrenergic receptor agonists that cause relaxation of smooth muscle. Thus, he found that the effect is given by two transcription factors, a glucocorticoid receptor and C/EBP-α, working in synchronicity.

In 2004, he became the part-time Head of the Molecular Medicine division at the Woolcock Institute for Medical Research of the University of Sydney, Australia, while retaining his role as the Head of the Pulmonary Cell Research group at the University Hospital Basel. ‘The collaboration of the two institutes produced more publications in leading peer reviewed scientific journals in which we described new pathologies of asthmatic airway smooth muscle cells and which could be linked to the lack of C/EBP-α,’ Professor Roth explains. ‘In regard to asthma research, our studies formed the basis for several other research groups to investigate the role of tissue forming airway cells in the pathogenesis of asthma and COPD.’

Between 2010 and 2013, Professor Roth worked on the intracellular signalling related to the regulation of translation control, which was the cause of the lack of C/EBP-α specific to asthma airway smooth muscle cells. In 2010, he presented his work on chronic obstructive pulmonary disease and asthma in China, at the Fourth Military Medical University and Xijing Hospital. Later on, his work granted him a Chinese governmental scholarship, who sent researchers to Basel



Role of C/EBP-a translation control in asthma and its consequence for remodelling and inflammation.

'The anti-proliferative effect required the presence of active glucocorticoid receptor and C/EBP-α, which was lacking cell type specifically in ASMC of asthma patients, and this finding explained the cause of ASMC hyperplasia'

for Professor Roth to train in basic medical studies. In 2012, his research results led to a fruitful collaboration with researchers from the University of Manitoba, Canada, who investigated the role of non-immunogenic immunoglobulin E antibodies in allergic asthma. These investigations have resulted in three peer reviewed papers published in renowned journals. In 2014, Professor Roth became one of the first Fellows of the European Respiratory Society for his lifelong contributions to respiratory medicine.

During the visit to China in 2010, Professor Roth was invited by Professor Lu, another leading asthma researcher, to present his work at the Xi'an Jiaotong University. Their collaboration has continued for the past six years and has resulted in confirming an animal model for acute and chronic lung inflammation. 'The studies showed that a histone modifying protein, PRMT1, was essential for structural changes of the airway wall under inflammatory conditions,' Professor Roth explains. PRMT1 or protein arginine N-methyltransferase 1 is an enzyme produced from the PRMT1 gene. The PRMT1 enzyme is seen today as the main regulator for tissue remodelling in several abnormal processes involved in pathogenesis. Crucially, PRMT1 controls the production of C/EBP-α and is regulated by C/EBPs – this may explain the role of C/EBP-α in asthma. Another consequence of the activity of PRMT1 is the presence of hyperactive mitochondria in the airway cells, which has been reported by other asthma researchers, but the cause has remained unknown.

The latest research performed by Professor Roth and his team showed that when C/EBP-α is down-regulated and therefore absent from tissue, C/EBP-α will take its place in the DNA binding sequence of microRNA-19a. This replacement increases the production of Erk1/2 MAPK and PRMT1, the former being protein kinases involved in growth factors signalling and therefore up-regulating cell production, and the latter being the enzyme previously discussed. Because these factors are up-regulated and hence their production increases, they stimulate asthma airway smooth muscle cells to proliferate, secrete more pro-inflammatory cytokines attracting immune cells, and produce more pro-inflammatory extracellular matrix components. Growth factors favouring inflammation have the ability to decrease the production of C/EBP-α and increase that of C/EBP-α. This phenomenon describes a self-stimulating pathway for asthmatic airway smooth muscle cells. Given that Professor Roth identified and documented this pathway, the knowledge offers a target for strategies to control the airway wall remodelling and inflammation present in asthma and give patients a chance at a normal life. As he points out: 'at least in vitro, this circle can be broken and the pathology can be corrected on different levels. Therefore, our research has opened new targets for curative therapeutic strategies for asthma.'

The Next Steps in Asthma Research

From his previous findings, Professor Roth and his collaborators have been assessing whether the pathway enrolling immunoglobulin E antibodies merges with other different asthma triggers such as Erk1/2 MAPK and PRMT1. Among other future projects, the team are working on translational studies investigating the role of biomarkers of chronic obstructive pulmonary disease, an ailment affecting 65 million people worldwide, which also claimed the life of the beloved actor Leonard Nimoy.

Other targets for Professor Roth's research are the involvement of the other four human PRMTs, and their regulation by signalling proteins in charge of forming the airway structure. 'We want to find out if these proteins should be regarded as cause or result of the pathology of exacerbation in COPD,' says Professor Roth.

Meet the researcher

Professor Michael Roth
Department of Biomedicine
University Hospital Basel
Basel
Switzerland

Professor Michael Roth is currently the group leader of the Pulmonary Cell Research unit for the Clinics of Pneumology at the University Hospital Basel, Switzerland. Prior to his current position as the Head of the Pulmonary Cell Research unit in Basel, Professor Roth held the position of Head of Molecular Medicine, Woolcock Institute of Medical Research in Sydney, Australia. His career spans more than 28 years of research in the fields of human biology, genetics, and molecular cell biology. Throughout this time, Professor Roth has authored more than one hundred peer reviewed publications. His prolific research and ground-breaking results have attracted over a dozen large grants that secured the continued funding of his scientific work.

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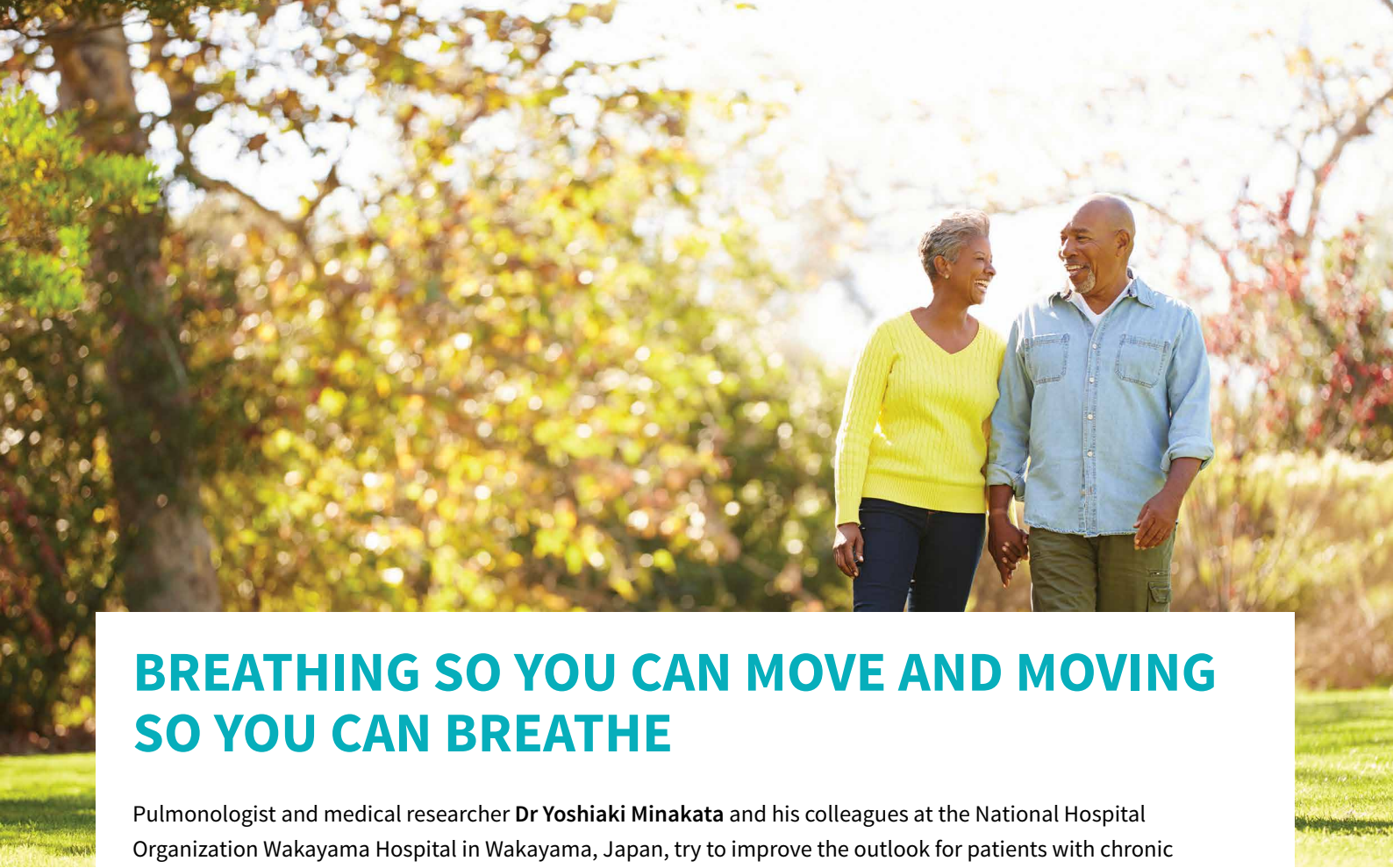

BREATHING SO YOU CAN MOVE AND MOVING SO YOU CAN BREATHE

Pulmonologist and medical researcher **Dr Yoshiaki Minakata** and his colleagues at the National Hospital Organization Wakayama Hospital in Wakayama, Japan, try to improve the outlook for patients with chronic obstructive pulmonary disease by examining the relationship between that serious lung condition and physical activity.

The Breath of Life That Most of Us Take for Granted

When a baby takes its first breath – often a sudden cry – it's the sign of new life. In fact, in many countries a baby isn't legally born until it takes the first breath. Then, at the end of life, a person's final breath signals the crossing over into the so-called 'great beyond', that place we go after our Earthly race is finished. But between those two bookends – life and death – we experience an estimated 680,000,000 breaths if we live to be 80 years old. Of course, the number may be higher for some, lower for others, depending on how long you live or how often you exercise. A question to think about, though: do you notice those breaths as you go about your everyday existence? Do you worry that you may not be breathing fast enough or getting enough air into your lungs? People with chronic obstructive pulmonary disease certainly do worry about these things. They can live their everyday lives in fear of not getting enough air.

Chronic obstructive pulmonary disease (COPD) is the current medical term for a condition that includes diseases with older names – chronic bronchitis and emphysema. COPD results in the inability to properly push air out of the lungs when exhaling – thus, obstructive disease – thereby resulting in insufficient air flowing back into the lungs upon inhaling. Inflammation of the bronchial tree causes thickening of the air passages and production of mucus in chronic bronchitis. Inflammatory damage of the air cells in the lungs – the alveoli, where oxygen exchange takes place – causes these cells to disintegrate and form large, useless pockets in emphysema. In either case, the lungs cannot deflate properly to allow a new breath. The lungs simply don't exhale enough air initially to be able to enough to draw in enough fresh air with each subsequent breath. The patient suffering from COPD classically suffers from dyspnea – shortness of breath – where normal individuals simply breathe comfortably. This is where Dr Minakata as a pulmonologist strives to treat patients with COPD and make their lives more comfortable. However, as a scientist, Dr Minakata wants more than that – he wants to find out the whys and wherefores of the illness and find ways to treat it scientifically.

A Disease That Leaves the Whole World Breathless

COPD is a worldwide disease, affecting rich and poor, rural and city dwellers. According to the American College of Physicians, in the United States COPD affects more than 5% of the adult population and is the third leading cause of death. The economic costs of COPD in the United States were 50 billion USD in 2010, and the total direct cost of medical care is almost 30 billion USD annually. In the UK, 1.2 million people are living with diagnosed COPD, according to the British Lung Foundation. This makes COPD the second most common lung disease in the UK, after asthma. Around 2% of the whole population, and 4.5% of all people aged over 40, live with the diagnosis of COPD. Importantly, an aging population implies an increasing risk of COPD.

In Japan, Dr Minakata's country, COPD is not as prevalent as in the US or the UK. According to the World Health Organisation, the latest estimates from 2004 indicated 64 million people worldwide with COPD and 3 million deaths per year due to the illness.

‘It may be that improvement of physical activity could improve the prognosis of COPD and might elongate the healthy life expectancy’

WHO calculates that COPD will become the third leading cause of death in the world by the year 2020. However, while the US has an age-standardised mortality rate from COPD of 248.2 per million population and the UK has a rate of 210.7 per million, Japan has a rate of 40.9 per million. However, Dr Minakata worries that in Japan ‘there are many COPD patients who need or will need treatment, since 8 to 10% of the population over 40 years of age have COPD.’

According to the WHO, the causes for COPD vary depending upon the geographic area. In high- and middle-income countries, tobacco smoke is the biggest risk factor. We all know smoking is bad for your health. However, in low-income countries exposure to indoor air pollution, such as the use of fuels for cooking and heating, is the prime cause of COPD.

Since almost three billion people throughout the world use coal or other biomass fuel as their main energy source, indoor air pollution is actually responsible for a greater fraction of COPD risk than smoking or outdoor air pollution. Biomass fuels used for cooking by women are the source for the high rate of COPD among non-smoking women in areas of the Middle East, Africa and Asia. Indoor air pollution due to the burning of wood and other biomass fuels is estimated to kill two million women and children each year. But in either case – be it cigarette smoke or indoor cooking smoke – the longer an individual is exposed to the smoke or fumes, the higher the risk of COPD. So that risk obviously rises as the person gets older and older, spending more years in contact with cigarette smoke or village fires or other sources of lung irritation. This is what concerns Dr Minakata about his patients in Japan. The population is getting older and COPD is on the rise. The question is, what to do about it?

How Do You Exercise If You Can’t Breathe?

Everyone knows – if they talk to their primary care doctor or other healthcare provider – that exercise treats lots of diseases or at least covers some of our unhealthier sins, like over-eating. Indeed, Dr Minakata the pulmonologist has medical training and experience that tells him ‘improved physical activity might improve the conditions or the prognosis of comorbid diseases, because physical activity is the third risk factor of death for lifestyle-related diseases in Japan.’ But what about patients with COPD who can’t even catch their breath at rest, much less during exercise? How are they to get the benefits of exercise? And even more, will exercise help their COPD like it might help, say, their diabetes or hypertension? Those are questions that Dr Minakata the scientist is trying to answer. He wants to know whether exercise can help COPD, not to mention

how COPD patients can exercise in spite of their breathing difficulties. Because, according to Dr Minakata: 'It may be that improvement of physical activity could improve the prognosis of COPD and might elongate the healthy life expectancy.'

First, Dr Minakata and his associates are quite cognisant of the fact that patients with COPD do not exercise as much as patients without COPD. In a paper published in the journal Rehabilitative Nursing, Dr Minakata and his colleagues studied the activity and walking pattern of patients with COPD and compared them to control subjects. The average walking velocity – as well as time spent sitting, standing, and lying – and the numbers of steps per day were measured in nine people with COPD and eight healthy control subjects. The walking speed in individuals with COPD was the same as the control subjects, but the people with COPD walked a lot less than the control subjects. They concluded that the walking speed of people with COPD tended to minimise their energy cost per distance. In other words, presumably because they couldn't catch their breath well, COPD patients tried to walk as little as they could to conserve oxygen, or at least minimise the increase in oxygen demand. This underscored the need to maintain walking velocity in any exercise prescription for individuals with COPD so they can benefit from exercise just like any other patient with medical problems. COPD patients can't let their breathing issues interfere with their doctor's prescription for exercise. The obvious question, though, is how does one exercise if you can't catch your breath? Dr Minakata believes that problem can be addressed by judicious use of drugs to open the respiratory passages to allow COPD patients to exercise properly.

One of the standard treatments for people with COPD, especially when they have sudden exacerbations of their problems, is bronchodilator therapy. Bronchodilator medications open up the respiratory passages that are closed or obstructed by COPD and allow easier breathing. Used with or without steroids – to treat the underlying inflammatory process – bronchodilators are a mainstay of COPD treatment.

The positive effects of using bronchodilators on the 'exercise capacity' – the maximum potential of a patient for physical exertion – of COPD sufferers have already been reported by many researchers. However, the effects of bronchodilators on patients' 'physical activity' – the level of usual daily activity but not the maximum potential – have been much less clear. Furthermore, the relationship between improving patients' potential exercise capacity and their actual daily physical activity has been found to be surprisingly weak. Thus, it was believed that behavioural changes along with optimisation of therapy would be necessary to improve daily physical activity, representing a big challenge in the field of COPD therapy. As Dr Minakata explains: 'The improvement of "exercise capacity" is relatively easy, but the improvement of "physical activity" is difficult, because not only pulmonary function but also other physical or psychogenic conditions or circumstances can affect a patient's physical activity.'

Dr Minakata, however, was hopeful that bronchodilators might be able to improve physical activity in COPD patients. To explore this relationship, he carried out a study, published in the International Journal of COPD, investigating bronchodilator use in people with COPD during their daily activities. Remarkably, he found that bronchodilator medication actually improved physical activity in patients with COPD, especially at a relatively high intensity of activity if medication was administered based on measures of airflow limitation and breathlessness. This improvement was seen mostly in the patients with

better baseline lung volume – patients with initially poor lung function didn't respond as well. But the results were encouraging. Patients with COPD – especially those with early disease – can look forward to getting their physical activity by using bronchodilator medication. This is a great benefit, seeing as how lack of exercise is related to poor health. Dr Minakata's COPD patients don't have to sit on the side at the health club any more.

Where Do We Look Next?

For the foreseeable future, Dr Minakata and his research associates will continue their quest to unravel the questions of physical activity and COPD. They want to better understand the relationship between COPD and the person's daily physical activities. For example, they recently published a report in the International Journal of COPD looking at the differences in physical activity in patients with COPD of differing degrees of severity. They found, not surprisingly, that worse degrees of dyspnea predicted lower levels of physical activity in those patients. Getting those patients to exercise more is a prime goal of future research.

As a scientist, Dr Minakata wants to investigate interventions that could improve physical activity in COPD patients at the molecular level. It's nice to know what works clinically and what doesn't. But for the big picture, understanding the mechanisms of the improvement on a cellular and biochemical level will allow a more informed discussion of possibilities for clinical and laboratory research. The aim is the same, though. We would all like COPD patients to breathe easier, both while they exercise and while they are at rest. Ideally Dr Minakata wants everyone to breathe as freely and effortlessly as they did when they took that first cry on their mother's tummy the day they were born.

Meet the researcher

Dr Yoshiaki Minakata, MD, PhD
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Dr Yoshiaki Minakata received his MD from Wakayama Medical University in Wakayama, Japan, in 1986 and did a residency in general medicine at the Third Department of Internal Medicine of the Wakayama Medical University and pulmonary medicine at the Department of Respiratory Disease there. From 1986 to 1989 Dr Minakata was a member of the clinical staff in the Internal Medicine at the Saiseikai Wakayama Hospital, during which time he did medical research at Wakayama Medical University. He received his PhD in 1994 and did a stint as research scientist from 1995 to 1997 at Hotel Dieu de la Montreal in Quebec, Canada. In 1997, Dr Minakata returned to Wakayama Medical University as an assistant teacher, and in 2004, he became associate professor. Since 2014, he is Director of Hospital in the National Hospital Organization Wakayama Hospital.

Dr Minakata's research interests include the pathophysiology and treatment of chronic obstructive pulmonary disease, especially the role of physical activity and exercise in improving the outcome in patients with COPD. He has authored or co-authored over 90 articles published in peer-reviewed journals and other professional proceedings and is authorised by the Japanese Societies of Internal Medicine, Thoracic Diseases and Bronchology, as well as the Japan Primary Care Association.

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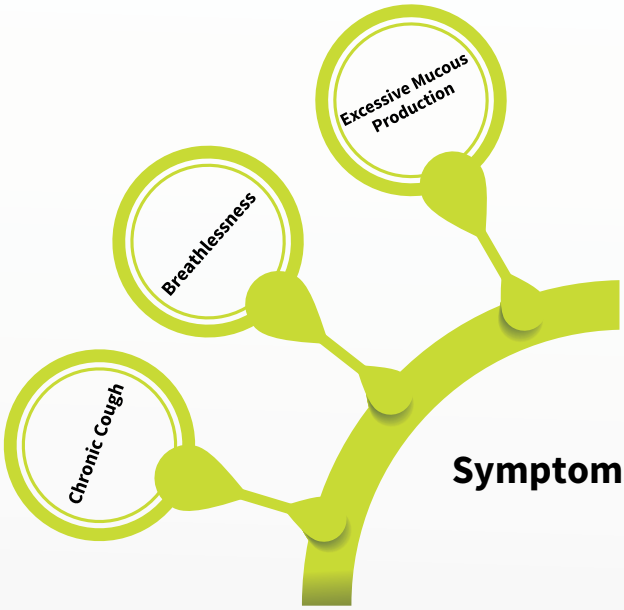
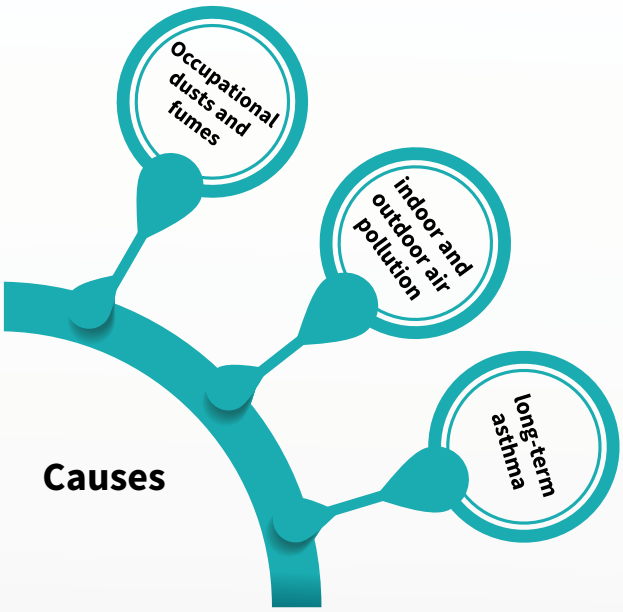
COPD WORLDWIDE



Symptoms



Causes

>3 million
Number of annual deaths caused by COPD globally (~6% of all deaths)

>90%
Proportion of COPD deaths that occur in low- and middle-income countries

30%
Expected rise in COPD-related deaths in the next 10 years

65 million
Number of people living with moderate to severe COPD worldwide

Tobacco smoke

May be responsible for about 9 in 10 cases

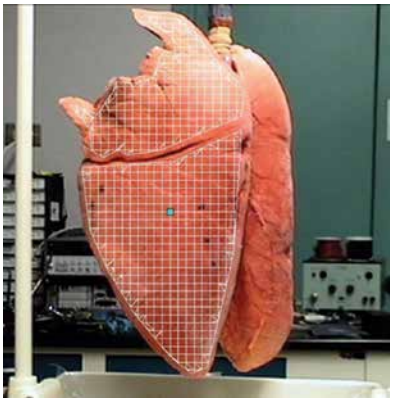
THE AUDIBLE HUMAN PROJECT: HEARING WHAT THE BODY HAS TO SAY

Professor Tom Royston is applying his expertise in the fields of acoustics and engineering to diagnostic medicine by developing the Audible Human Project, which aims to use sound to detect disease and injury within the body, particularly in the complex structure of the lungs.

We use sound to detect problems every day, probably more than we realise. When a mechanic asks a customer what seems to be wrong with their car, the answer is often a description of the unusual sound it has started to make. The mechanic usually knows what an engine should sound like, and can often diagnose the problem by listening. Historically, the movement of sound waves through the body has been, and remains, a highly valuable source of information for clinicians. Like mechanics, doctors use sound to aid in their diagnoses of diseases and injury. We are all familiar with the use of the stethoscope in medicine, but sound waves are also integral to cutting edge imaging methods which rely on elastography. These techniques, which are integrated into MRI or ultrasound, can analyse the elastic properties of soft tissues by detecting and imaging the vibratory motion produced by sound waves moving through them. Diseases of the liver, for example, can cause it to stiffen, while cancerous tumours will usually be harder than the tissues surrounding them, and are therefore detectable by elastographic methods.

Professor Tom Royston began his academic life studying engineering as an undergraduate in the late 80s 'During my undergraduate and graduate studies in engineering I was drawn to the area of acoustics and vibrations.' he recalls. 'The mathematics of wave theory was challenging and wide-reaching, while the experimental work was fun to do. Back then I was focused on active sound and vibration control, which was a relatively hot area of practical development in the 80s and early 90s.' He continued in this field throughout his postgraduate studies. The same year that Professor Royston completed his PhD, he was appointed as director of the Acoustics and Vibrations Laboratory at the University of Chicago (UIC). Upon joining UIC, he was approached by Dr Richard Sandler, who was working at the nearby Rush Medical Centre. Dr Sandler also had a degree in engineering and was interesting in applying mathematical analysis to sounds recorded by stethoscopes and other acoustic contact sensors. They worked together with another engineer, Dr Hansen Mansy, and started to apply their combined knowledge of engineering, acoustics, vibration control and the mathematics of wave theory to medical diagnostic purposes.

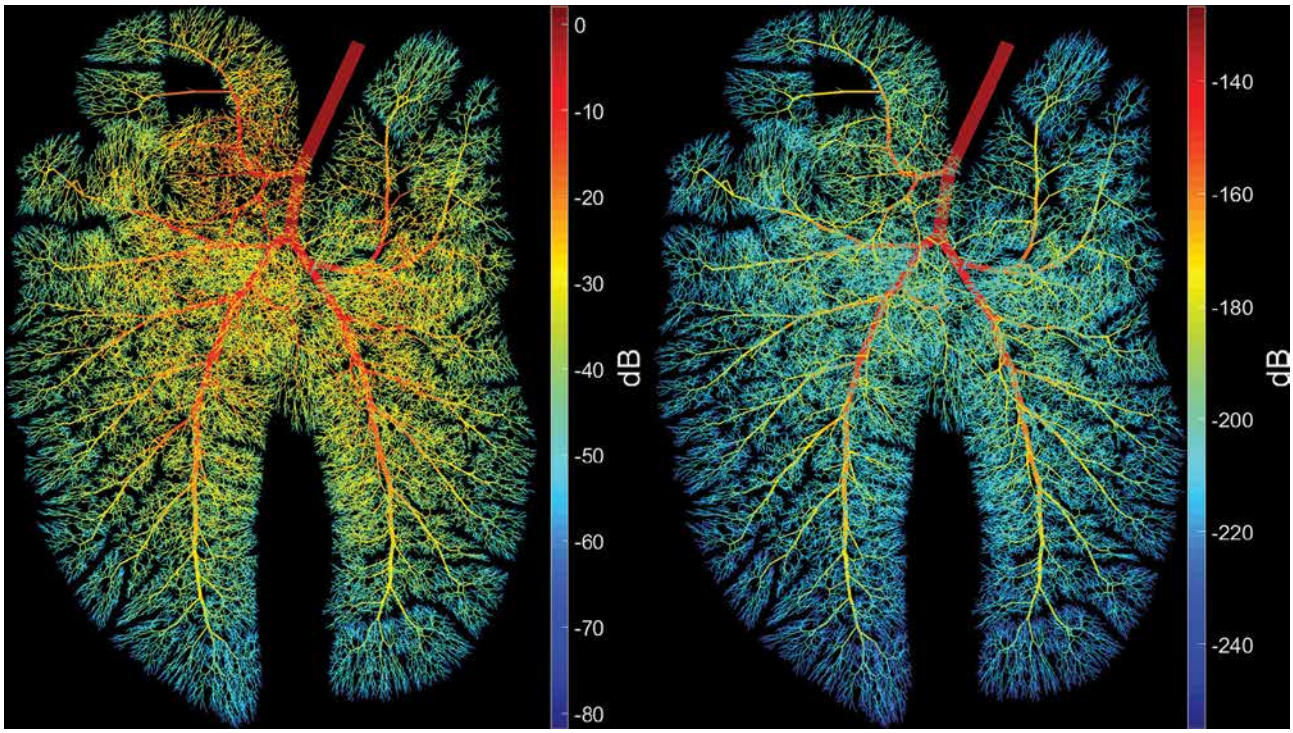
Among many early projects, one stood out to Professor Royston as being a particularly interesting challenge: 'we wanted to identify the best acoustic approaches to quickly and reliably identify a pneumothorax, or collapsed lung', he explains. The lungs are probably the most difficult organs from which to gather useful diagnostic information. 'From an acoustic perspective, the lungs make the rest of the body seem kind of boring', Professor Royston tells us. This is due to the fractal nature of the architecture of the lungs, where the highly complex bronchial airway tree branches through the tissues producing self-symmetry over multiple dimensional scales. This complexity is also a problem for conventional imaging techniques such as ultrasound and magnetic resonance imaging (MRI). Professor Royston



envisioned applying computer modelling methods to the analysis of data gained from acoustic measurements from contact sensors (stethoscopes), using either passive listening or percussive techniques which measure response to externally generated acoustic stimuli.

Around the same time, Professor Royston was contacted by PhD student, Shadi Othman, who was being supervised by a Professor of Bioengineering at UIC, Richard Magin, PhD, an expert in magnetic resonance imaging (MRI). They were interested in developing an imaging technique called magnetic resonance elastography (MRE) and needed someone with a background in acoustics to collaborate with. Professor Royston realised that his goal of using computer modelling to simulate the movement of sound in the body would be the key to interpretation of their MRE measurements. The logical outgrowth of these two ongoing efforts was the development of the Audible Human Project.

‘The purpose of the Audible Human Project has been to develop a computer simulation model of how sound travels in the body and is altered by disease or injury in order to improve stethoscope-based and elastography-based diagnostic methods’



The big picture for the Audible Human Project

The main goal of the Audible Human Project is to develop a comprehensive computer simulation model of sound and vibration in the body. This project can also be seen as a complement to the Visible Human Project, wherein male and female cadavers were cut into very thin cross-sectional slices to build a detailed visual dataset of the inside of the human body.

As mentioned before, the stethoscope is viewed as a symbol of medicine around the world, but Professor Royston’s vision for the Audible Human Project was that more than just the qualitative, subjective and skill-dependent nature of this instrument – sound can also be used for diagnostic techniques which are more quantitative, objective and automated. This is not so much to replace older methods such as the stethoscope, but to complement them and provide another highly useful additional resource to the medical toolbox.

Listening to the lungs

As mentioned before, the complexity of the lungs makes them a challenge for acoustics-based diagnostic methods. Though a collapsed lung causes a major change in the geometry of the lung, and should therefore produce a concomitant and detectable change in its acoustic properties, confounding factors can still affect these properties, which the simulations of the Audible Human Project must take into account. Pulmonary edema (fluid in the lungs), effusion and mucous plugs all have an effect on the way sound moves through the lungs. Many diseases of the lungs also cause changes in their acoustic properties. In chronic obstructive pulmonary disease (COPD) for example, the walls between the alveoli (air sacs where gas exchange takes place) break down, meaning there are fewer, but larger, alveoli. The bronchioles (very small airways leading to the alveoli) also lose their shape and can fill with mucous. Other lung diseases can lead to fibrosis, scarring, narrowing of airways or changes in their elasticity. Cancer also produces changes in the structure and composition of the lungs. Lung cancer remains the most common cancer-related cause of death in men and women, killing around 1.4 million people per year, so any advancements in the area of its diagnosis are sure to have a positive effect on people’s lives. One of the main ideas behind the Audible Human Project is that these microscopic mechanical changes will cause macroscopic changes in the acoustic properties of the lungs, which will be characteristic of the particular disease elements present. A better understanding of these changes will lead to improvements in the detection and diagnosis of lung diseases.

Work on the project so far

Work so far on the project has taken multiple variables into account in developing the computer simulations, such as tissue viscoelasticity, fractal airway modelling and different breathing sounds or externally generated percussion sounds. Each of these variables poses its own mathematical and

engineering challenges for Professor Royston's team to overcome. Synthetic models of lungs, constructed from a gel called 'Ecoflex' filled with air passages, which shares many properties with body tissues, were used by the team to gather data on how sound moves them. The team measured the movement of sound through this model using a piece of equipment more commonly used in engineering than for biomedical purposes, called a scanning laser Doppler vibrometer. This instrument shines laser light onto a surface and then measures the reflected light. As the surface vibrates, the colour (wavelength) of the light is altered by a small amount, due to the Doppler effect created by the surface moving closer or further away from the instrument. Videos of these measurements made on the Ecoflex model using different sound frequencies, can be found on YouTube, by searching for Audible Human Project.

The predictions made by the team's simulations were tested against experimental measurements performed on pig lungs, first in just the major airways and later on whole lungs. Testing was also performed on human clinical subjects. The results so far are highly promising, with experimental measurements producing similar data to the software's predictions, though there is still a great deal of work left to be performed in this area, in refining the predictive power of the model.

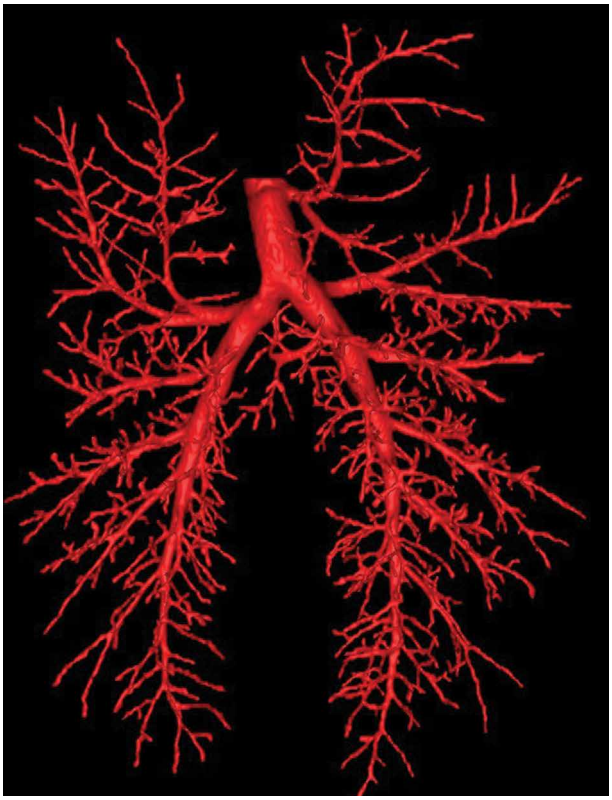
Future work: Expansion into the cardiopulmonary environment

Professor Royston plans to expand the scope of the Audible Human Project beyond the lungs, to producing simulations of the cardiopulmonary environment and how it is affected by pulmonary hypertension. He hopes that in the future, their research will be useful in identifying additional diagnostic signatures of pulmonary hypertension which can be identified through imaging. Like the team's work on the lungs, these indicators might also be detectable acoustically by using contact sensors or ultrasonic methods, such as echocardiography and elastography, as well as magnetic resonance methods, either independently or by combining multiple approaches. Combining the Audible Human Project with current and future diagnostic methods will make it an invaluable tool in the detection of pulmonary hypertension. The non-invasive nature of these acoustic techniques is highly useful in gaining diagnostic information in this area, as well as the lungs. Pulmonary arterial pressure, vascular resistance, cardiac output as well as the type of pulmonary hypertension are all measurements which are difficult to acquire currently without using invasive techniques, and all could have medical value beyond just the management of pulmonary hypertension.

Future work: Multiscale capability and enhanced visualisation

Professor Royston's grandest plans for the Audible Human Project are those relating to the multiscaling of its capabilities and enhanced visualisation. Spatially, the project is currently limited to the whole lung and larger airways, but Professor Royston's vision is one of the Multiscale Audible Human Project. Once developed, he believes the simulations could work across multiple spatial scales, from the cellular up to the whole organ. He hopes to use fractal and fractional calculus-based mathematical methods to more effectively use macroscopically measured mechanical wave motions to make quantitative predictions of microscopic changes at the cellular and tissue level which could be indicative of disease or injury.

'From an acoustic perspective, the lungs make the rest of the body seem kind of boring'



Enhanced visualisation is another major area of development in the Audible Human Project's future. Professor Royston plans to use the emerging technologies of 3D visualisation and augmented reality to enhance the project's usefulness, seeing conventional 2D monitor viewing methods as a limitation for a methodological toolkit such as this. These techniques would allow better visualisation of the data for diagnosticians and aid in their interpretation of it.

Once up and running, the initial focus of the program will be the detection of difficult-to-diagnose pathologies of the pulmonary system. Professor Royston plans to make the source code for the program freely available in all formats. There is still a lot of work to be done on the Audible Human Project, but the team are making great progress in this exciting field, which is sure to be of great benefit to medical science in years to come.

Meet the researcher

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Professor Tom Royston performed his doctoral studies on active sound and vibration control at the Ohio State University, earning a PhD in Mechanical Engineering in 1995 and later being awarded an NSF Career Award to expand upon this work. He then joined the Mechanical Engineering department at University of Illinois at Chicago (UIC) where upon speaking with a clinician scientist, he became interested in applying his knowledge to medicine. He is a recipient of the Acoustical Society of America Lindsay Award (2002) and his work on the Audible Human Project has been recognised with the NIH National Institute for Biomedical Imaging and Bioengineering Nagy New Investigator Award (2014). Tom is also a Fellow of the American Society of Mechanical Engineers (2007). He became department head of the Richard and Loan Hill Department of Bioengineering at the UIC in 2009, where he has overseen its expansion into both UIC Colleges of Engineering and Medicine.

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UNDOING THE DAMAGE CAUSED BY MODERN LIVING

Overeating, smoking, binge drinking, eating an unhealthy diet and leading a sedentary life – these practices are now commonplace in our modern world. Although science and technology have advanced our medical care tremendously over the past few decades, leading to overall increases in our lifespans, this progress has been severely dampened by our poor lifestyle choices.

Indeed, the near eradication of many infectious diseases, particularly in developing countries, has been paralleled by an emergence of allergic disorders, chronic inflammatory diseases, cancer, and metabolic disorders such as diabetes. In this section of the edition, we highlight the work of two research teams, each dedicated to undoing some of the damage caused by our modern lifestyles.

First up is Dr Hidetaka Hamasaki's research into improving the lives of patients with metabolic disease, conducted at the National Center for Global Health and Medicine in Chiba, Japan. Through their work, Dr Hamasaki and his team discovered a valuable lifestyle tweak that allows diabetic patients with reduced physical stamina to successfully improve their outcomes when it comes to managing their disease.

Next, we discuss several experiments that are about to take place at the University of Bern in Switzerland which will investigate if our Western diets are a leading cause behind the food allergy epidemic. Dr Mario Noti and his team will test whether changes in our gut bacterial communities caused by the Western diet are a contributing factor. If the team's hypothesis is confirmed, they hope that a cure could be developed by manipulating the body's microbial population.

To conclude this section of the magazine, we'd like to introduce Scientia's charity partner, Trees for Cities. In this exclusive interview, we speak with Kate Sheldon, Development Director and Deputy Chief Executive at Trees for Cities, who discusses the many public health benefits associated with their work. From creating green spaces where people can get active, to encouraging healthy eating by building edible playgrounds, Trees for Cities are making it easier for us to improve our lifestyles.

A NEAT WAY TO PREVENT AND FIGHT DIABETES

Metabolic disease and in particular diabetes are the focus of **Dr Hidetaka Hamasaki's** work at the National Center for Global Health and Medicine in Chiba, Japan. Dr Hamasaki and his team discovered a valuable lifestyle tweak that allows patients with reduced physical stamina to successfully improve their outcomes when it comes to diabetes management.

The chances of patients developing cardiovascular and metabolic diseases are dramatically increased if they are overweight. In 2012, the International Diabetes Federation found that more than 400 million people worldwide have diabetes. In 2015, the Federation estimated that this figure was 415 million people, of which 90% are affected by type 2 diabetes. By 2030, the number of patients suffering from diabetes will reach more than half a billion people. More than three quarters of these individuals live in Western countries, where the incidence of type 2 diabetes has been constantly increasing during the past few years. On a worldwide scale, almost five million patients succumb yearly to the consequences and complications of the disease. Type 2 diabetes is caused by insulin resistance, a condition preventing cells to respond appropriately to the release of insulin in the body. Having diabetes more than doubles the lifetime risk of early death.

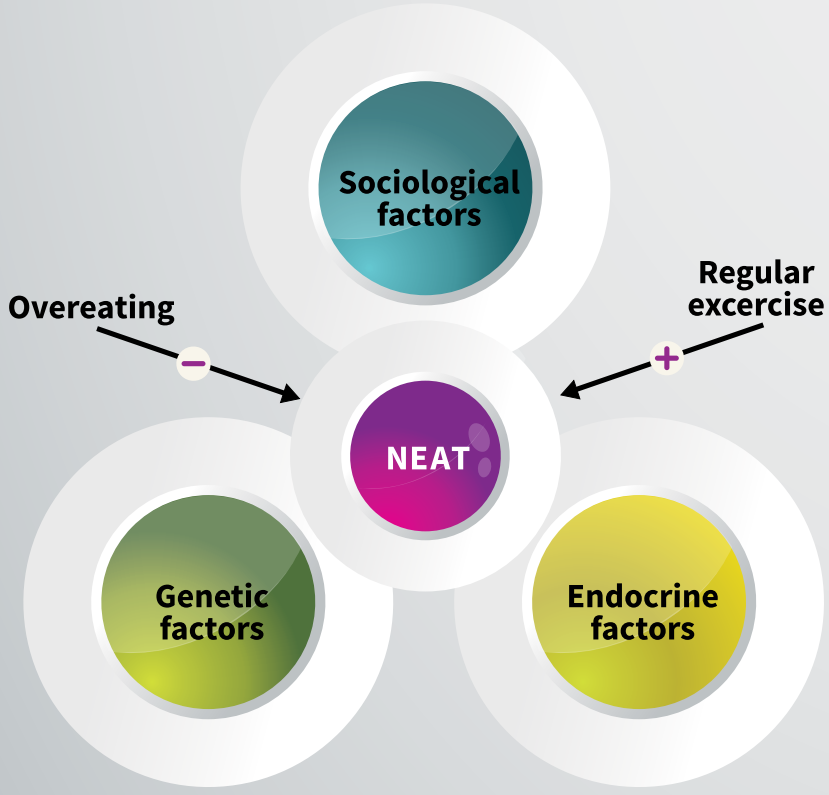
Scientists have been able to confirm that the causes of type 2 diabetes are insufficient physical exercise and excessive body weight. To be exact, the patients with diabetes are those with increased abdominal fat and with diets containing high levels of lipids and sugars. The World Health Organisation defines overweight individuals to be those with a body mass index of over 25, while those with a body mass index over 30 are considered obese. At the same time, the disease is diagnosed based on abnormally high levels of sugar in blood plasma. What is worrying for scientists is that more than 65% of people living in the United States and Europe are overweight or obese. Currently, almost a tenth of the adult population of the world is affected by the disease, in equal proportions of men and women.

One of the major problems for diabetes patients is that they have lower physical stamina than healthy individuals. In other words, it is more difficult for them to maintain the healthy exercise level that is recommended by physicians to keep their disease in check. Against this backdrop, Dr Hidetaka Hamasaki became interested in defining finding better ways for diabetes patients to augment their lifestyles and disease fighting routines. 'The recommended intensity and duration of exercise, which is at least 150 minutes per week of moderate to vigorous intensity aerobic exercise combined with resistance training, may be a considerable physical burden to older patients with type 2 diabetes or with diabetic complications, and lead to cessation of exercise therapy because they have a lower physical performance threshold than healthy individuals. Non-exercise activity thermogenesis (NEAT) consists of mostly light to moderate intensity physical activity, and continues without cessation for as long as we live. To clarify the beneficial effects of NEAT on patients with type 2 diabetes will be helpful for the management of type 2 diabetes,' he explains.

Using NEAT to Improve Patient Outcomes

Dr Hamasaki works as a physician with the Department of Internal Medicine, National Centre for Global Health and Medicine, Kohnodai Hospital, Japan. He completed his residency in medicine in 2010 and obtained his PhD in 2016 in healthcare.

‘NEAT plays an important role for treating type 2 diabetes as well as obesity. It also has favourable associations with metabolic parameters in patients with type 2 diabetes and glucose intolerance. Stand up, and increase NEAT!’



NEAT is regulated by sociological, endocrine, and genetic factors. The most important factor to increase NEAT is the sociological factors such as occupation, family structure, and residential environment.

His main research interests are diabetes, endocrinology, physical activity, and non-exercise activity thermogenesis. He became interested in non-exercise activity because he knew that light physical activity accounts for most of the variation in daily energy expenditure between individuals. NEAT physical activity is defined as non-exercise motion such as washing dishes, cleaning the floor, walking to work, typing, gardening, typing on a keyboard, or fidgeting. To generalise, NEAT is anything that requires spending energy and is not sleeping, eating, or doing anything similar to sports.

Although previous studies had found a link between the reduction of obesity and non-exercise activity, prior to Dr Hamasaki’s work it was not clear whether the metabolic risk factors in pre-diabetic stages and untreated early type 2 diabetes can be mitigated through this type of activity. In a series of studies, Dr Hamasaki demonstrated that non-exercise activity increases insulin sensitivity, favours waist circumference reduction, aids in lowering blood pressure in patients with type 2 diabetes, and helps increasing high density cholesterol. In order to improve the accuracy of measuring non-exercise activity undertaken daily by the patients, he and his colleagues are preparing new experiments using omnidirectional accelerometers capable of precisely determining and reporting it.

In 2013, Dr Hamasaki found correlations between the metabolic characteristics of individuals and their level of non-exercise activity in a study on 45 Japanese type 2 diabetes patients. ‘We studied 45 subjects who did not take any hypoglycemic, anti-hypertensive, or cholesterol-lowering agents and asked them about NEAT using an original questionnaire modified from a compendium of physical activities. We studied the association of the NEAT score to body weight, waist circumference, blood pressure, glucose and lipid metabolism, and arterial stiffness,’ Dr Hamasaki told us. What they found was that a higher level of NEAT is associated with a reduction in waist circumference and lower serum insulin levels, which means an increase in sensitivity to insulin. At the same time, non-exercise activity correlates with increased high density cholesterol levels. The researchers also found that this type of activity is associated with lower blood pressure in patients with abdominal obesity. Finally, yet importantly, smokers undertaking non-exercise activities had a lower pulse wave velocity – an important indicator of cardiovascular health. When they analysed the data obtained during this study, the scientists noticed that there was a relationship between NEAT and heart rate variability. Heart rate variability depends on the health of the heart and autonomic nervous system, therefore being a crucial component of the overall health state of individuals. Although it was assumed that the relationship between NEAT and heart rate variability was mediated by the glycaemic

status of patients, no such correlation was found, suggesting that more work is necessary to understand this phenomenon.

But Dr Hamasaki wanted to make sure that the results he obtained were correct. His biggest doubt was that the methodology based on reporting activity levels via a self-assessed questionnaire was insufficiently accurate. Therefore, in order to validate the results he had obtained in 2013, he started a new study with the purpose of comparing automated measurement and reporting methods with the questionnaires he had previously used. To do so, he measured the level of non-exercise activity by triaxial accelerometers and self-administered questionnaires simultaneously, and then he compared the two sets of data. By this procedure, he was able to confirm that the questionnaire answers are highly correlated with the results reported by accelerometry, and therefore they can be used in clinical practice on a regular basis.

Dr Hamasaki continued his activity with three more studies resulting in several significant findings regarding the relationship between non-strenuous activities and cardiovascular and nervous system health. By studying 80 Japanese adults, the first study collected data regarding the daily physical activity and metabolic risk factors in patients with prediabetes or untreated early type 2 diabetes. During this study, the information was taken via triaxial accelerometers. After accounting for age and weight, Dr Hamasaki was able to confirm that non-exercise activity was associated with smaller waist circumference, lower triglycerides and insulin. Additionally, the study found significant differences between genders. In men, higher levels of physical activity decreased systolic blood pressure and fasting plasma glucose. However, no significant associations were found between physical activity level and metabolic risk factors in women. Although non-walking activities improved the health of both genders, men had significantly greater energy expenditure from walking than women.

Dr Hamasaki continued his work with a study on 60 patients without diagnosed heart failure and renal impairment. He describes the motivation behind the study: 'In spite of accumulating evidence suggesting an inverse association between insulin resistance and plasma B-type natriuretic peptide (BNP) levels, the effect of daily physical activity on plasma BNP in individuals with glucose intolerance remains unknown. We investigated the association of physical activity level (PAL) with plasma BNP in patients with impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. Our findings propose the possibility that plasma BNP may be increased by daily physical activity and that BNP is associated with insulin resistance.'

A paper published by Dr Hamasaki's colleagues, called *'Nonexercise Activity Thermogenesis in Obesity Management'*, explains several key factors of NEAT. Firstly, a strong case is made for using non-exercise activity due to the worldwide obesity pandemic and this argument is supplemented by showing the daily energy expenditure that can be obtained through this type of intervention. In this paper, the mechanism of action and how NEAT changes the brain for the better, and the multiple benefits of non-exercise activity are presented. Because of its structure and language, the paper is accessible to a general public and, moreover, it is available online as open access, thus making a good lecture for all those interested in diabetes intervention.

In 2016, Dr Hamasaki published a paper showing that patients with mental disorders can gain major benefits from non-exercise activity.

It is well known that such patients are less able to take care of their health and often have worse metabolic situations than patients without mental disorders, which is why NEAT methods could prove a valuable aid to them. Dr Hamasaki studied 150 type 2 diabetes patients out of which 50 also had a mental illness, such as schizophrenia or mood disorders, between September 2010 and September 2014. Although the levels of non-exercise activity in mentally ill patients were much lower than those of patients who only had diabetes, the results suggested that NEAT would be beneficial for the management of obesity, insulin sensitivity, and lipid profiles in patients with mental disorders. In particular, patients with schizophrenia showed an increase in high density cholesterol and a decrease in the levels of glycated haemoglobin, an important marker of how well diabetes is controlled. Earlier this year, Dr Hamasaki also found a correlation between handgrip strength and non-exercise activity thermogenesis in patients with type 2 diabetes.

Next Steps

Although Dr Hamasaki made several important findings showing the benefits of non-exercise activity to patients with metabolic ailments, there is still a lot to be done in the future. 'We still don't know how to accurately measure NEAT under free-living; should we use accelerometry, the doubly labelled water method, or a completely new method? We are still investigating how to better make NEAT interventions, for example what works best between a medical recommendation and a supervised program,' Dr Hamasaki explains. 'Dr Shigeho Tanaka and I are working on the intervention study of NEAT measured by a triaxial accelerometer in patients with type 2 diabetes. To elucidate the effects of NEAT on type 2 diabetes is a challenge for the future.'

Meet the researcher

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Dr Hidetaka Hamasaki is a staff physician at the Department of Internal Medicine, National Centre for Global Health and Medicine, Kohnodai Hospital, Japan. Starting from April 2017, he will take his position as the Director of the Hamasaki Clinic. Dr Hamasaki received his PhD in general internal medicine in 2016 from the Jichi Medical University Graduate School with a thesis in community healthcare studies. After completing his residency in internal medicine between 2008 and 2010 with the National Hospital Organization Yokohama Medical Center, he continued his professional career with the Fellowship in Diabetes and Endocrinology at the Department of Diabetes and Endocrinology, National Centre for Global Health and Medicine, Tokyo, Japan. His major research interests are in diabetes, endocrinology, geriatrics, physical activity, and non-exercise activity thermogenesis (NEAT). During the past 5 years, he authored almost 50 scientific papers focussed on the biochemistry and phenomenology of metabolic disease. Among other societies, he is a member of the American College of Physicians, Japanese Society of Internal Medicine, and Japan Diabetes Society.

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DO MODERN LIFESTYLES CAUSE FOOD ALLERGIES?

Over the last 30 years, there has been an explosion in the prevalence of food allergies in the Western world. What's going on and what are the culprits for this epidemic? While genetics may not be blamed for the rapid increase in food allergies over such a short time, microbial deprivation in response to changes in our Western lifestyle may make our immune system overly sensitive to otherwise harmless foods. Research about to take place at the University of Bern led by **Dr Mario Noti** and his team is going to test whether alterations in gut commensal community structures associated with a Western diet are contributory factors for the observed rise in food allergies, and therefore, whether a cure could be developed by manipulating the body's microbial population.

Food allergies are one of the epidemics of the modern world affecting up to 8% of children and adults. There is currently no cure, and for now, the best remedy for food allergies is avoiding high risk foods. However, as many food labels are confusing, finding hidden ingredients in food is not as easy as it should be. Thus, food allergies not only affect a patient's quality of life, but also negatively impacts public healthcare organisations, such as the NHS in the UK, that have to meet the costs associated with a large and growing public health concern.

Food allergies are defined by an adverse immune response that occurs repeatedly following exposure to a given food and can manifest in symptoms ranging from itching, hives and diarrhoea to acute anaphylaxis accompanied by a life-threatening drop in blood pressure and airway constriction. As a result, individuals must avoid certain foods to guard against accidental exposures. What factors cause our immune system to react so sensitively to otherwise harmless food? It wasn't long ago that genetics was used to explain everything that's going wrong in our bodies. These days, we have started to realise that environmental changes have a huge impact on host physiology. 'Although genetic predisposition is a significant risk factor for developing allergic inflammation, the skyrocketing increase in food allergies over the last three decades suggests that genetics are not solely to blame for the observed phenomenon,' Dr Noti explains. In the past, a number of different ideas and theories have been forwarded by experts, including pollution, genetically modified food, synthetic chemicals in personal care products, changes in diet, antibiotics or a decline in gut microbial complexity and diversity. Whatever the reasons are for the food allergy pandemic, it falls upon us to come up with new intervention strategies to target this debilitating disease.

The Little Friends That Call Us Home…

The human body is an ecosystem in its own right. It is host to trillions of microorganisms that live in peace and harmony with us in a co-evolved mutualistic relationship. These intimate friends regulate numerous aspects of normal host physiology and pathophysiology. Although there's a long list of suspects that may fuel the emergence of disorders associated with a Western lifestyle (i.e. autoimmunity, allergies), changes in the composition, richness and balance of the gut microbiota have become one prominent candidate in recent years, says Dr Noti.

For the 200,000 or so years that Homo Sapiens have been around, we have been exposed to a wide variety of bacteria that impact the body in many ways. There have been pandemics such as (bacterial) cholera and (viral) smallpox that we have naturally sought to eradicate to prolong our lifespans through medicine. As a result, in Western countries, our lifestyles have changed markedly over the last 150 years as medicine and public health has found ways of preventing infectious disease outbreaks from killing and disabling millions of people. However, such radical changes in our lifestyles have taken their toll on the beneficial symbiosis with our bodies' microorganisms.

Modern living has a wide-ranging impact on modulating the composition and metabolic activity of the gut microbiota, which in turn can impact health. Through evolution, our body has adapted to consume a variety of fruits, pulses, vegetables and much less meat and sugar than is in the Western diet, and this has led to a dramatic change in the makeup of the ecosystems within our bodies. In short, as we have learned new ways of stopping outbreaks of infectious diseases through modern medicine and improvement in sanitary installations, the human immune system hasn't adapted at the same pace as it's biome shaped by our modern lifestyles. Thus, we may have developed the allergy pandemic as a result.

‘We will investigate how changes in the bacterial community structure affect the pathogenesis of food-induced allergic inflammation, and whether engraftment of selected microbial communities into germ-free mice alters the susceptibility to food allergies’

To put it simply, would a better understanding of the host-microbial handshake be the key for the development of new cures to treat the observed prevalence of various disorders in the West? The emergence of new technologies has allowed us to have an intimate look at our little friends in health and disease. Loss of diversity or expansion of the ‘wrong’ bugs is a hallmark of many chronic and infectious diseases. However, whether dysbiosis (remodelling of the composition of our internal friends) is a consequence of a changing environment or the cause behind certain disorders is not well understood.

Striking evidence for causality comes from recent animal studies. Feeding the host-microbiota superorganism a Western diet – a mix of foods that are high in fat, high in simple carbohydrates, and low in fibres – not only results in weight gain and metabolic disease in the host, but in vast changes in the gut microbial community structure. What’s more, lean mice transplanted with the gut microbiota of obese donors gain weight and vice versa. Another example highlighting the importance for keeping up gut microbial diversity comes from clinics where faecal transplantation – an emerging procedure involving the transfer of a healthy person’s microbiota into a sick person’s gut – is an efficient therapeutic approach to treat an antibiotic-resistant intestinal pathogen named Clostridium difficile that causes thousands of deaths a year. This treatment sounds appalling, but seems to work by restoring gut microbial complexity and to fight of C. difficile.

Breaking-up with Our Intimate Friends: A Betrayal with Consequences?

People live very different lifestyles to one another, eating different foods and experiencing different environmental exposures. Put simply, a clean-living vegan who spends much of their time gardening will have a very different makeup of microorganisms in their system to an overweight hamburger loving cosmopolitan office worker. Between these two extremes there is a huge variety of lifestyles that people choose.

There is increasing evidence that the alarming increase in food allergies in the Western world may be due to a disruption in the ancient relationship between us and our old friends – the commensal microbes that co-evolved with us for thousands of years. In short, our Western lifestyle has confined the natural complexity and diversity of germs needed for a proper maturation of our immune system that has become overly sensitive to otherwise harmless food. Changes in dietary habits are major contributory factors that shape the landscape of our gut microbiome. In many ways, the commensal flora is like a sparring partner in boxing, as it educates our immune system how to fire against invading

pathogens, but stay relaxed upon encounter with harmless antigens such as food. However, our radical change in the diet (e.g. addiction to junk food) associated with the lifestyle in the West seems to take its toll on our bodies intimate friends that fail to control our army inside. As Dr Noti explains: 'Understanding the mechanisms by which microbial communities or microbial-derived signals regulate type-2 immune responses will help in developing new therapeutic approaches to modulate allergic inflammation.'

Dr Noti's Experiments

Dr Noti and his team have two primary questions to answer. Firstly, are food allergy-associated changes in the gut microbial community structure a simple consequence of an inflammatory milieu or causative for disease? Secondly, do dietary-induced changes in the gut microbial community structure increase susceptibility to food allergies? One way to obtain a concrete biological model of the theory described above is to use genetically identical animals in highly controlled environments. These settings allow scientists to formally test causal relationships between characteristic differences in the gut microbial community structure and the development of food allergies.

One of Dr Noti's approaches will be to use germ-free mice that are born and raised in sterile plastic isolators. These animals have no microorganisms in their bodies whatsoever, including those that aid digestion in the gut. By using these mice, Dr Noti's team will perform a series of experiments to assess a potential role of the microbiota in the pathogenesis of food allergies. 'We already know, that germ-free mice harbouring no bacteria are more susceptible to food allergies compared to mice with a complex microbiota. Similar findings have been made in mice with a compromised microbiota due to exposure to antibiotics. These studies tell us that the microbiota is intimately involved in the regulation of type-2 immune responses that trigger allergic inflammation,' says Dr. Noti.

To get a better idea of the microbial dynamics in health and disease, Dr Noti's team will first assess changes in the microbial community structure of healthy versus food allergic mice using 16S ribosomal RNA sequencing, a culture-free method that enables analysis of the entire microbial community within a sample. In a second phase, germ-free mice will be colonised with the microbiota of either healthy or food allergic mice. These studies will allow the team to test a potential causal relation between changes in the gut microbial community structure and susceptibility to food allergies.

The considerable inter-individual variation in gut microbiome species in humans has been demonstrated in large scale projects such as the Human Microbiome Project. These studies have highlighted a huge variability in the gut microbial community in healthy individuals, with non-identical twins sharing less than 50% of their core microbiome. Such a large variability in the bacterial community under healthy conditions within close relatives makes it difficult to correlate changes in the microbiota with disease states.

In collaboration with the Children's Hospital of Philadelphia, Dr Noti's team isolated bacteria from faeces of identical paediatric twins, one allergic, the other healthy. 'This is a truly unique sample that allows us not only to rule out genetics but also significant changes in the composition of the microbiota due to different diets, as these kids are living in the same household and eat similar meals. Using these samples, we will perform faecal transplants into germ-free mice and assess whether mice receiving the microbiota of the allergic donor are more susceptible to food allergies as mice harbouring the "bugs" of the healthy twin,' says Dr Noti.

To study the above discussed role of the Western diet on the host-microbiota superorganism, current research in the Noti-lab is testing whether feeding mice a Western diet rich in fat and sugar alters the body's immune response to react against harmless food. Knowing that a Western diet alters not only the gut's microbial community structure but also its barrier function, it is likely that mice fed a high fat/high sugar diet will be more prone to food allergen sensitisation and the development of food allergies compared to animals fed a normal diet. 'Similar to our other approaches, we are currently testing whether colonisation of germ-free mice with the microbiota of mice fed a Western diet alters their susceptibility to become food allergic,' says Maryam Hussain, a PhD student in Dr Noti's team.

Together, Dr Noti and his team hope that by adjusting mice's diets and the microorganism populations in their intestines, food allergy can be significantly reduced. If this is the case, further experiments will take place ultimately to assess whether these changes could help to stop the food allergy pandemic across the Western world.

Meet the researcher

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Dr Mario Noti received his BSc and PhD in immunology and microbiology at the University of Bern, Switzerland. It was here that he also carried out his first postdoctoral training in immunology, followed by work at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA. He then returned to the University of Bern where he now holds his current post, as a research group leader at the Institute of Pathology. In addition to research, Dr Noti is an active member of the Swiss Society of Allergy and Immunology (SGAI), Junior Member of the European Academy of Allergy and Clinical Immunology (EAACI), and a COST Member Improving Allergy Risk Assessment Strategy for new food proteins (ImpARAS).

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TREES FOR CITIES: BOOSTING PUBLIC HEALTH

Trees for Cities – Scientia's charity partner – has been working on an international scale to create greener cities, engaging over 70,000 people to plant almost 700,000 trees to date. Here, we have had the pleasure of speaking with Kate Sheldon, Development Director and Deputy Chief Executive at Trees for Cities, who describes the many public health benefits associated with having more trees in urban environments.

To start, please explain a few of the many physical health benefits that people can enjoy as a result of having more trees in urban environments?

Urban trees aren't only beautiful – they perform a vital function to help make our cities healthy places to live. These 'ecosystem services' include filtering fine air particles, reducing chemical smog formation, air cooling, and shading out harmful solar radiation, all of which have a positive effect on the incidence of diseases such as asthma, skin cancer and lung disease.

Although most people love urban trees, most don't realise the full range of benefits that trees provide. In 2005 Trees for Cities worked with the National Urban Forestry Unit to document these benefits in Trees Matter! http://www.treesforcities.org/benefits-urban-trees/. Since then, with advances in IT, some of the ecosystem services provided by urban trees are now quantifiable using models such as i-Tree Eco. In 2015, Trees for Cities was involved in the London i-Tree Eco project – this exemplar project put a monetary value on certain ecosystem services provided by trees in the capital city. The i-Tree approach adds substantial weight to the importance of investment into managing, maintaining and planting urban trees.

Air pollution is currently a hot topic, so using that as an example, the London i-Tree Eco project valued the annual ecosystem service of pollution removal by trees at £126.1 million. Trees remove pollutants by reducing air temperature (which lowers ozone levels) or direct removal – trees with large, sticky or hairy leaves are especially good at this! A study in the West Midlands suggests that doubling tree cover across the region would reduce the concentration of fine PM10 particles by 25%. This could prevent 140 air pollution related premature deaths in the region every year.

An abundance of trees in our towns and cities must also have an enormously positive impact on the psychology of city dwellers. How do you think trees can benefit our mental health?

We can all relate to the sense of relief from stepping out of harsh sunlight into the cool shade of tree canopy. Trees are aesthetically very attractive – they soften the hard edges of buildings, and have a wonderfully stimulating yet calming effect. This helps to reduce stress, one of the main causes of ill-health for people in the urban environment.

At Trees for Cities we are strong believers in place-shaping. We plant trees that perform a function and instil a sense of purpose to a space, so that people are encouraged to spend time outdoors and have something to do there. Places such as community orchards and urban woods become a focal point and give residents a reason to meet up to socialise and exercise. These mental health benefits – stress alleviation, reduced anxiety, greater social cohesion, improved self-esteem – all help to prevent ill-health in later life.

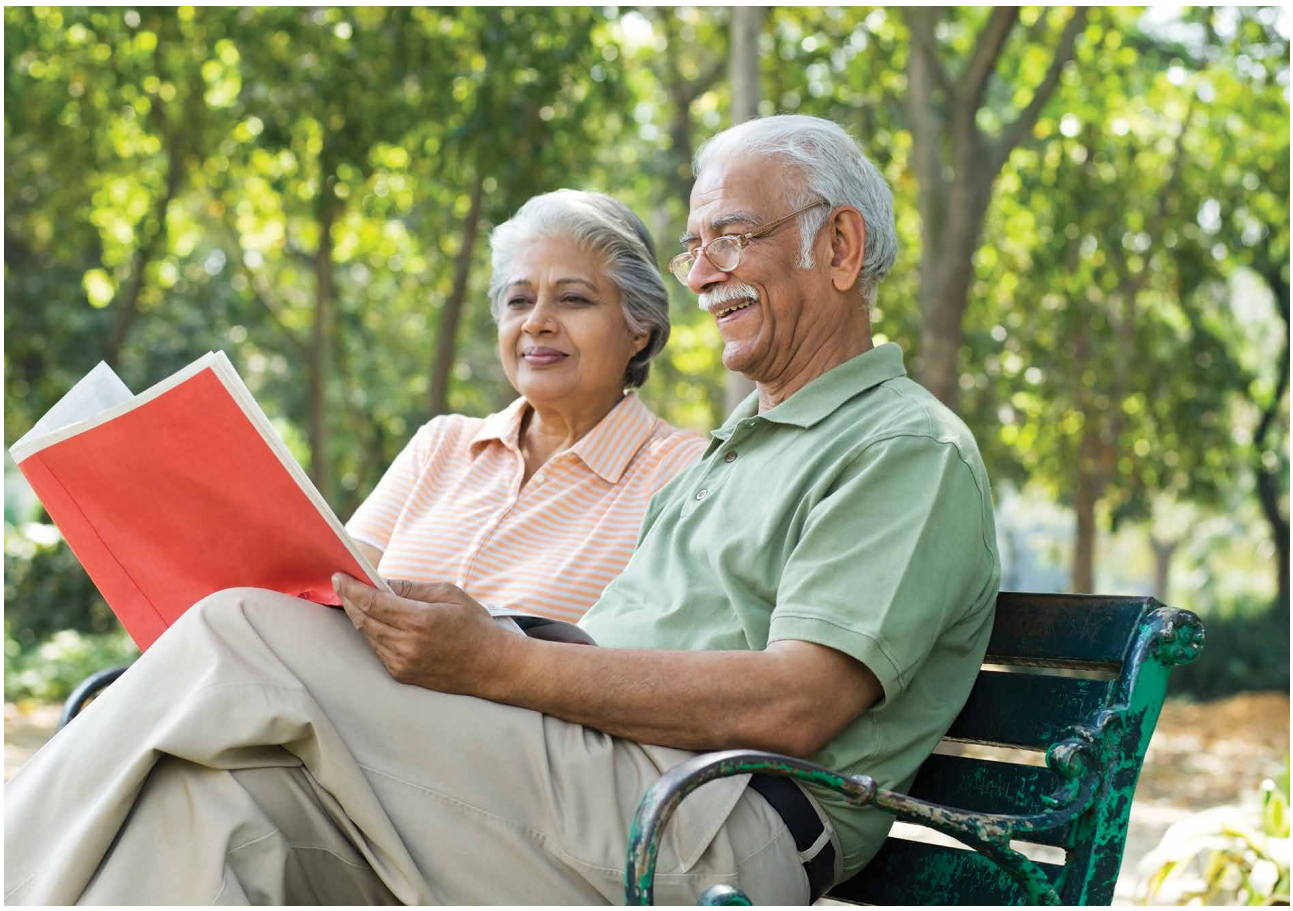
Trees for Cities has actively engaged thousands of volunteers to help plant trees in UK cities and internationally – describe how these individuals benefit from such work? On a larger scale, engaging in charitable work must also positively affect the health of communities.

Trees for Cities
Breathing life into your neighbourhood

www.treesforcities.org/

We have network of a fantastic, dedicated volunteers who come out to plant trees with us on cold, wet and windy days each winter. Some live locally to projects, others travel to different sites, and many volunteer through community groups. Whatever their motivation, all our volunteers enjoy a day of physical outdoor activity alongside people from different backgrounds, faiths, ethnicities and ages who share their values and want to engage in doing something positive for the environment.

Trees for Cities has run some fantastically creative volunteer events over the years: the charity began by raising funds through our infamous Tree Parties! 'Young, Tree and Single' in Manchester was our first tree planting speed dating, whilst in 2013 we celebrated our 20th anniversary by colouring trees in central London a beautiful shade of blue to raise awareness of their importance. In February of this year, 280 volunteers had fun getting fit at our annual Plant to the Beat urban woodland creation day.



Volunteering has a powerfully uplifting and galvanising effect which has health benefits for individuals and communities. Planting trees instils pride of local green space and supports sustainability, empowering residents to care for their trees and harvest the fruit. This brings people together and builds community cohesion – by planting trees together, we plant hope for the future.

In addition to your amazing work in planting almost 700,000 urban trees to date, Trees for Cities has also developed many 'edible playgrounds' and 'forest gardens' in schools throughout the UK. Tell us about the many ways in which these gardens benefit children's health.

We have been planting trees in schools since 1993. Over time, in response to the childhood obesity crisis, we saw increasing demand from Head Teachers to create a resource for children to grow food and encourage healthy eating. In the UK, almost 20% of children are obese on leaving primary school and diet-related illnesses cost the NHS £10 billion each year.

We created our first edible playground at Rotherfield Primary School in 2009. Edible playgrounds provide the practical, functional solution that Head Teachers craved. Our edible playgrounds take a whole school approach and provide a comprehensive service – designing, building raised beds, planting, and providing support for a year through teacher training and planning, linking food-growing to the school curriculum. To date we have created 50 edible playgrounds in London, Reading, Manchester, Liverpool and Sheffield.

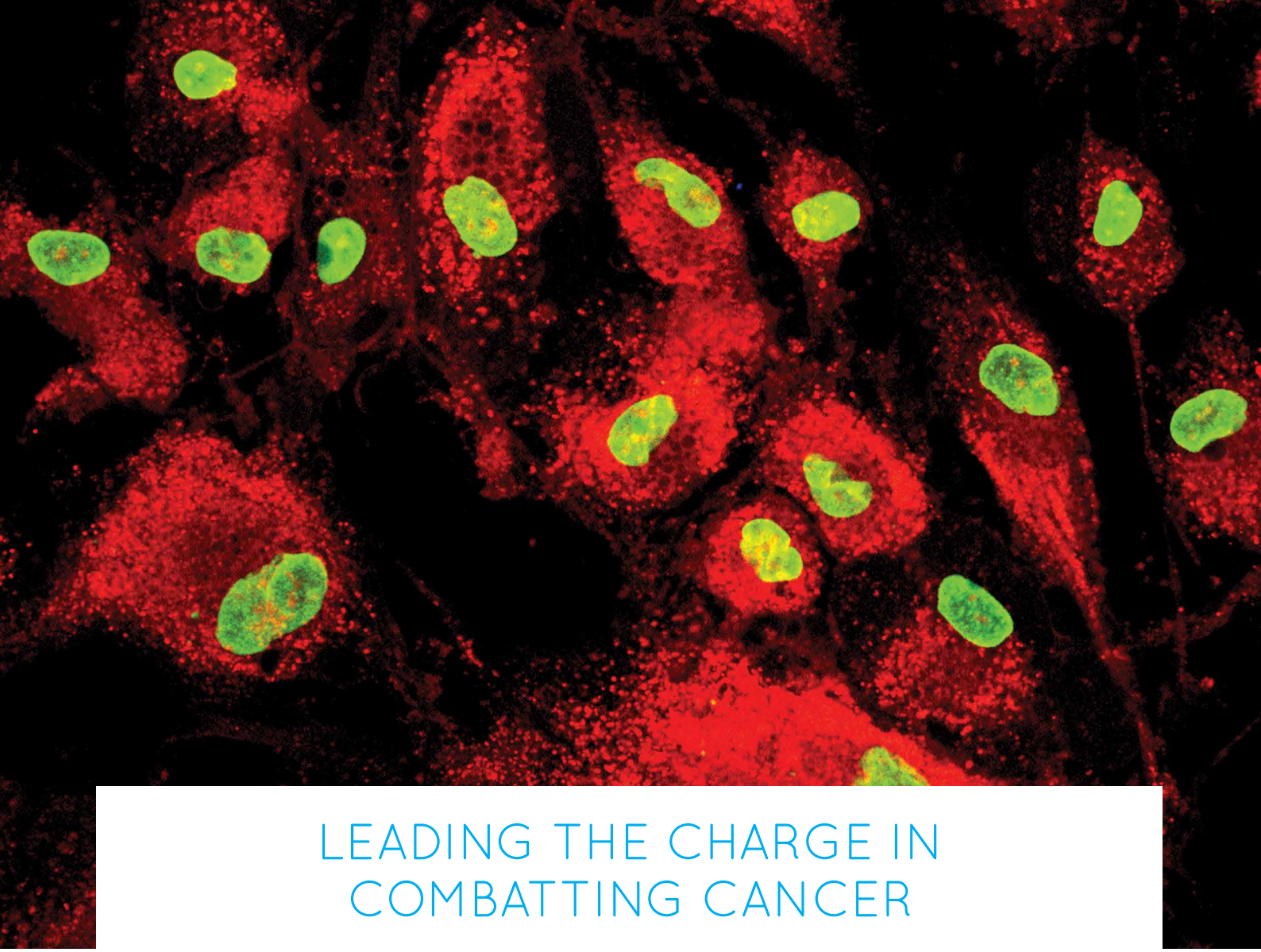
School forest gardens take a more naturalistic approach to growing food that mimics agroforestry systems. The benefits of both programmes radiate to the whole school community to create a culture of community food-growing in school and improved environmental awareness.

Finally, I hear that Trees for Cities also works to increase the number of trees in health settings, such as hospitals. Please tell us about your work to date in this regard.

Trees for Cities has been working with the South London and Maudsley NHS Foundation Trust to create a high-quality environment for service users and their families. Maudsley Hospital is a psychiatric hospital in South London. We have created a horticulture therapy garden for adults with severe mental illnesses, and are now embarking on a wider programme to transform the hospital grounds into an accessible community green space. Our planting design has created a place where hospital staff can offer a range of outdoor treatments, from occupational therapy to food-growing, cooking and yoga.

Our focus now is to connect hospitals with their local parks, which provide additional green space and facilities that help to improve the hospital experience. Across a busy road from Maudsley hospital, Ruskin Park offers an ideal location, where Trees for Cities runs tree trail walks, community training sessions and offers free surplus fruit and vegetables grown in the community garden.

Trees for Cities needs your support: please donate at
www.treesforcities.org/donate



LEADING THE CHARGE IN COMBATTING CANCER

Year after year, cancer survival rates continue to increase across the globe. Back in 1975, the average 5-year survival rate for all cancer types was a mere 50% in the US – meaning only half of all people diagnosed with cancer would still be alive 5 years following their diagnosis. According to the National Institutes of Health, this figure reached 68% in 2007, and has been steadily increasing since. Similarly, here in the United Kingdom, Cancer Research UK estimates that the 10-year survival rate for all cancers has more than doubled in the past 40 years, from just 24% in 1970 to 50% in 2010.

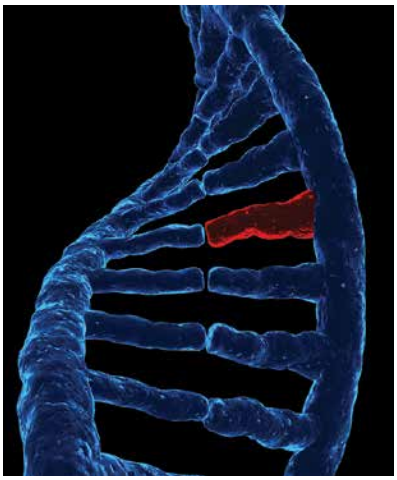
These remarkable improvements in our prognoses are in large part due to the tremendous advances made in cancer research over the past few decades. Due to the tireless efforts of cancer scientists, our understanding of how this disease arises and progresses has been enormously enhanced, leading to improved diagnostics and a multitude of new therapeutic options. Despite these advances, cancer remains a leading cause of mortality worldwide, so more work needs to be done.

In this section of the edition, we highlight the work of two research teams, each dedicated to combatting this terrifying disease. First, we introduce the work of Drs Ivan Stamenkovic and Nicolo Riggi at the University of Lausanne in Switzerland, who are figuring out new ways to combat paediatric cancer. Although childhood cancer is rare, comprising less than 1% of all cancers diagnosed annually, it is actually the leading cause of disease-related death among children beyond infancy in the US. Paediatric tumours often develop and behave differently than their adult counterparts, meaning that different approaches to treatment are required to achieve the best outcomes. For this reason, Drs Stamenkovic and Riggi have dedicated their research to unravelling the mysteries of paediatric cancers, by illuminating the epigenetic pathways that cause them.

From childhood cancer, we move on to investigate a cancer primarily affecting the elderly, called chronic lymphocytic leukaemia (CLL). The most common form of blood cancer in the Western world, CLL accounts for around one-quarter to one-third of new cases of leukaemia, while the median age of diagnosis is approximately 70 years in the USA, Europe and Australia. At the forefront of the fight against this disease is the CLL Research Cluster at CancerCare Manitoba and the University of Manitoba in Canada. In the second article of our cancer section, we meet 12 dedicated team members of the cluster, and discuss their research plans. The team aim to better understand the biology of metabolism and migration in CLL, and develop new therapeutic and management strategies for patients with CLL. This work can then be translated into improving patient care, survival and quality of life.

SHINING LIGHT ON PAEDIATRIC CANCERS

Paediatric tumours often follow different developmental pathways than adult cancers, and may require different approaches to treatment for the best outcomes. **Drs Ivan Stamenkovic and Nicolo Riggi** work to unravel the mysteries of paediatric cancer by illuminating the epigenetic pathways that cause them.



While a cancer diagnosis can be devastating at any age, a diagnosis of paediatric cancer is particularly shocking, both for the afflicted child and their family. Paediatric tumours often develop and behave differently than their adult counterparts, and recent studies have demonstrated that this is due to major differences in mechanisms of gene regulation between the two. Drs Ivan Stamenkovic and Nicolo Riggi and their research teams at the University of Lausanne in Switzerland, work to understand the genetic and epigenetic factors that cause paediatric tumours and make them unique from adult cancers. Their findings are shaping clinical practices and treatment strategies, to help make childhood tumours a thing of the past.

It All Starts with Stem Cells

Your body is composed of many different types of specialised cells, such as the spindly muscle cells in your heart, the flattened cells that make up your skin, and the unique neuron cells that compose the network building your brain. Each of these types of cells are defined as terminally differentiated cells; and although they may divide to form identical daughter cells, they are unable to generate a different cell type. A skin cell can make more skin cells, but a skin cell can't make a neuron. Most of the cells in an adult's body are differentiated cells, but our organism didn't start that way. Every cell in your body originated from a single fertilised egg, the original undifferentiated cell from which all of your other cells eventually formed. Undifferentiated cells, commonly known as stem cells, are cells that have the potential to form multiple types of differentiated cells. Healthy adults and older children have limited reserves of stem cells that only occur in specific parts of the body, except in one situation: cancer.

Cancer cells do not behave like normal, healthy cells. They divide and grow out of check, can spread to other parts of the body, and in some cases, may display stem cell like abilities allowing them to retain some of the key biological features of normal stem cells. Cells with this ability, deemed cancer stem cells, are able to renew themselves and form many types of cells within a growing tumour, but it has only been in recent years that scientists have begun to understand how these cells are able to do this. Several research groups around the world have shown that a single cancer is not a homogenous mass of cells, but, on the contrary, is composed by several different cell types, displaying a wide spectrum of differentiation and proliferation abilities. Therefore, one of the major areas of focus while trying to unravel the mysteries of cancer has been looking at the genes involved in cancer stem cell formation.

Genes act as the fundamental instructions for forming the protein blocks required to build every cell in your body. The combination of all the genes active in a given cell type at a precise time point, will finally determine the identity of the cell itself. While the cells in your body have differentiated into many different specialised cells, they all have one thing in common: every cell contains the exact same set of genes. What distinguishes them is the specific set of genes that are turned on, or expressed. For example, though a neuron cell has all of the same genes as a skin cell, it only expresses the genes needed to keep a neuron functioning. Dr Riggi's cancer biology career began under the mentoring of Dr Stamenkovic, with an interest in understanding what was going on with the genes in cancer stem cells that allowed them to switch on stem cell like capabilities.

When comparing embryonic stem cells to cancer stem cells in paediatric and adult tumours, Dr Riggi and his colleagues discovered a few interesting similarities, and important differences. Abnormal behaviour of adult cancer cells can often be attributed to the build-up of genetic mutations in genes that normally tell a cell that it cannot

‘We utilise a translational approach involving several national and international collaborations, facilitating the access to cutting-edge technologies and the rapid bench-to-bedside translation of the most relevant and clinical impactful findings’

keep dividing. This means adult cancers most often occur when a gene that was supposed to be on is damaged such that it is permanently turned off. However, Drs Stamenkovic and Riggi found a different situation in paediatric cancer cells. Unlike adult cancer cells, paediatric cancer cells have very few genetic mutations, but numerous genes turned on that are normally only expressed in normal stem cells. The gene profiles of paediatric tumours more closely resemble those of embryonic stem cells, in some cases requiring only a single mutation of a key gene to start the cancer development. To Drs Stamenkovic and Riggi this indicated that paediatric tumours have a different cause and distinctive behaviour compared to adult tumours, spurring further research into the unique biology of paediatric cancer.

MicroRNAs and Major Possibility

Since every cell shares the same set of genes, the team turned their focus to the factors that control which genes are turned on and off – a diverse set of mechanisms commonly lumped under the term epigenetics.

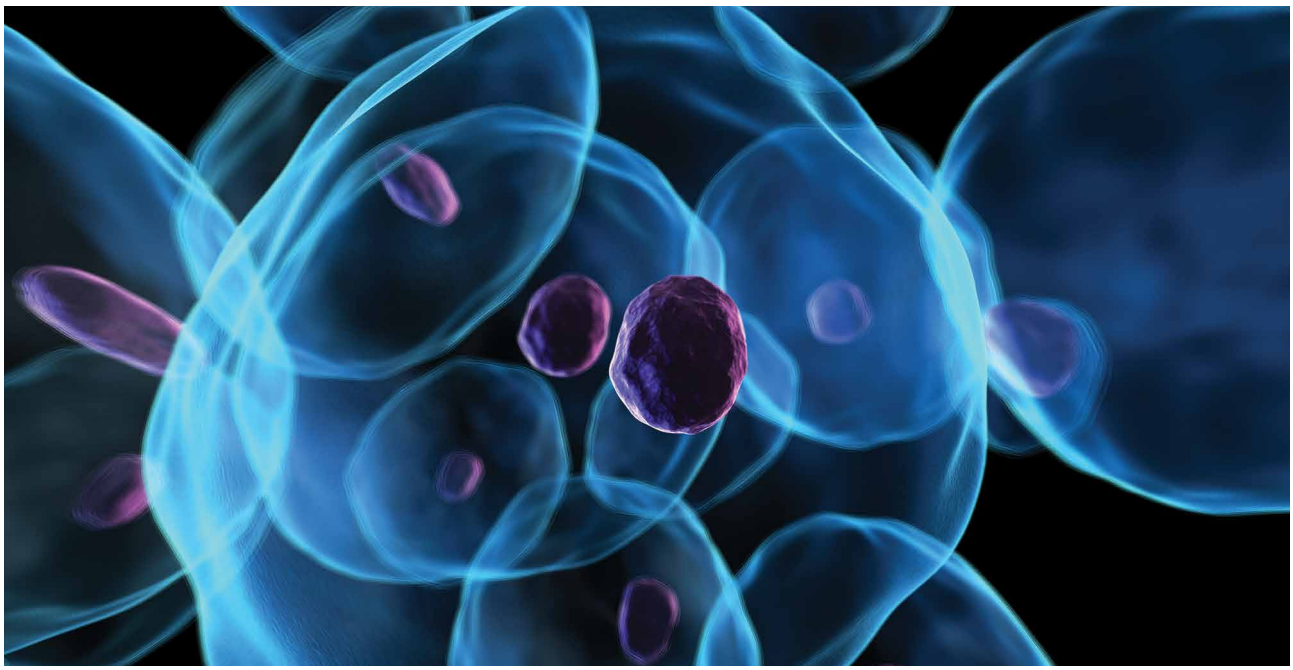
Epigenetics literally means ‘above genetics’ and refers to a suite of controls that our cells use to regulate gene activity. These controls determine how cells differentiate from stem cells, and how differentiated cells behave under different conditions. While epigenetic mechanisms are massively important to understanding many aspects of biology, most of them have only been discovered in the past 20 years, and as such epigenetics is a relatively new branch of science.

In the team’s initial paediatric Cancer Cell work, they discovered that deregulation of an epigenetic mechanism governed by microRNAs (miRNAs), may underlie the emergence of cancer stem cells in some paediatric tumours. miRNAs are tiny strands of nucleotides that bind to certain pieces of our gene sequence to regulate normal gene activity. Drs Stamenkovic and Riggi found that the activity of a specific group of microRNAs was reduced in both embryonic stem cells and paediatric cancer stem cells. Further, the expression level of a gene known as TARBP2 predicted the levels of microRNA that would be found in the tumour. Whereas tumour cells with higher levels of TARBP2 mostly displayed terminal differentiation, the depletion of TARBP2 was associated with an increase in cancer stem cell properties.

Drs Stamenkovic and Riggi took this discovery a step further and treated cancer stem cells with a compound that stimulates the activity of TARBP2. To their excitement, the addition of this compound disrupted stem cell-like growth. The cancer cells were no longer able to continue cloning themselves or forming new growths of differentiated cells. The compound restored normal microRNA levels and tumour growth was effectively halted. This discovery provides the possibility of a promising treatment for this class of aggressive paediatric cancers – one that could prevent the cancer from growing and surviving traditional cancer treatments.

Stopping Paediatric Cancer Before It Starts

While microRNAs led Drs Stamenkovic, Dr Riggi and their colleagues to a promising treatment option, they were still interested in understanding how the cancer came to be



in the first place. The paediatric cancers that the research team focuses on – a class of bone cancers known as Ewing sarcomas – tend to be very aggressive and fast growing, so pinpointing the processes at the initiation of the tumour could provide a basis for future early detection and prevention that could save lives. Unlike the vast majority of adult cancers, which are typically associated with genetic mutations in numerous genes, Ewing sarcoma is invariably tied to a single abnormal gene product. Despite the discovery of this genetic alteration more than 20 years ago, the mystery of how this abnormality tied into the onset of Ewing sarcoma remained unsolved.

The gene product in question is known as EWS-FLI1. The presence of the abnormal EWS-FLI1 protein characterises paediatric Ewing sarcoma. It had been previously shown that Ewing sarcoma cancer cells cannot survive without the protein, and the protein has the ability to transform normal cells into cancerous cells. This alteration occurs when the normal EWS gene, whose function is poorly understood, fuses with a gene coding for a transcription factor known as FLI1, during a rare abnormal genetic event known as a chromosomal translocation. Transcription factors are proteins that bind to specific sequences in our genome, and dictate the increase or decrease in expression of specific target genes.

The team made the fascinating discovery that the abnormal EWS-FLI1 protein is so effective at creating tumours because it utilises two distinct modes of driving cancer cell formation. The strategy it takes depends on the ability of EWS-FLI1 to bind different but specific genomic sequences: at some genomic locations EWS-FLI1 works by displacing healthy transcription factors and turning off target genes needed to prevent a tumour, while at others it hijacks normal epigenetic processes to turn on and enhance genes that lead to cell proliferation and cancer development. While the team focused on the intricacies of Ewing sarcoma to make these discoveries, this new understanding of how the malfunction of a solitary gene product creates multiple routes to cancer has the potential to serve as a template for understanding the development of other types of paediatric tumours where a single genetic event may play the key roles.

Illuminating the Role of Epigenetics in Cancer Biology

While Drs Stamenkovic and Riggi's research has shed light on how tumours begin and a potential way to help end them, they are also interested in understanding what goes on within the tumour while it is growing. An important factor in the treatment strategy for a given tumour is the degree of tumour heterogeneity. Tumour heterogeneity refers to the presence of multiple different cell subpopulations, both within and between tumours in the same patient. Highly heterogeneous tumours can be more challenging to treat because different cell subpopulations often require different medications to destroy the cancer completely. Understanding the mechanisms that drive tumours to become more heterogeneous could help lead to novel treatments that require less medications and less strain on the patient.

Epigenetic processes, particularly those that allow cancer cells to behave like stem cells, likely play a large role in the development of distinct cell subpopulations within a single tumour. By studying the mechanisms that allow a differentiated cell to be reverted back into a stem cell, or to be directly converted into a different cell type, Dr Stamenkovic, Dr Riggi and their colleagues have identified multiple potential pathways by which cancer cells may be formed and may create heterogeneity in a tumour. Their work has determined numerous transcription factors and epigenetic mechanisms that may play a role in the development of stem cell properties in cancer cells, and begun to identify potential targets for future research that could inform treatment strategies for some of the most difficult to treat paediatric cancers.

Drs Stamenkovic and Riggi's work has revealed some of the intricate mechanisms through which cancer hijacks our genes to create destructive cancer stem cells. Their current research seeks to continue shining light on the inner workings of cancer by delving deeper into the genetics and epigenetics that underlie tumour formation, particularly in paediatric cases. Drs Stamenkovic and Riggi's primary goal is to use cutting-edge science to develop innovative and effective treatment and prevention measures for cancer.

Meet the researchers

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Dr Nicolo Riggi completed his MD at the University of Lausanne in 2001, and went on to obtain a PhD in Cancer Biology in 2009. He completed his residency in Pathology at University Hospital Lausanne, Switzerland and worked as a post-doctoral research fellow in Cancer and Epigenetics at Massachusetts General Hospital and the Broad Institute of Harvard and MIT in Boston, Massachusetts. Dr Riggi is currently an Assistant Bursary Professor of Experimental Pathology at the University of Lausanne, where his laboratory's research focuses on the epigenetic mechanisms involved in malignant cancer development and tumour composition in paediatric patients.

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Dr Stamenkovic obtained his MD from the University of Geneva in 1978. Following a residency in Internal Medicine and a residency in Pathology, he moved to Boston for a post-doctoral fellowship in the laboratory of Dr Brian Seed in the Department of Molecular Biology at the Massachusetts General Hospital and the Department of Genetics at Harvard Medical School. In 1988, he was appointed Assistant Professor of Pathology at Harvard Medical School and in 1990 he started his own laboratory in the Department of Pathology at the Massachusetts General Hospital, with a joint appointment at the MGH Cancer Centre. In 1992, Dr Stamenkovic was appointed to Associate Professor of Pathology at HMS and Director of the Molecular Pathology Unit within the MGH Cancer Centre. In 2001, he accepted a position as Professor of Experimental Pathology at the University of Lausanne.

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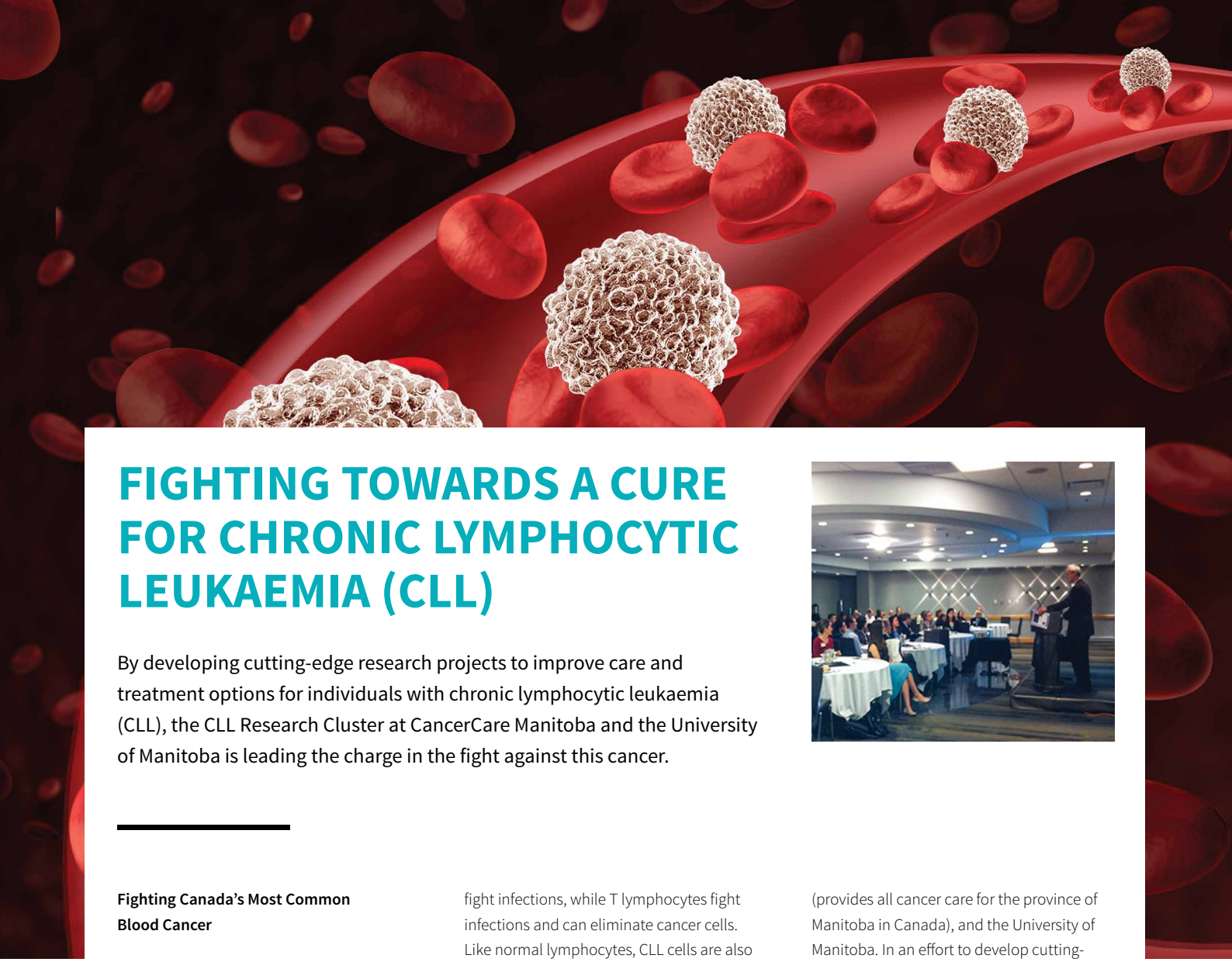

FIGHTING TOWARDS A CURE FOR CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

By developing cutting-edge research projects to improve care and treatment options for individuals with chronic lymphocytic leukaemia (CLL), the CLL Research Cluster at CancerCare Manitoba and the University of Manitoba is leading the charge in the fight against this cancer.

Fighting Canada's Most Common Blood Cancer

A cancer diagnosis is always difficult to accept, particularly if the cancer is incurable. Such is the case with chronic lymphocytic leukaemia (CLL), the most common type of adult leukaemia in Canada. This cancer is mainly diagnosed in older people, although one-third are less than 65 years. The rates of this cancer are also on the rise due to the ageing population. Although current treatments for this disease are generally effective, relapse does occur and there is an increased risk of developing infections and additional cancers. The prognosis for this disease is highly variable, ranging from a stable condition to rapid disease progression.

CLL is characterised by an accumulation of abnormal B lymphocytes in the blood, bone marrow, spleen and lymph nodes. Normally, lymphocytes function as part of the immune system within the lymph node network and at these sites lymphocytes are nurtured and stimulated to divide and grow. This milieu is termed the microenvironment. The normal function of B lymphocytes is to produce antibodies (immunoglobulins) to fight infections, while T lymphocytes fight infections and can eliminate cancer cells. Like normal lymphocytes, CLL cells are also nurtured and stimulated to grow in the lymph node microenvironment.

As CLL progresses, there can be a progressive drop in blood counts due to the replacement of bone marrow, leading to tiredness, bleeding and risk of infections. In addition, over time the immune system (B and T lymphocytes) loses its effectiveness (called immunosuppression) resulting in an increase in the incidence of infections and second cancers. Dr Spencer Gibson and Dr James Johnston at CancerCare Manitoba have previously published a study demonstrating that skin cancers occur five to ten times more frequently amongst patients with CLL, when compared to people without CLL, and that CLL patients are also two times more likely to develop other types of cancer, such as bowel, breast or prostate cancers. This increased incidence of second cancers is a unique feature of CLL.

The Research Institute in Oncology and Haematology (RIOH) is a partnership organisation between CancerCare Manitoba (provides all cancer care for the province of Manitoba in Canada), and the University of Manitoba. In an effort to develop cutting-edge treatments and improve the care of people with CLL, Dr Spencer Gibson and his colleagues established the CLL Research Cluster, a patient-centred research program and a joint research venture between the University of Manitoba and CancerCare Manitoba. This cluster comprises an integrated multidisciplinary team conducting research in basic science, clinical care and epidemiology. Two major themes will be addressed by the CLL Research Cluster: first, the development of new therapeutic and management strategies for patients with CLL, and second, to develop a better understanding of the biology of metabolism and migration in CLL. These discoveries can then be translated into improving patient care, survival and quality of life.

Improving Patient Management

The Cluster's work can be divided into four main projects focused on improving patient management, optimising clinical care, developing novel therapies, targeting CLL metabolism and using innovative

‘Understanding the biology behind cancer cells gives us the necessary context to develop therapies that can kill cancerous cells, but not the normal cells that surround the cancer. That is one of the major challenges in cancer therapy today.’

technology to investigate CLL cell migration. The projects are designed to integrate research into patient-focused programs with attainable outcomes. The cluster is also committed to an integrated knowledge translation strategy that will shape the process and dissemination of research with the underlying principle of ‘from bedside to bench and back again’. This employs a model where CLL patients are seen in a centralised clinic, patients’ samples are collected and stored in a biobank, provincial health care databases are linked, and innovative technologies are utilised. This combination is unique to Canada and will serve as the foundation for our research.

The first project, Improving Patient Management, is based on the hypothesis that comorbidities – such as high blood pressure, high cholesterol and diabetes – may increase the rate of progression of CLL and impair the immune system, leading to a higher risk of infection and second cancers. Because survival is inversely related to the number of illnesses and second malignancies experienced by a patient, the team aim to identify what factors contribute to these complications, allowing for better monitoring and treatment.

A retrospective study will analyse a decade’s worth of clinical details using CAISIS – an innovative CLL patient database that links clinical features and outcomes with biomarker data from the CLL biobank housed in CancerCare Manitoba. This will be followed by a prospective study in which the physician of every Manitoban CLL patient will be provided with current CLL guidelines to ensure standardised investigations and follow up. The researchers will then analyse which clinical factors are significantly associated with disease progression, infections and second cancers to allow for appropriate monitoring and cancer screening. The changes in the immune system of CLL patients will be assessed using advanced confocal microscopy and flow cytometry technologies. Understanding the specific changes in immune cell populations and functions may also help predict the risk of life-threatening infections or second malignancies. CLL patients will be assessed for major subsets of T lymphocytes, monocytes and natural killer cells, as well as expression of activation markers and immune checkpoint receptors in the patient’s immune system. The association of changes in the immune system with patient outcomes will be determined and this may identify new predictive biomarkers useful for clinical decisions regarding immunisations, infectious disease treatment or monitoring for second malignancies. By uncovering these associations, physicians will be better equipped to monitor high risk patients and educate patients and caregivers.

The second aim of the project explores the factors associated with the referral of CLL patients to specialist care. The team have shown that non-referred CLL patients have a much shorter overall survival than referred patients, and this is particularly true for the elderly who are more likely to receive chemotherapy if referred. Thus, the team aims to determine if there is a difference in the referred and non-referred cohorts regarding clinical features, social factors, illnesses and healthcare utilisation. A retrospective study will explore the factors that decide whether or not patients are referred to the CLL clinic. The outcomes of this decision, including differences in survival, causes of death, quality of life and progression of disease at referral will also be investigated. It will also address differences in costs associated with referred and non-referred patients. A prospective study will then follow, which compares survival and healthcare utilisation in referred and non-referred patients, in order to demonstrate the effectiveness of distributing CLL guidelines to physicians. It is hoped that this will influence the survival of non-referred patients through increased education of primary care providers.

Clinical Trials to Improve Patient Care

The second project contains two branches that aim to optimise clinical care. Patients with infections and low antibodies are eligible for immunoglobulin replacement. Traditionally this has been done intravenously (into the blood). The first branch is a provincial pilot program that trains patients how to self-administer subcutaneous immunoglobulins (SCIG) at home, rather than requiring intravenous immunoglobulins in a hospital setting. SCIG has been shown to yield high and stable immunoglobulin levels and is well tolerated with few side effects. The team hypothesises that SCIG will be cost effective in reducing the incidence of infections as well as increasing the quality of life of CLL patients. The approach involves analysing clinical characteristics in order to predict which patients may benefit from SCIG as well as conducting a cost-benefit analysis to track savings to the healthcare system

against the resources required to support the SCIG program versus intravenous immunoglobulin treatments.

The second branch of this project is a Phase II clinical trial to test gefitinib as a new cost-effective and specific treatment for CLL patients with ZAP-70 positive CLL. Gefitinib is already a commonly used and well tolerated treatment for lung cancer, but the CLL Research Cluster has shown that it can also kill ZAP-70 positive CLL cells in the laboratory. ZAP-70 is present in half the cases of CLL and is a marker of aggressive disease. This clinical trial will determine whether gefitinib targets CLL cells in patients, without damaging the normal lymphocytes or bone marrow.

In a recent study, the team looked at the effects of siramesine on CLL cells. Siramesine is another drug that has been shown to mediate cell death in other cancers through lysosome membrane permeabilisation (LMP). Lysosomes are cell organelles which contain many different types of enzymes, and are involved in the digestion and removal of waste products from the cell. The team found that CLL cells contained many lysosomes, and were very sensitive to siramesine. Other lymphocytes were not affected by siramesine. Therefore, targeting lysosomes could be a novel therapeutic strategy for CLL patients. The researchers will further determine the clinical relevance of this treatment for CLL patients using the knowledge gained from the clinical trial above.

Innovative Experimental Technology

The third project will investigate novel targets of CLL metabolism. Because cancer cell metabolism has adapted to support high rates of cell proliferation and growth, targeting metabolic pathways in CLL may be effective in preventing and treating disease. Researchers hypothesise that metabolism altering drugs such as metformin and statins will reduce CLL incidence and improve overall survival. First, a population-based study will assess the relative risk of CLL initiation in connection to the duration and dose of metformin or statins use before diagnosis of CLL. Secondly, a prospective study will compare overall and progression-free survival of patients with and without metformin or statin use after diagnosis. The team expect that metformin and statin use will be associated with a lower incidence of CLL and increased survival in patients affected patients.

This project's second study will investigate how the drug FK866, an inhibitor of cancer cell metabolism, could be used in combination with other chemotherapeutic drugs. FK866 is known to inhibit NAMPT, an enzyme that promotes B-cell maturation, and is highly expressed in cancer cells. When treated with FK866, CLL cells show a time dependant loss of energy and increased production of oxidative species leading to cell death. However, the mechanisms by which this occurs are not well understood. Therefore, the team aims to understand this process in order to best utilise this drug as part of CLL treatment. They also aim to evaluate if there are additive, synergistic or antagonistic effects of combining FK866 with other chemotherapies.

The final project makes use of innovative technologies to investigate the migration capacity of CLL cells, and determine how this correlates with clinical and prognostic markers. CLL cell migration enables cancer cells to escape from cell death, leading to drug resistance. Novel technologies give researchers the ability to quantitatively assess migration behaviours at a single cell level and assess the impact of novel kinase inhibitor therapeutics on migration behaviour.

CLL cell migration enables cancer cells to escape from cell death and causing drug resistance. A microfluidic chamber developed by the group offers the ability to quantitatively assess migration behaviours at a single cell level. The chamber will also allow for analyses of CLL cells to gain new insights into the role of phosphatidylinositide 3-kinases (PI3Ks) in CLL cell migration. PI3Ks are enzymes involved in certain cellular functions of cancer, such as cell proliferation, migration and survival. The team hypothesises that a distinct branch of the PI3K signalling network mediated by PI(3,4)P2 (an intracellular signalling molecule) controls the migration of CLL cells. They aim to determine the functional impact of PI(3,4)P2 signalling in CLL migration as well as the impact of PI3K inhibitor therapy on migratory behaviours. This is clinically important, as a new therapy targeting PI3K using a drug called Idelalisib is being used to treat patients that have failed front-line therapy. The hope is that this innovative technology will provide new insights into how PI3K targeted drugs could be even more effective.

Mentoring the Researchers of Tomorrow

Running alongside these projects is a novel mentoring programme, in which senior scientists mentor young investigators in their first five years of research. As well as receiving advice on experimental design, support in obtaining grants, and exposure to different research areas, the programme will permit expansion of young investigators' overall research programmes. Junior scientists will also gain experience in mentoring the next generation of researchers through co-supervision of trainees. Finally, they will be encouraged to present their research at national and international conferences and develop collaborations beyond the research cluster.

Meet the researchers

Dr Spencer Gibson, Head of Cell Biology in the Manitoba Institute in Oncology and Hematology and leader of the CLL Research Cluster, is an expert on the mechanisms of cell survival and cell death, in the context of the mechanisms of action of cancer therapeutics.
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University of Manitoba

CancerCare Manitoba

FROM HUMAN TO HORSE HEALTH

So far, the research showcased in this edition of Scientia has been focused on improving human health. But what about our equine friends? Our close relationship with horses dates back to around 4000 BC, and domesticated horses are thought to have been widespread by 3000 BC. These estimates are based on archaeological evidence from sites in Kazakhstan and Ukraine, and later throughout Europe, where horse skeletons have been discovered at many human settlements. Now quite genetically distinct from their wild ancestors, domesticated horses are believed to have been bred from a large number of mares, but very few stallions. This is reflected by the results of genetic analysis, which shows a wide variation in horses' mitochondrial DNA (inherited through the maternal line), but very little in their Y chromosomes (inherited from father to son).

Although historically employed in transportation, agriculture and warfare, horses are now more commonly bred as companions, and for both leisurely and competitive riding. Indeed, horseracing has grown to become an enormous industry, being worth an estimated £3.4bn in the UK alone, according to a 2013 study commissioned by the British Horseracing Authority.

To reduce financial and welfare impacts on the equine industry, much recent research has been dedicated to improving the health of these majestic beasts, and helping them to recover from injury.

At the forefront of this research is Professor Christine Theoret at the University of Montreal, who has dedicated her career to understanding wound healing disorders in horses. Injuries and wounds are extremely common in horses, and are a leading cause of death in young foals. To reduce this suffering, Professor Theoret's team investigate the genetics associated with problematic healing, in addition to advancing stem cell therapies to create skin substitutes for horses. As humans possess similar 'tight skin' that is not amenable to wound contraction, the results of Professor Theoret's work may also be carried over to the field of human wound healing and scar formation.

Also working to boost the health and wellbeing of our equine allies are Dr Julia Felippe and Dr Rebecca Tallmadge of Cornell University. The pair has been gaining insight into the development and function of the horse immune system, and are applying their new knowledge to help immunodeficient horses and young foals that are especially susceptible to infection. By unravelling the epigenetic factors that lead to a cessation of B cell production (a particular type of immune cell), the researchers are coming up with new ways to reactivate their creation.

THE HORSE AS A MODEL FOR THE STUDY OF HUMAN WOUND HEALING DISORDERS

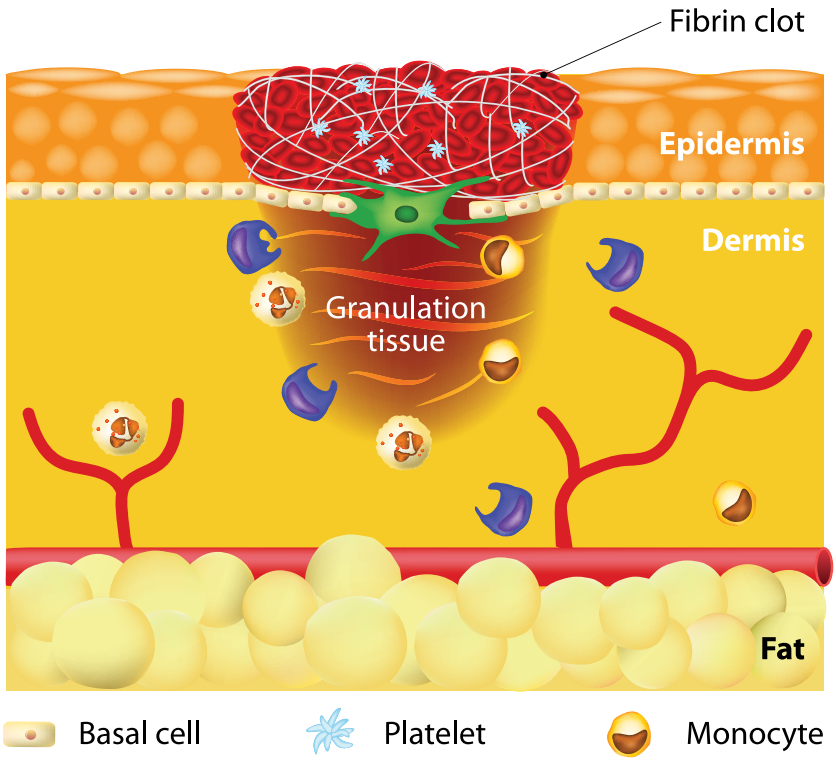
Professor Christine Theoret at the University of Montreal studies dermal fibroproliferative disorders in horses with the aim of reducing financial and welfare impacts on the equine industry. The results of her work may also be carried over to the field of human keloids.

'Proud flesh'

Skin wounds exert a tremendous emotional and financial impact on horse owners and on the equine industry. Wounds in horses are difficult to treat and frequently require multiple veterinary visits and interventions. Moreover, when wounds are located on the legs of horses, they commonly lead to the development of a dermal fibroproliferative disorder. In humans, these benign tumour-like growths are referred to as 'keloids', while in the horse they are coined 'exuberant granulation tissue' or 'proud flesh'. These lesions present cosmetic concerns and functional problems often leading to lameness, since they are most frequently located on the legs. Upon beginning her surgery residency and graduate training in Western Canada, Professor Theoret noticed the large number of horses suffering from skin wounds. 'I was confronted with numerous serious skin wounds in horses kept in pastures fenced with barbed wire,' she recalls. Because horses are prey, they normally attempt to flee when feeling threatened. For horses kept in pastures with barbed wire fences, this response can result in deep and extensive lacerations that may never fully heal. Injuries, wounds and trauma are cited as the most common medical condition affecting horses and as a leading cause of death in foals less than 6 months old. In addition to the financial burden caused by slow wound healing, proud flesh is a significant welfare concern. For this reason, Professor Theoret aimed her PhD studies towards an improved understanding of wound healing in horses. 'I sought to improve my understanding of the physiopathology of wound healing in this species, which apparently differed from what was described in other veterinary species, in an effort to accelerate the healing process and ameliorate its outcome,' she explains.

Suturing is required for 'first intention healing', and is mostly used for clean wounds in which the edges can be brought together without creating undue tissue tension. Conversely, 'second intention healing' is generally required for wounds with larger tissue defects and in which suturing the wound edges together is not possible. Large open wounds in horses are prone to a number of complications, including bacterial colonisation and infection, prolonging recovery. Moreover, like humans, horses have 'tight skin' that does not allow wound contraction. Instead, wounds healing by second intention do so mainly by the slow process of epithelialisation; this new epithelial cover is fragile and susceptible

‘We’ve developed and used an experimental equine model to study wound healing in an effort to better understand the mechanisms that govern this complex biological process in view of designing appropriate preventive and therapeutic strategies’



to reinjury. Most wounds in horses require open management with frequent bandage changes and multiple veterinary visits, often resulting in cost-prohibitive treatment plans. Although skin grafting is a viable option in other species, its use in the horse is limited by the scarcity of donor skin. Many adjunctive therapeutic approaches exist in the realm of equine wound care, including maggot debridement therapy, platelet concentrates, honey, negative-pressure wound therapy, and cell therapy, as described in the Equine Wound Management textbook edited by Professor Theoret and published by Wiley.

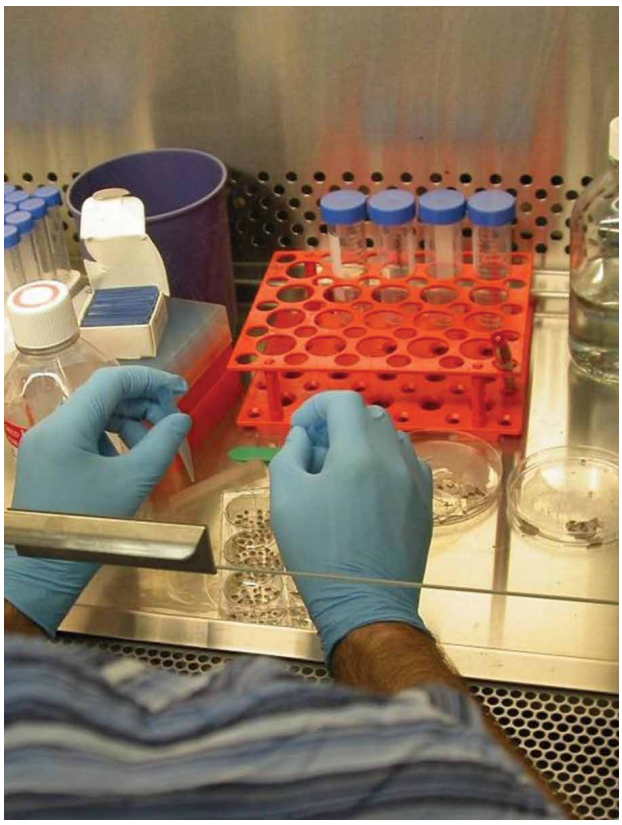
However, none of these alone is sufficient to uniformly accelerate second intention healing nor to prevent or treat common complications such as proud flesh.

Professor Theoret and her colleagues developed a model that enables the study of this healing disorder in horses, with the aim of improving the preventive and therapeutic options. They began by identifying specific equine genes associated with problematic healing in order to eventually target them for therapeutic purposes. Genes involved in inflammation, angiogenesis, epithelialisation and matrix remodelling were then cloned and the spatiotemporal expression of their associated proteins was mapped to distinguish their action during normal and pathologic healing.

Because molecules controlling angiogenesis were found to differ in wounds on the leg, which are prone to fibroproliferative disorders, the Theoret lab took a closer look at blood vessel development within the granulation tissue of wounds. Using transmission electron microscopy, they demonstrated that microvessel occlusion, due to endothelial cell hypertrophy, characterizes leg wounds developing proud flesh. The result of microvessel occlusion is poor perfusion, leading to hypoxia of the wound, as confirmed with infrared thermography and near infrared spectroscopy. Hypoxia present in leg wounds leads to a prolonged inflammatory response thereby delaying the progression of healing, since the ability of leukocytes to kill bacteria is oxygen-dependent. Additionally, profibrotic mediators are upregulated in response to hypoxia, thereby encouraging the production of extracellular matrix and, ultimately, promoting the development of proud flesh, or keloids.

The horse as a model to study wound healing in man

For obvious ethical reasons, it is difficult to study wound healing and scar formation in human subjects, yet scarring exerts an immense economic and social impact. For example, keloids are disfiguring and often pruritic and/or painful. In spite of the numerous therapeutic modalities currently in use including occlusive dressings, compression, corticosteroids, excisional surgery, radiation, cryosurgery, laser therapy, and anti-neoplastic drugs, the recurrence rate of keloids is very high. Horses may provide a superior model to study scarring compared to laboratory animals such as rats and mice because horses are the only known mammals (aside from humans) that naturally develop dermal fibroproliferative disorders. Only 53% of studies using rodent wound healing models yielded results likely to translate to improved clinical outcomes in human trials. This poor concordance no doubt reflects the numerous anatomic and physiologic differences between small mammals and humans. For example, mice heal primarily through contraction due to the presence of a muscle, the *panniculus carnosus*, in their subcutaneous tissues,



which is absent in humans and on the legs of horses. Morphologic similarities between equine 'proud flesh' and human keloid include excessive accumulation of extracellular matrix characterized by poorly organised collagen fibrils, and a thickened epithelial cover in mature lesions, as described in a collaborative study undertaken by Professor Theoret's team and researchers at the Baylor College of Medicine. Consequently, equine 'proud flesh' may offer researchers unprecedented opportunities to develop and test new treatments that should speed the healing process and counter fibrosis and scarring in all types of patients, thereby dually advancing veterinary and human wound care.

Professor Theoret's experimental equine model has garnered the attention of scientists studying human wound repair and she was invited to present this model at the Symposium on Fibrosis and Scarring of the NIH Center for Wound Healing Research, at a Gordon Research Conference on Tissue Repair and Regeneration, and at the First International Keloid Symposium. However, Professor Theoret openly discusses limitations to using the horse as a model and areas in which the scientific community can improve upon. Unlike mice, horses are large and expensive to maintain, requiring housing and research facilities available only in certain research centres or veterinary schools. It is difficult to examine gene regulatory mechanisms and signal transduction pathways due to the paucity of equine cell lines and reagents. But Professor Theoret is confident that with the increasing use of next-generation sequencing she and her team will be able to provide more information on the genomics behind wound healing and repair in coming years. 'Although the use of horses as translational models is not appropriate or practical for widespread use in wound healing research, I think my model may be superior for specific investigations, for example those relating to naturally-developing fibroproliferative disorders.'

'My childhood Christmas wish list always included a horse. Although I never found one under the Christmas tree, I eventually became an equine surgeon and have dedicated my research program to improving equine welfare'

Regenerative wound repair

Skin, the largest organ of the body, is our first line of defence against many infectious and traumatic insults. Currently, there is no method of artificial skin replacement that results in complete emulation of the original tissue. Recent developments in stem cell therapy have prompted scientists to investigate this option for the generation of tissue-engineered constructs. Professor Theoret tells us about her work in this area: 'We recently developed an efficient protocol to differentiate equine induced pluripotent stem cells (eiPSC) to a keratinocyte lineage (eiPSC-KC), thereby achieving an important advancement for equine regenerative medicine since, in principle, eiPSC should provide an inexhaustible source of cells that might be used to engineer a fully functional skin substitute for horses suffering from wounds or skin disease.'

While stem cell therapy often faces controversy, generation of iPSC does not require the destruction of an embryo and iPSC have a much lower probability of immunological rejection since cells obtained from the patient's own tissues may be grafted. By marrying eiPSC-KC with technologies like autologous equine platelet-rich fibrin gel and tissue scaffolding, regeneration may occur with fewer errors in migration, proliferation, differentiation and orientation. Stem cells also possess chemotactic properties that may enhance the recruitment, to the site of injury, of native cells critical for proper regeneration.

Future directions

The next steps for Professor Theoret's group include grafting eiPSC-KC on to horses and determining whether or not they have the capacity to regenerate a stratified epidermis with all of its components, and introducing eiPSC into different organs of the body to ensure that induction of differentiation is not variable. It will be necessary to test this approach in a large number of subjects because biological therapeutics are generally inconsistent in their success due to variations in host immunity. If these trials are successful, iPSC-KC may eventually be utilised in the treatment of wounds. Ultimately, the goal is to reduce equine euthanasia rates and the proportion of horses retired from competition due to the effects of poor wound healing and associated dermal fibroproliferative disorders.

Meet the researcher

Professor Christine Theoret

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Christine Theoret is currently a Professor in the Département de biomédecine vétérinaire and Director of the Comparative Veterinary Tissue Healing Laboratory at the Université de Montréal's Faculty of Veterinary Medicine. After obtaining her DMV degree at the Université de Montréal, she pursued MSc and PhD programs in veterinary surgery and molecular biology, respectively, at the University of Saskatchewan. It was also here that she completed her surgery residency and subsequently became a Diplomate of the American College of Veterinary Surgeons. She has served appointments as visiting professor at universities worldwide and has received multiple awards for leadership and teaching. She has served as advisor to a number of biotech companies and as board member for international associations, and sat a term as President of the Veterinary Wound Management Society. She has mentored numerous graduate and undergraduate students studying wound healing, new therapeutic modalities, tissue regeneration, and the role of the horse as a model for the study of human wound healing and scarring.

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ANTIBODIES, EPIGENETICS, AND A BIT OF HAY

Dr Julia Felippe and Dr Rebecca Tallmadge of Cornell University's College of Veterinary Medicine are attempting to understand the complex world of the equine immune system. We talk to them about their discoveries and plans.

Imagine a gingerbread house, tall as a mountain, warm and cosy, full of all the proteins and nutrients which you could possibly need to grow, reproduce, and start a giant family. Sounds tempting, doesn't it? This is you, from the point of view of the millions of microbes swarming over your skin, your hair, in your gut and in your nose. A delicious mountain of food protected only by the tireless defence offered by the bodies' own immune system. Small wonder then that those who lose this vital protection rapidly succumb to diseases which would barely even irritate a healthy individual.

There are many ways in which we can be left without a functioning immune system. Perhaps the most famous is AIDS, in which infection with HIV leads to a progressive loss of immune capability and eventual death from minor secondary infections. Otherwise known as immunodeficiencies, these situations are also brought about by cancer, by chemotherapy, by infections with various pathogens, even just by being born.

Just by being born?

Though we don't often think about it, an immune system *develops* – it expands in capabilities over time. Infections trigger expansions in antibody-producing cells which can target those pathogens, a memory of sorts which remains long after the infection is gone, protecting against the next infection (this, of course, is the basis of immunisation). The flip side of this, however, is that an immune system which has not yet had time to develop is also far weaker than it could otherwise be.

Although a large portion of the bodies' immune system is developed while in the womb, babies tend to be born in an immunologically 'naïve' state – they have not yet had any exposure to the outside world, full of bacteria and other antigens. This means that the intrinsic protection provided by exposure has not yet been developed and so newborn mammals have a much higher risk of catching disease than those just a few months older. To offset this window of vulnerability, the newborn receives the antibodies produced by its mother – these antibodies continue to circulate for a while after birth and so effectively act as a borrowed immune system. Borrowed, but not as effective as it could be; newborns ranging from human babies through to horse foals are highly susceptible to pathogenic attack.

Something old, something new, something borrowed

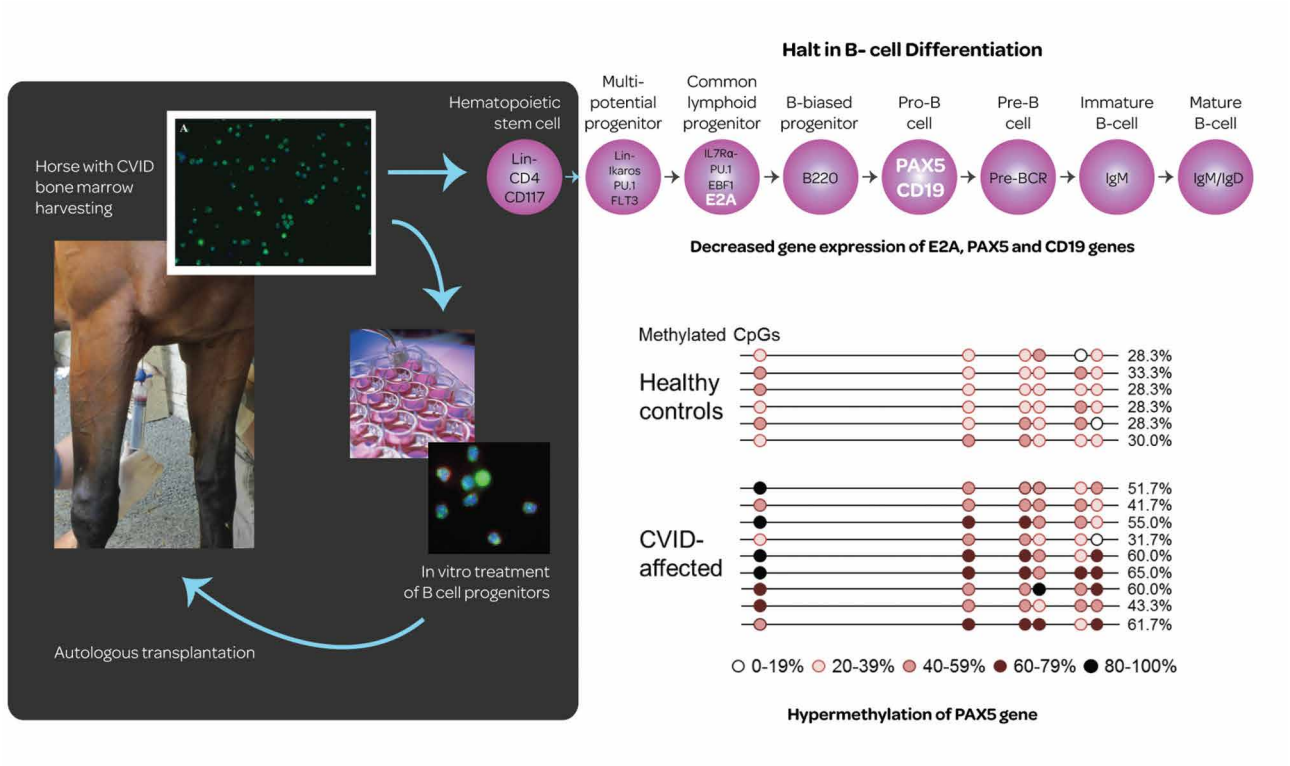
A cavalcade of complexity is thus occurring in a newborn, mixing new-developing with decaying-borrowed immune systems, all reacting to the colonisation of bacteria which occurs moments after being born. Sounds impossible to untangle? Even more complex when your subject is up and running around within hours of being born – as is the case with those who study the immunology of horses.

Untangling this complexity is the lofty goal of Dr Julia Felippe and Dr Rebecca Tallmadge, both of Cornell University. Dr Julia Felippe is one of the top researchers in the field of equine immunology, having spent the last 27 years either as a practicing equine veterinarian, studying equine clinical medicine, or researching equine immunodeficiencies and immunodevelopment. Dr Tallmadge is newer to the field than Dr Felippe, but nonetheless brings an exceptionally broad array of knowledge and experience derived from both equine immunology and genetics. As she comments, her current role allows her to 'provide insight from my training in equine immunogenetics – combining data we obtain in the lab with genome sequences to characterise the strength or limitations of an immune system, whether it be an immunodeficient horse or a young foal.'

Their studies focus on the role of the developing immune system in diseases such as those caused by pathogenic infections or developmental difficulties. The two have been, in Dr Tallmadge's words, 'gaining insight into the development and function of the immune system, then applying that knowledge to the benefit of immunodeficient horses and young foals during that period of time where they are especially susceptible to pathogens.'

These pathogens include particularly nasty examples such as *R. equi*, a dust-borne bacterium which, like the agent responsible for Tuberculosis, is able to avoid destruction by hiding within the lungs' own immune cells. By hijacking these cells, known as macrophages, *R. equi* is able to grow without fear of detection and thus can rapidly spread throughout the lungs, causing an often severe pneumonia. The bacterium is exclusively dangerous to newborn horses and foals, as (despite their loaned set of antibodies), they have yet to develop the innate immunity which would otherwise protect them from infection – this same effect can be seen in immunocompromised human or adult horse patients, who can be susceptible to the same disease.

‘The overall focus of our work is to gain insight into the development and function of the immune system, then applying that knowledge to the benefit of immunodeficient horses and young foals during that period of time where they are especially susceptible to pathogens.’ – Dr Tallmadge



The trick, then, is to develop a way to target a bacterium which can hijack and kill the very immune cells which are meant to be killing it. This sounds difficult, and indeed it is – despite many different approaches the only sure-fire way to induce a robust immune response in foals is to infect them with the microbe itself. As part of the road to better understand how the pathogen deceives the immune system, the group demonstrated the ability to make a miniature lung segment – complete with the ability to clean itself of inhaled dust, and then used this to watch in detail the manner in which *R. equi* infected macrophages. Knowledge of these processes allows the further development of targeted treatments, and indeed Dr Felippe has collaborated with other groups assessing effective non-infectious vaccines.

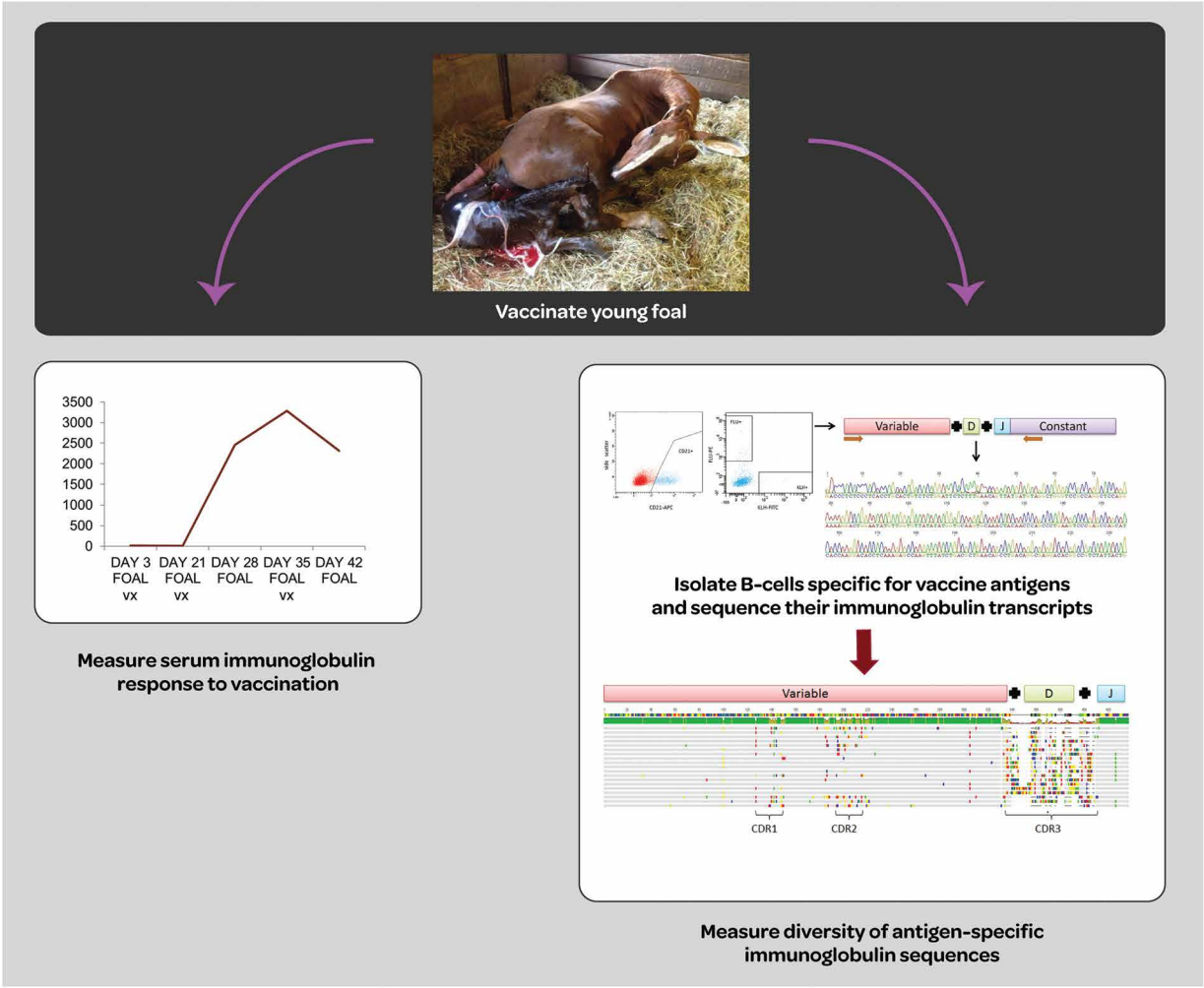
Epidemics of epigenetic

Another major focus of their work is known as common variable immunodeficiency (CVID for short). One mechanism involved is the sudden halt in the production of B cells within the bone marrow. As B-cells are the major source of antibodies within the body, this leads to a rapid drop in circulating antibodies and thus significantly weakens the ability of the affected horse to resist disease. CVID is a disease found both in horses and humans, though the origins of the symptoms often remain mysterious, as Dr Felippe explains: ‘though known in human patients for the last 6 decades, only about 10% of patients have been described with a genetic mutation, and the cause of disease is unknown for 90% of patients.’ The lack of a genetic source led her group to follow other possibilities, with the eventual discovery that, in her words ‘target gene expressions were downregulated in affected equine patients, and aberrant *epigenetic* mechanisms were associated with gene silencing, with the resulting halt in B cell production.’

Fine words, I hear you say, but what does this actually mean? The traditional view of genetics was that each trait held by a person or animal (strong legs, black hair, brown eyes) was the product of one or more genes, passed down from parents to children and set in stone from the moment of conception. This view turns out to be incomplete. There are a number of ways in which DNA can be modified at a later stage, changing the expression of the genes involved without modifying their basic code. The study of these secondary genetic factors is known as epigenetics, and this is the field in which Dr Felippe found herself.

Because CVID involves epigenetic mechanisms, can epigenetic factors also help to provide a cure? Bone marrow transplants are rarely used in humans with CVID to provide a fresh source of the precursor cells which can differentiate into B-cells – essentially overwriting the patients’ immune system with one from a healthy donor. Dr Felippe’s group is studying a novel approach, attempting to take the patient’s own derived bone marrow and reactivate the affected B-cell precursors using epigenetic modifiers. These cells can then be retransplanted into the affected horse, essentially allowing them to be the healthy donor for themselves.

Epigenetics are also involved in mediating the overall effect of other diseases such as equine herpesvirus-1 (EHV-1), a highly contagious virus which not only leads to neurologic damage but remains latent –



'once infected, infected forever' – even once apparently cured. Latent viruses such as EHV-1 tend to hide their genetic components within the bodies' own cells, safe from immunological response but able to reactivate at a later date. By testing the use of epigenetic modifier proteins (such as histone demethylase inhibitors), the group was able to control the expression and number of these genetic copies which occurred – an excellent first step towards developing therapeutics. Indeed, Dr Felippe is already thinking along these lines, as she comments 'our results are encouraging, and we are moving along in the path toward *in vivo* trials, then clinical trials.'

'In the last few years, we have developed tools and knowledge on equine hematopoietic regenerative medicine in order to promote B cell differentiation in vitro from bone marrow precursors of CVID-affected horses.' – Dr Felippe

Beyond a cure

Dr Tallmadge agrees with these plans, commenting that 'while we use basic science and not each experiment can be directly applied clinically, our projects address questions with biological relevance. Further, what is learned in one project can often be applied to the other project; that synergy reinforces the value of our efforts and findings, and further drives my motivation.' Both enjoy the opportunities which this work grants for teaching and educating the next generation of researchers. 'Training and enabling students and veterinarians in research is a major component of our work,' says Dr Tallmadge, 'it is not unusual for colleagues (often international) to visit our laboratory for specific training.' Dr Felippe notes that her work, as well as including teaching and lecturing, often involves her acting as a consultant for clinical veterinarians with particularly tricky cases.

Dr Felippe's work is not limited to horses, but extends to far larger mammals as well. In her own words, 'In the last decade, our knowledge and research tools have served projects in wildlife conservation and education in conservation. I am part of a team that studies disease risk factors for a rare population of Javan rhinos in Indonesia; through this program we also promote conservation education in the local schools and improve the capacity of local veterinarians.' The pair also does a significant amount of work studying those viruses threatening elephants as well – as Dr Tallmadge explains: 'I have had amazing opportunities to contribute to projects addressing a variety of species, including rhinos, elephants, and cats in addition to horses.'

There's an old joke that human medicine is much easier than veterinary medicine – after all, how hard can learning about a single species be? The wide range of projects, species, and talents that the two researchers at Cornell share between them would seem to prove this more than ever.

Meet the researchers

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Dr Tallmadge has been in the field of equine research for many years, beginning with her first scientific employment as a technician taking part in the horse genome project. This quickly led to other roles in equine science: a PhD project examining immunological proteins, postdoctoral work studying infectious diseases and immunodeficiencies, and her current role investigating CVID. Along the way she has placed her name on over 20 publications, several book chapters, aced a couple of mentoring roles and given more conference presentations than can be counted – Dr Tallmadge has certainly had her share of success.

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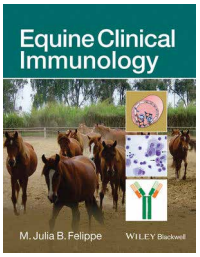

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Trees for Cities

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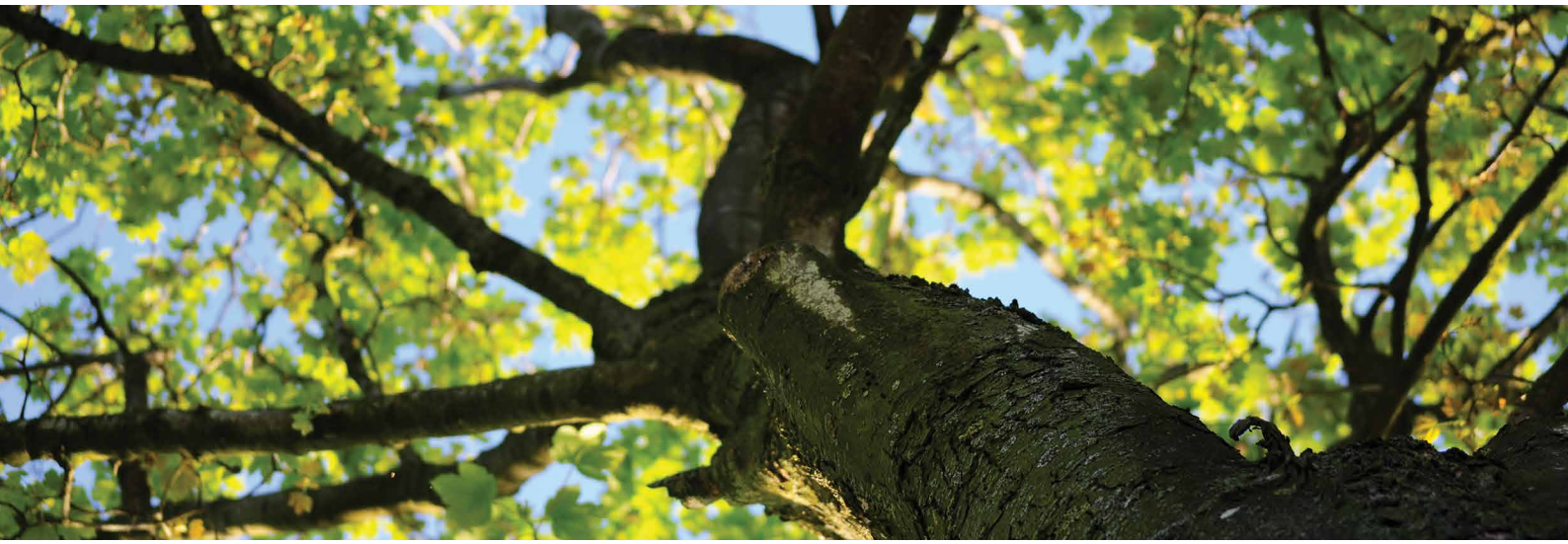

WHO WE ARE

Trees for Cities is the only charity working on an international scale to create greener cities. Since 1993, we have engaged over 70,000 people to plant over 650,000 urban trees in parks, streets, schools and housing estates across the UK, as well as internationally, revitalising these areas and improving the lives of the people who live in them. We strengthen communities through volunteering opportunities and inspire children to grow and eat good food and to connect with nature.

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We focus on planting trees and greening community spaces where the social and environmental impact on local people is greatest. In London this might mean planting trees to clean the air or transforming unused community spaces into vibrant green areas, making our communities happier and healthier places to live, whilst in Nairobi it's planting fruit trees for food and sustainable livelihoods.

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MISSION

- Planting trees and greening cities worldwide.

VALUES

- **People-led:** Although our reach is global, we value the importance of a local focus. We always work through and within local communities to strengthen them and empower their members.
- **Quality-driven:** Both the quantity and quality of the trees we plant are at the forefront of our planning so that we constantly strive to maximise the impact of our projects to the environment and society.
- **Delivery-focused:** We are an organisation that gets things done. What we talk about, we do – effectively, efficiently and on-time.

WHY TREES MATTER

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- They can cool the air by 2 - 8 degrees C
- Trees absorb water , lowering stress on storm water drains and mitigating flood risk
- A single mature oak tree can host up to 423 different species of invertebrates that support birds and mammals
- Each year Trees for Cities plant around 65,000 trees in cities worldwide, revitalising cities and enhancing the lives of the people that live in them.