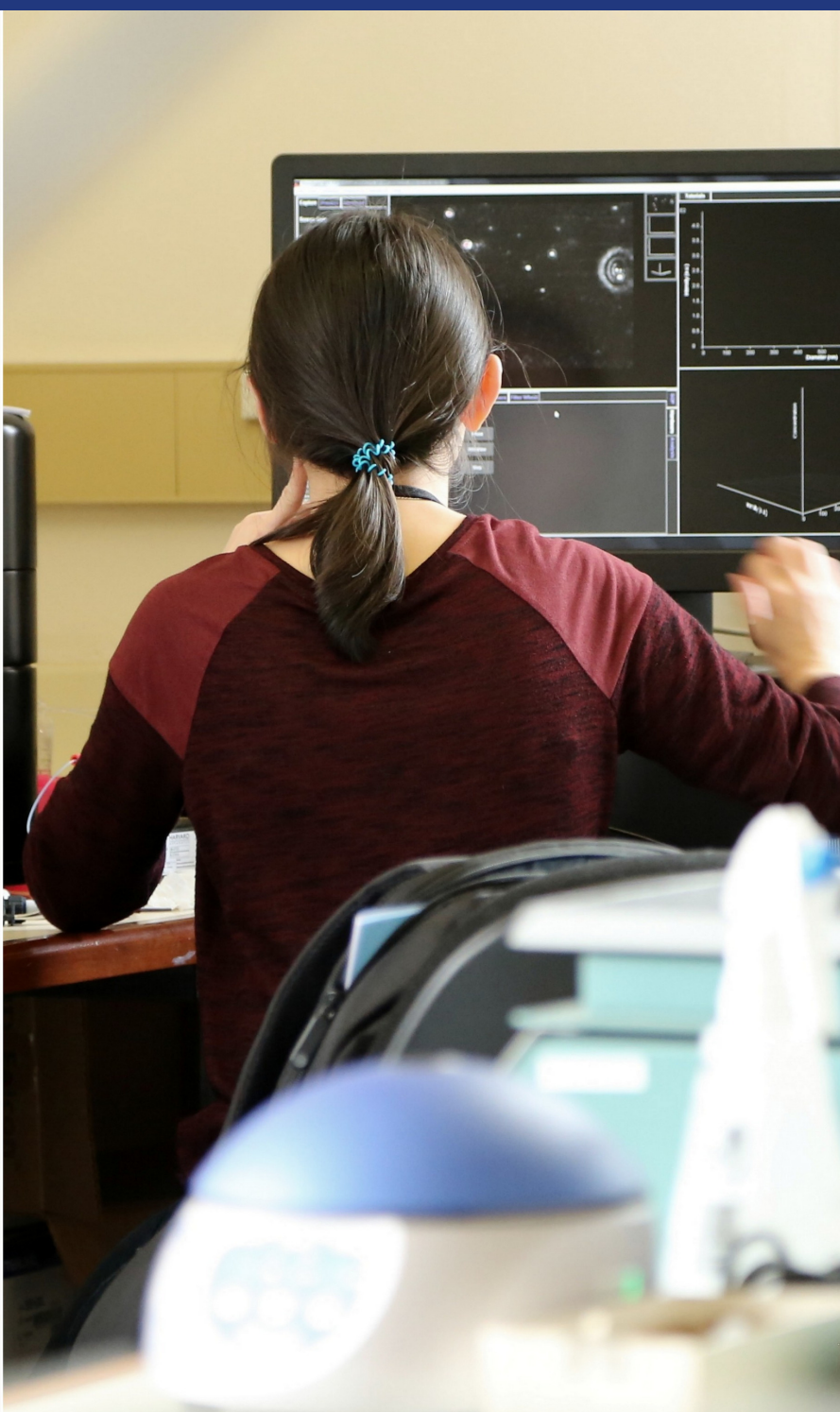


DISCOVERIES

In Medical Science



The Bosch Institute

The Bosch Institute is a major centre for medical research at the University of Sydney. The Institute's laboratories carry out research into the normal functioning of the human body and the way this changes in disease. The emphasis is on finding new ways of detecting, preventing, and treating human disease, and discovering the factors essential for the health of the individual. Our aim is to carry out fundamental research with projects that range from studies at the molecular level through to the application of research findings in a clinical setting.

Since our inception in 1995 the Bosch Institute has represented and facilitated research undertaken in the School of Medical Sciences, and in many other laboratories throughout the University of Sydney. The Institute now has over 70 member laboratories and 6 multi-user research facilities.

The Institute is named after George Henry Bosch, whose benefaction to the University in the 1920's has benefited the establishment of the Institute.

A special thank you
to the Bosch family and to the Sir Zelman Cowen Universities Fund
for their generous support at key stages of the Institute's establishment.

MESSAGE FROM THE EXECUTIVE DIRECTOR

This past year, 2016, was the 21st year of the Bosch Institute, which began in 1995 with a decision by two departments (Anatomy and Physiology) to develop a cooperative effort to build research infrastructure. Under successive Directors, this initiative has grown to be a networked Institute, which supports the work of the five disciplines of the School of Medical Science, and many other laboratories throughout the University of Sydney.

It is with great pride that I share with you *Discoveries*, a look back at some of our achievements over these 21 years, superb results in many areas of medical science. The following pages show how just a selection of our talented researchers have dedicated their careers to understanding the human body, the diseases that afflict us, and how they can be prevented, managed or cured. I am sure you will join me in celebrating these successes and our ongoing pursuit of answers to persisting mysteries of bodily function and to the continuing intractability of many diseases. The discoveries will over time touch not only us, but also the generations to come.

The legacy of our discoveries is testament to the support we have enjoyed and continue to receive from all parts of our community. It is with this help that our scientists are able to carry out this important work that will help to reduce the impact of these devastating diseases on our lives.

Professor Jonathan Stone DSc FAA
Executive Director
The Bosch Institute for Medical Research

Sydney, December 2016



Professor David Allen is a world-class researcher trained at University College London. David also spent 2 years at the Mayo Clinic where he made the first ever measurement of intracellular calcium in the heart. David has spent his career focusing on muscle cell function.

Professor David Allen is at the forefront of research into muscular dystrophy. Muscular dystrophy is a devastating genetic disease affecting only boys, caused by the failure of a single protein. It is marked by a progressive weakening and wasting of the body's muscles. Muscular dystrophy affects 1:3500 boys, having a devastating impact on their lives and on their families. David has reinvigorated the understanding of muscular dystrophy with his studies of intracellular calcium in mouse muscle fibres.

David and his team set about challenging the dominant belief that the absence of the single protein weakened the cell membrane causing muscle damage by calcium entry. The Bosch team discovered instead there was an abnormally regulated membrane channel that allowed calcium entry to the muscles. This discovery presents new thinking and offers the prospect of therapy by blocking the channel with a drug. Research groups around the world are now exploring treatments based on David's important discovery.

NEW THINKING | MUSCULAR DYSTROPHY



Emeritus Professor Roger Dampney is a leading researcher in cardiovascular-neuroscience research. Roger conducted his post-doctoral research at Cornell Medical College in New York and at the University of Milan. He is widely published, with over 140 articles written and being cited over 9,000 times.

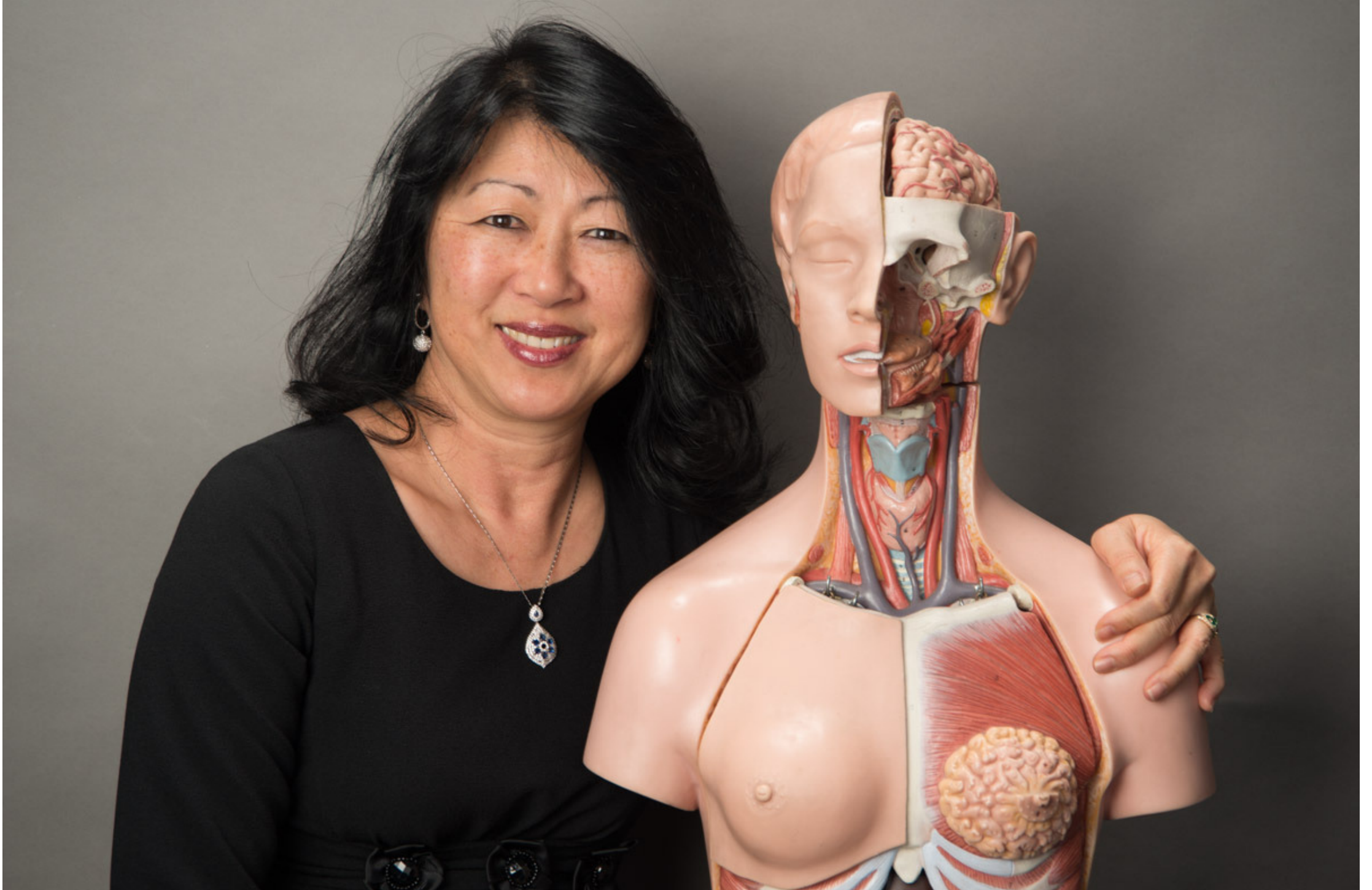
The hormone Leptin controls appetite and feeding, and also increases blood pressure. Professor Roger Dampney and his team discovered that Leptin increases blood pressure by an action on nerve cells in specific brain regions. Since Leptin levels in the body are increased in obesity, Roger hypothesised that this may be an important factor in causing obesity-related high blood pressure.

This hypothesis has since been supported by studies published in 2014 and 2016. These subsequent studies in mice, rabbits, and humans showed that the increase in

Leptin associated with diet-induced obesity increases blood pressure by an action on neurons in the brain regions first identified by Roger and his team. It was also shown that humans with a genetic Leptin deficiency have low blood pressure despite severe obesity.

The paper by Roger and his colleagues reporting this important discovery has been cited over 100 times. These studies pave the way for future work that may lead to the development of drugs that prevent high blood pressure that is commonly associated with obesity.

DISCOVERY | HYPERTENSION



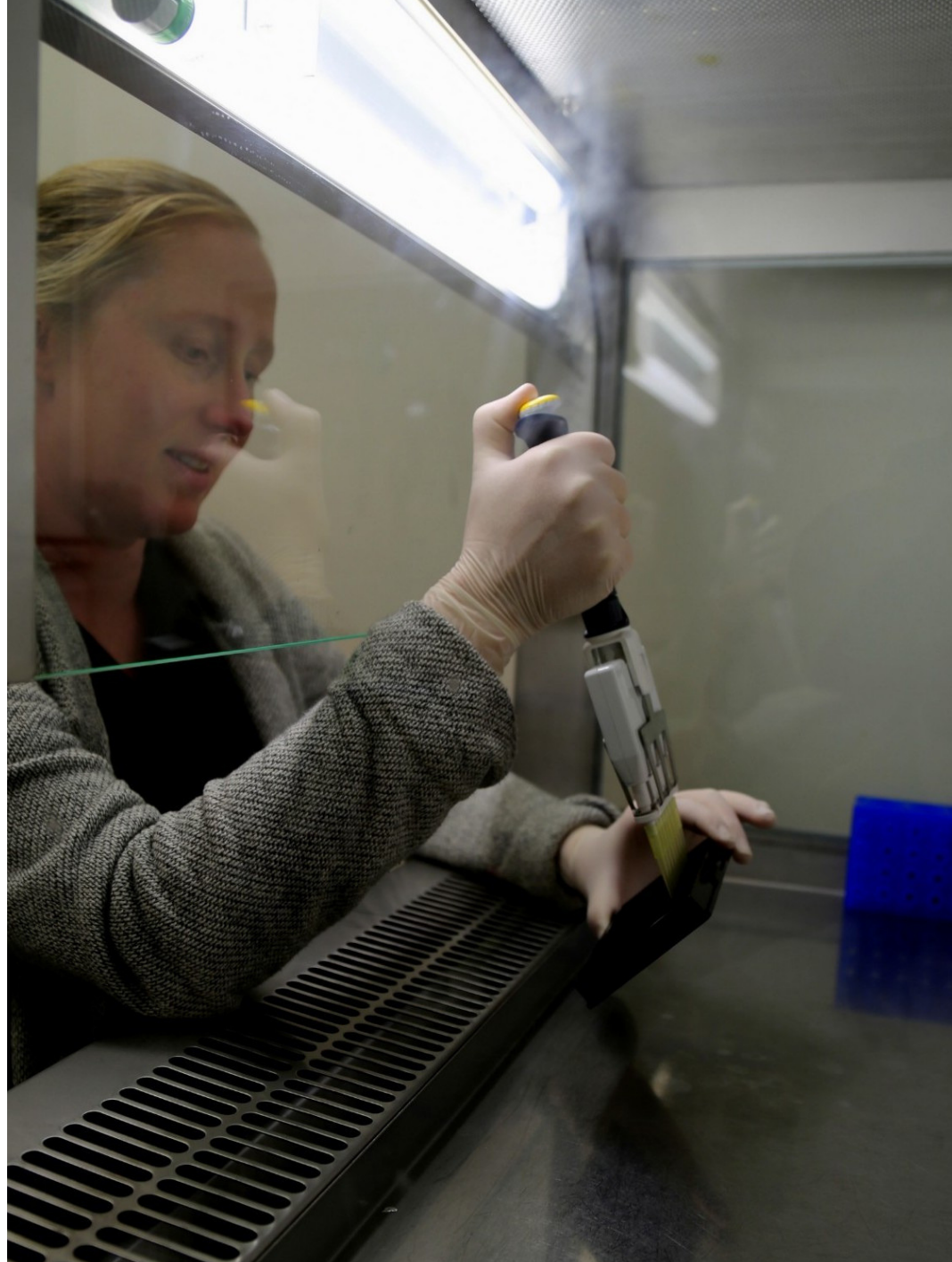
Professor Tailoi Chan-Ling is a highly regarded researcher with a passion for all things related to the eyes and brain. Tailoi trained as an optometrist gaining her Bachelor and Master degrees in Optometry, before going on to obtain a PhD in Corneal Physiology at the University of New South Wales. Tailoi is involved in many successful global research collaborations. She is currently Secretary of The International Society for Eye Research and Chair-Elect of the International Liaison Committee for Microcirculation.

Professor Tailoi Chan-Ling has made landmark contributions to the understanding of how blood vessels grow in the back of the eye and how this normal developmental process changes with disease. These insights have significant clinical relevance as diseases that affect the functioning of blood vessels are the leading causes of blindness in infants, young adults and the aged.

Through her research Tailoi has delivered key findings that are having a direct impact

on treatments. Her work, in collaboration with Professor Jonathan Stone also of the Bosch Institute, has provided the scientific basis for the development of anti-vascular endothelial growth factor (VEGF) drugs, which are currently utilised worldwide for the treatment of diseases that affect the functioning of blood vessels. Sales of these drugs are currently worth around \$4 billion p.a. This work has been recognised by *Nature* magazine, being identified as one of 13 classic articles on Angiogenesis.

LANDMARK CONTRIBUTION | **OPHTHALMOLOGY**



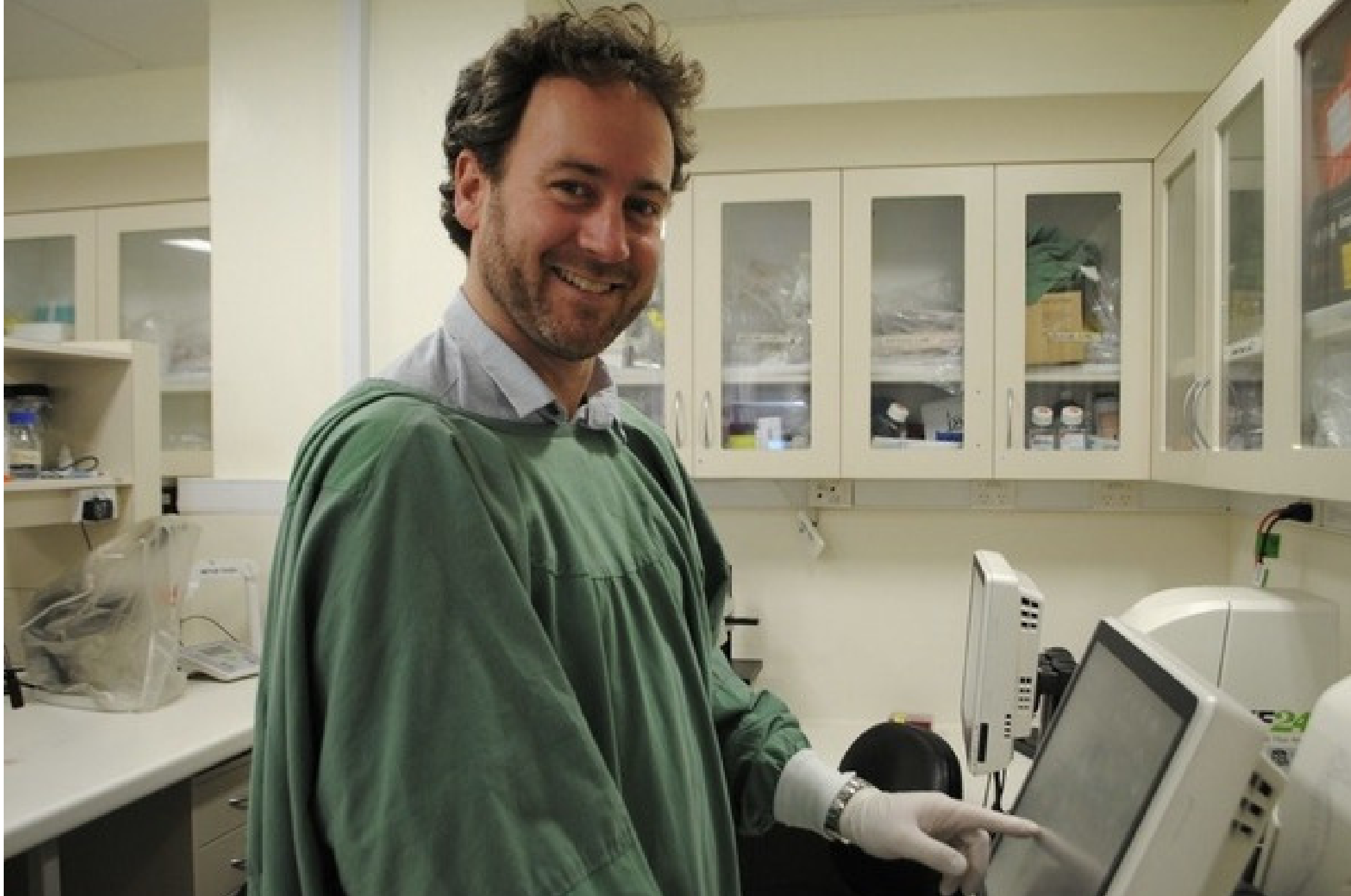
Dr. Katie Dixon is one of the Bosch Institute's talented young researchers. Katie is Secretary of the Molecular and Experimental Pathology Society of Australasia. Holding a Bachelor of Medical Science and a PhD in Medicine from the University of Sydney, Katie leads the Sunlight and Cancer Group in the Discipline of Anatomy and Histology.

Dr. Katie Dixon was intrigued by population data that suggested those who receive more chronic sun exposure tend to have better outcomes with treatments for Melanoma. This led her to investigate the actions of vitamin D in its active form, otherwise known as Calcitriol, in Melanoma. This research has shown that Calcitriol can inhibit Melanoma cell growth and its spread.

Katie and her colleagues at the Bosch Institute have discovered that Calcitriol is able to protect the skin from ultraviolet

radiation induced skin damage, prevent the depletion of tumor suppressor proteins in skin caused by sun exposure, as well as reverse this process. Moreover, studies by Katie's group show that Calcitriol can activate tumor suppressor proteins in melanoma cells. Katie's discoveries suggest a novel role for vitamin D compounds in the protection against skin cancer, a condition that affects 2 out of every 3 Australians by the time they reach 70 years of age and many millions of people around the world.

DISCOVERY | SUNLIGHT AND SKIN CANCER



Doctor Daniel Johnstone is a distinguished young researcher who recently received a Young Tall Poppy award from the Australian Institute of Policy & Science. He has also just been elected President of the Australian Society for Medical Research. Dan holds a PhD from the University of Newcastle.

Dr Daniel Johnstone is pioneering new and unexpected ways to protect the brain against degenerative conditions, such as dementia and Parkinson's disease. Dan's team has found that targeting specific wavelengths of low-intensity light at the head of animals can stimulate a response within the brain that protects it from degeneration, staving off the brain abnormalities usually associated with dementia and Parkinson's disease. More recently Dan has found that treating only the body of an animal with light can also protect the brain. This discovery suggests that low-intensity light may stimulate

protection of the entire body rather than just the directly irradiated tissues, opening the way for its use against a range of chronic diseases. Dan is currently conducting research to better understand exactly how something as simple and seemingly innocuous as light can stimulate such an extraordinary biological response, and what systems within the body are responsible for orchestrating the resulting protection against disease. Early signs from Dan's work indicate that light therapy holds great promise as a safe, simple, cheap and non-invasive intervention for degenerative brain disease.

DISCOVERY | **NEUROPROTECTION**



History of discovery - the eastern windows of the Anderson Stuart Building



Professor Nicholas King is an honorary fellow of the Royal College of Pathologists of Australia. Nick holds a Bachelor of Medicine and Bachelor of Surgery from the University of Capetown, and a PhD in Immunovirology from the Australian National University in Canberra.

Professor Nicholas King's research is focused on understanding how Flaviviruses interact with the human immune system and how this interaction causes immune-mediated disease. Flaviviruses are generally mosquito or tick-borne, causing many endemic and epidemic illnesses across the world today, such as West Nile virus, Zika virus, Dengue fever, Encephalitis viruses and Yellow fever.

Nick and his team have discovered that Flaviviruses paradoxically increase the visibility of infected cells to the

immune system and increase cell surface proteins that are essential for the immune system to recognise and then attack these viruses.

Nick proposed a novel immunological decoy theory to explain this paradox and the associated flaviviral immunopathology. His theory has generated strong interest in the mathematical community modelling infection. Nick's recent work highlights the mechanisms of this paradox and explains how viruses might trigger autoimmune disease.



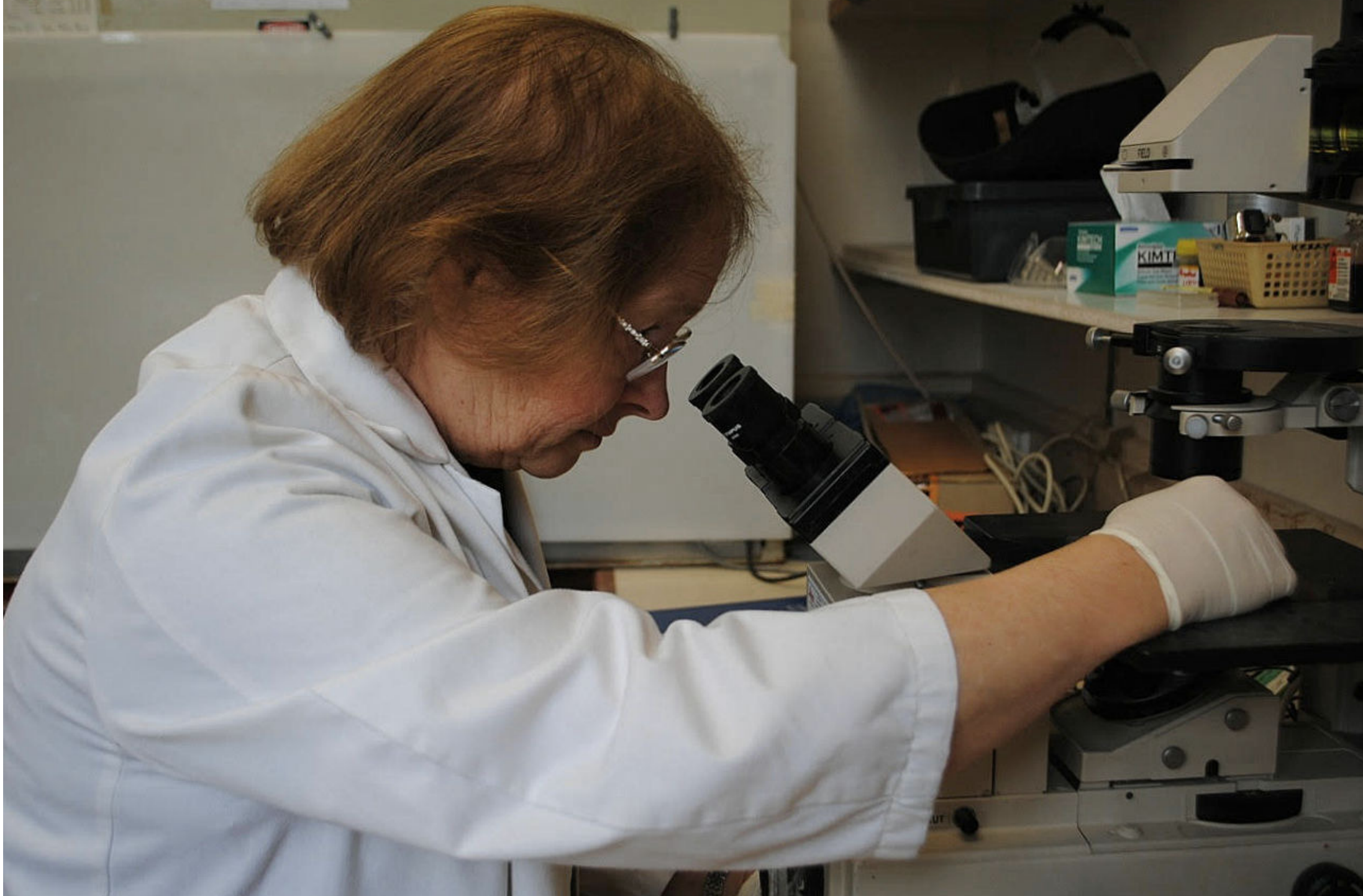
Professor Frank Lovicu is an internationally recognised researcher who currently leads the Lens Research Laboratory at the Bosch Institute. Frank holds a PhD from the University of Sydney and trained in Experimental Ophthalmology at the Baylor College of Medicine in Texas, USA.

Professor Frank Lovicu's research focuses on ways to prevent blindness by studying the changes in the eye that cause cataracts. The word "cataract" is used to describe the blurring of vision that occurs when the lens of the eye, which is normally absolutely clear and transparent, becomes opaque. Currently cataracts impact the sight of around 40 million people worldwide and are a common affliction of the aged. There is a surgical fix by way of an artificial lens, with usually excellent outcomes, but it is expensive, not readily available in many countries, and there are usually complications.

Frank and his team set a goal to keep the

lens clear. To do this, they looked at the molecular level of the lens to determine what causes the transparent cells of the lens to lose clarity. In isolated tissue models of the lens, Frank and his team are able to manipulate the factors that cause the lens to grow normally, inducing the formation of cataracts to mimic what happens in the ageing eye. This research has led to the identification of naturally occurring molecules that help keep the lens clear by preserving normal lens structure, effectively blocking the formation of cataracts. Frank's discoveries are particularly significant in light of the world's ageing population.

LANDMARK CONTRIBUTION | **OPHTHALMOLOGY**

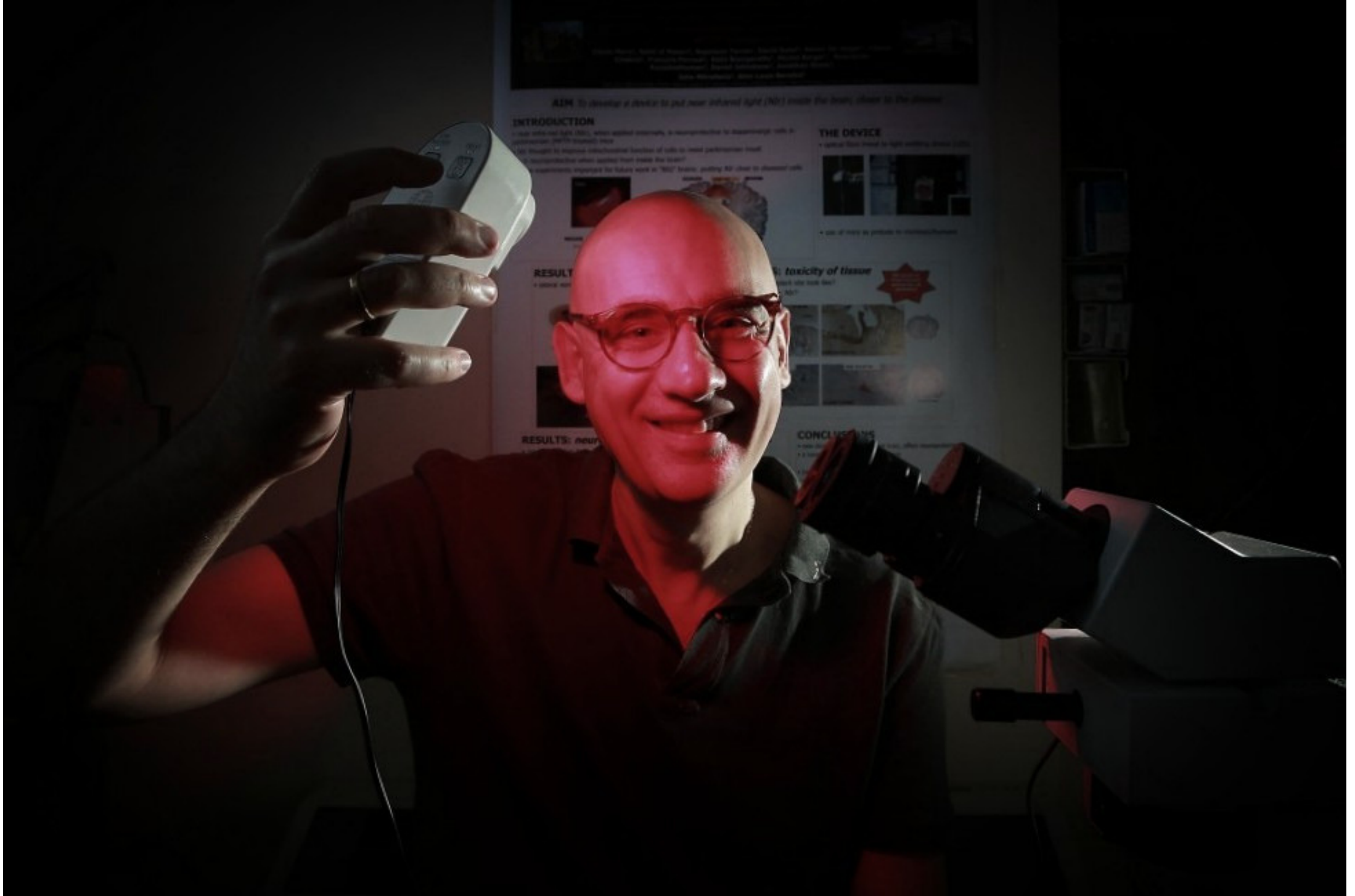


Professor Rebecca Mason is an internationally recognised leader in the role of vitamin D, particularly in the protection of skin from UV damage. Rebecca is a media commentator on the importance of vitamin D and is strongly involved in the broader medical research community. She serves on grant review panels, the Board of Osteoporosis Australia, and is a member of the Cancer Council of Australia's Sun and Health Working Party. Rebecca graduated in Medicine at the University of Sydney and completed her PhD at Sydney Hospital.

Professor Rebecca Mason's research program has developed over many years with studies in the fields of bone and skin, which are linked by vitamin D and its importance to prevention and treatment of related health conditions. In particular, her group's studies in skin have shown that the active vitamin D hormone Calcitriol can inhibit melanoma cell growth and its spread. The group has also shown, for the first time, that vitamin D compounds formed in skin by the action of UV light contribute to endogenous photoprotection.

Rebecca and her team are working to reduce the risks of sun exposure such as DNA damage and immune suppression, which can lead to skin cancer. They are currently investigating vitamin D-like compounds as potential additives to sunscreens or after sun lotions. With sun exposure causing 95% to 99% of skin cancers this work by Rebecca and her team is heralded to have the potential to reduce the occurrence of skin cancer, currently the third most common form of cancer suffered in Australia.

LANDMARK CONTRIBUTION | **SKIN, BONE AND SUNLIGHT**



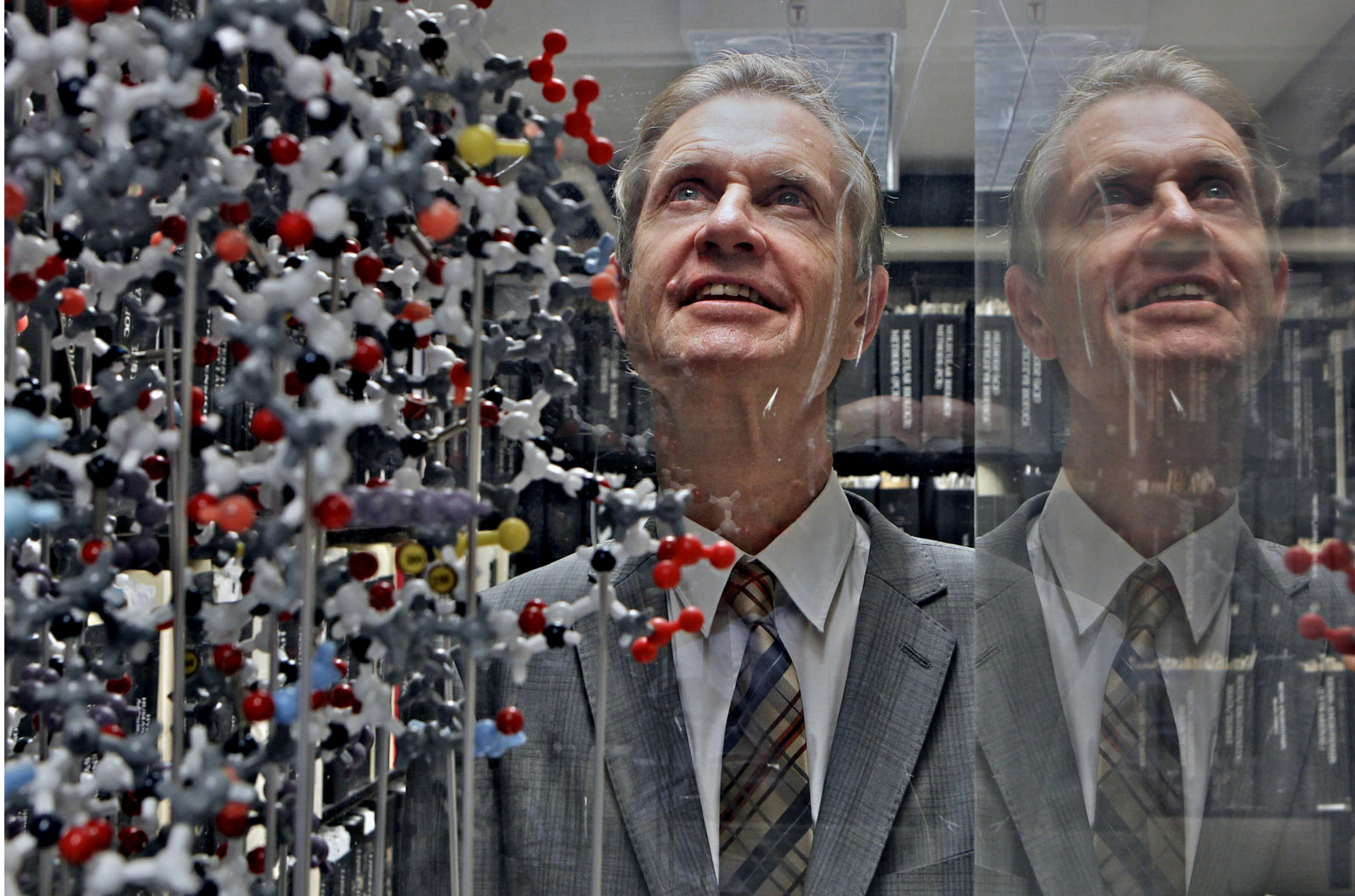
Professor John Mitrofanis is a world renowned researcher who has made significant contributions to the understanding and finding of treatments for Parkinson's disease. John's research into the treatment of Parkinson's disease is widely published. John is a Professor of Anatomy and Histology and holds a Bachelor of Science from the University of New South Wales and a PhD from the University of Sydney.

Professor John Mitrofanis hypothesised that infrared light might slow or stop the progression of Parkinson's disease. Utilising infrared lights John and his team set out to reinvigorate brain cells, to stem degeneration of healthy cells. John and the Bosch Institute team tested this hypothesis on mice. A form of Parkinson's disease was induced in the mice, which were then treated with daily doses of infrared light. The results were extraordinary. The light-treated parkinsonian mice had more cells and less behavioural impairment than the parkinsonian mice that were not light-treated. Infrared light treatment in animals

with forms of Alzheimer's disease, Multiple Sclerosis, retinal degeneration and traumatic brain injury has also shown improved brain cell survival rates. In 2011 John started to collaborate with a French group to trial infrared light treatment in monkeys. The results to date have been very promising.

John is currently developing an implantable prototype for further pre-clinical testing with the aim to deliver continuous infrared light to the brains of patients suffering from this degenerative disease and to change the evolution of Parkinson's disease in the brain.

DISCOVERY | STABILISING PARKINSON'S DISEASE



Professor Emeritus Brian Morris is one of Australia's leading genetic scientists and has made substantial discoveries in the field of hypertension. Brian graduated from the University of Adelaide with a Bachelor of Science and then completed his PhD at Monash University and the University of Melbourne. Brian went on to do postdoctoral research at the University of Missouri, and the University of California, San Francisco, first as a CJ Martin fellow, and then as an Advanced Fellow of the American Heart Association.

Professor Brian Morris has made major breakthroughs in understanding the cause of essential hypertension. When he started as a young researcher in 1970, the kidney, genetics, and the renin-angiotensin system were thought to be key factors in causing this 'silent killer'. After cloning the renin gene, Brian launched an international research program to find the genes responsible for hypertension. This research found that in hypertensive kidneys the renin gene was six times more active while the micro-RNAs were six times less so. As a result of low micro RNAs, renin levels went

up, and were found to contribute to an elevation in blood pressure. Using genome-wide approaches Brian and his colleagues further found all of the pathways that were disturbed in hypertensive kidneys. These discoveries laid the foundation for development of hypertension drugs specifically designed to reduce renin expression at its source in the kidneys. Brian's important work is heralded as life-changing for the large proportion of the world's population who suffer potentially lethal high blood pressure.

LANDMARK CONTRIBUTION | HYPERTENSION



→ The Anderson Stuart Building is one of several housing the Bosch Institute facilities and member laboratories



Associate Professor Matt Naylor is Head of the Developmental & Cancer Biology Group at the School of Medical Sciences and the Bosch Institute at the University of Sydney. Matt undertook his PhD at the Garvan Institute, where he graduated from the University of New South Wales. This was followed by postdoctoral research at the Wellcome Trust Centre for Cell-Matrix Research in the UK, before Matt returned to Australia to establish his laboratory as a NHMRC and NBCF Fellow.

Associate Professor Matthew Naylor's research focuses on the causes, treatment and cure of breast cancer. Matt and his team have identified a novel function for the gene "Runx2" as the master regulatory gene of both normal breast development and breast cancer progression. Prior to this discovery Runx2 was best known for its role as a key regulator of bone development, and these new findings provide the potential link that may explain why breast cancer preferentially undergoes metastasis to bone. In using breast transplantation techniques along with mice specifically altered genetically, Matt and his team found that

Runx2 regulates mammary cell populations to control normal breast development. He also identified Runx2 as the driver of the aggressive spread of breast cancer to other parts of the body. Importantly, Matt's pre-clinical studies also found that by inhibiting the Runx2 gene the progression of breast cancer is halted or slowed. This finding suggests Runx2 is a potential therapeutic target for the treatment of breast cancer, and offers the possibility of new treatments for the most common form of cancer in women worldwide.

DISCOVERY | **BREAST CANCER**

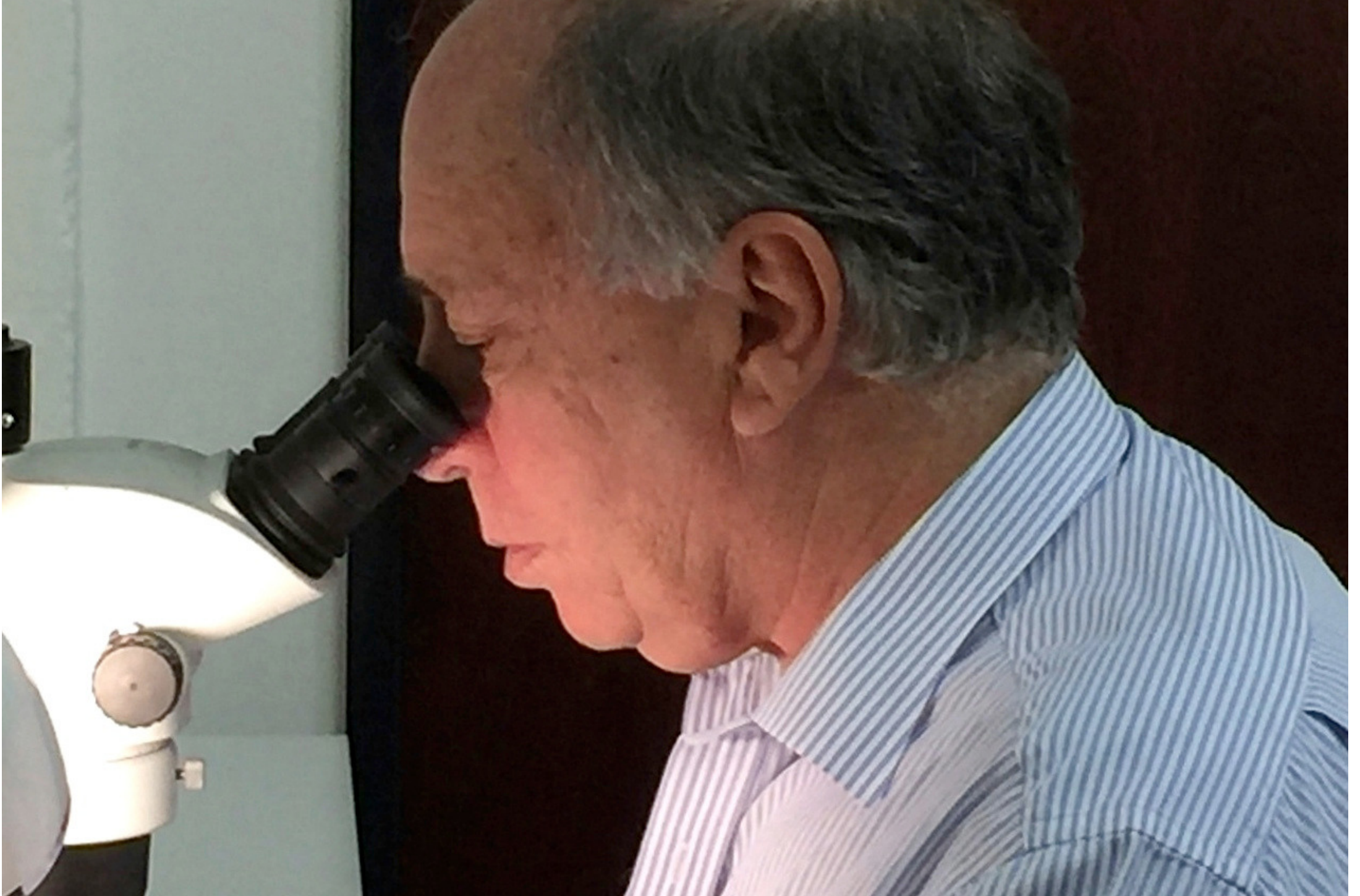


Professor Des Richardson is a preeminent investigator, a NHMRC Senior Principal Research Fellow, and Professor of Cancer Cell Biology. His entire career has been devoted to the field of iron metabolism and iron chelation, gaining him an international reputation for his work. Des also holds academic posts in both North America (Adjunct Professor, McGill University, Canada) and Europe (Charles University, Prague). His Doctor of Science degree was awarded after the minimum 10-year period following completion of his PhD.

Professor Des Richardson has taken an entirely new approach to cancer treatment. Despite marked resistance to the idea of iron chelation as a treatment, Des successfully elucidated the important structure-activity relationships of novel ligands necessary to impart highly specific and potent anti-cancer activity. This led to a major breakthrough with the development of DpT ligands, of which the lead agent, di-2-pyridylketone-4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC) has undergone

advanced preclinical development supported by NHMRC Development Grants and the venture capitalists, CTHULHU Ventures, San Francisco, USA. This new therapy has now entered multi-centre clinical trials. The development of therapeutic alternatives for treatment of cancer is a major public health priority. Des' important work gives hope to many millions of cancer sufferers around the world.

LANDMARK CONTRIBUTION | IRON AND CANCER

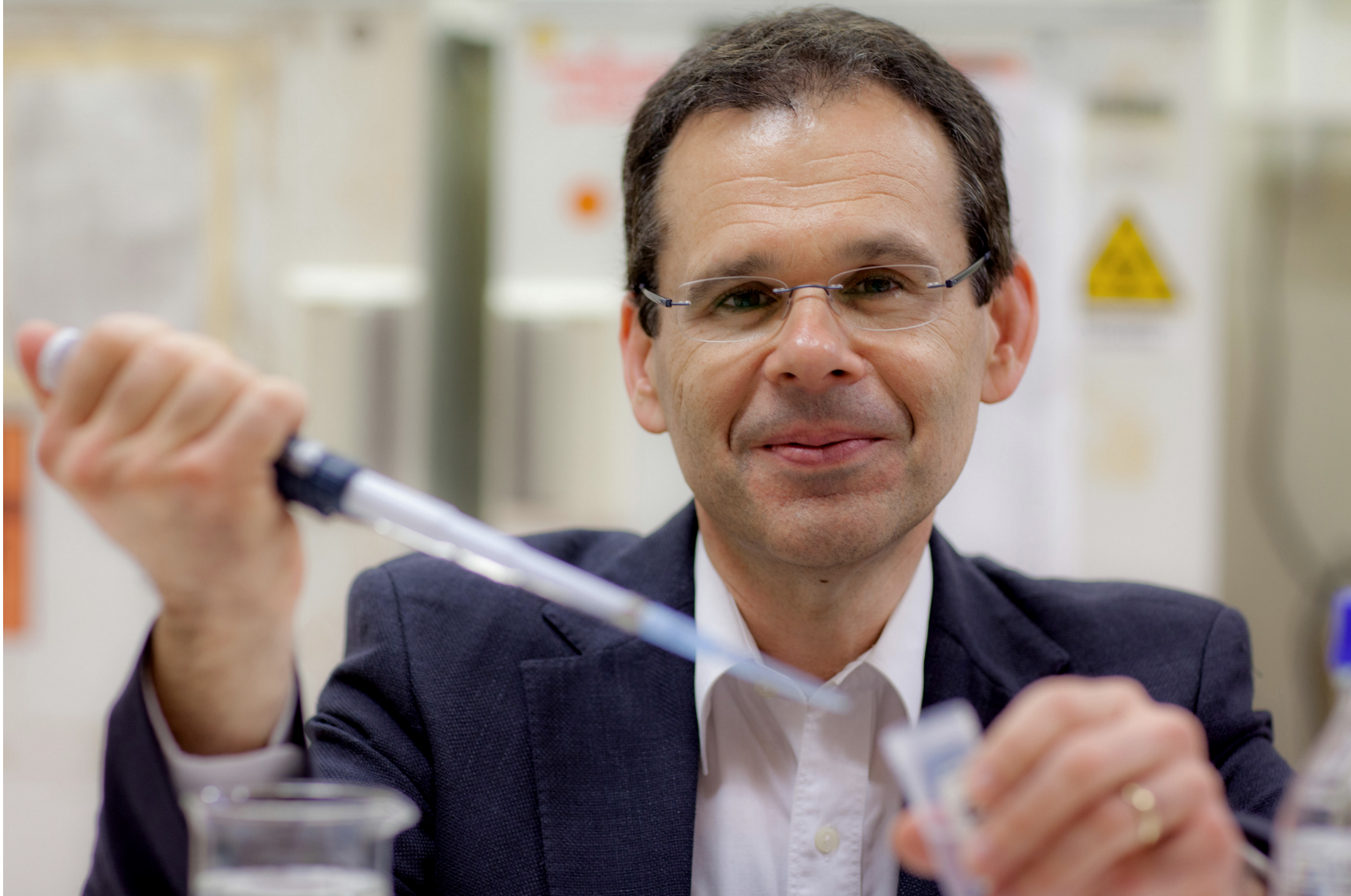


Professor Jonathan Stone is the Executive Director of the Bosch Institute and Professor of Retinal and Cerebral Neurobiology at the University of Sydney. With a long and distinguished career in medical science, Jonathan has recently focused his research on the stability and degeneration of the central nervous system, including age-related degeneration of the retina and brain. He holds PhD and DSc degrees from the University of Sydney.

In recent discoveries Professor Jonathan Stone and colleagues have linked the pathology and genetics of dementia to the ageing of the great blood vessels of the body, providing a compelling new understanding of the cause of dementia in vascular ageing. Jonathan and his team drew together evidence that the gradual hardening of the aorta and large arteries increases the intensity of the pulse, which in the later decades of life gradually damages the small blood vessels of the brain, producing the pathology (plaques, tangles

and inflammation) long associated with age-related dementia (Alzheimer's Disease). More recently Jonathan and colleagues have explored the phenomenon of acquired resilience, ways of making the brain (and other organs) resistant to the stresses of ageing, so delaying or preventing age-related degenerations such as dementia, Parkinson's disease, and age-related macular degeneration of the retina. The concept of acquired resilience is novel and may guide the optimisation of healthy ageing.

NEW THINKING | AGE-RELATED DEMENTIA



Professor Tony Weiss is a world leader in the study of human tropoelastin protein and its applications in elastic tissue repair. Tony is the McCaughey Chair in Biochemistry, Professor of Biochemistry & Molecular Biotechnology at the University of Sydney, Professor at the Charles Perkins Centre, Professor at the Royal Prince Alfred Hospital (Honorary) and a biotech company founder. Tony was a Fulbright Scholar at Stanford University and holds a PhD from the University of Sydney.

Tony's discoveries are on human elastic materials that accelerate the healing and repair of arteries, skin and three-dimensional human tissue components. Building on a sustained effort for over two decades, he is the acknowledged research leader in human tropoelastin. Tropoelastin is a structural protein, the fundamental building component of all elastin, that is responsible for providing strength and elasticity to tissues in the body. Used as a surface coating, tropoelastin can promote

cell attachment and spreading, while simultaneously allowing the modulation of surface elasticity. Tony has received multiple accolades, prizes and awards, and has also been awarded 35 international patents for his discoveries.

Tony's technologies have already been used in four clinical trials. This has been accelerated by his founding of the clinical stage company, Elastegen Pty Ltd.

LANDMARK CONTRIBUTION | TROPOELASTIN

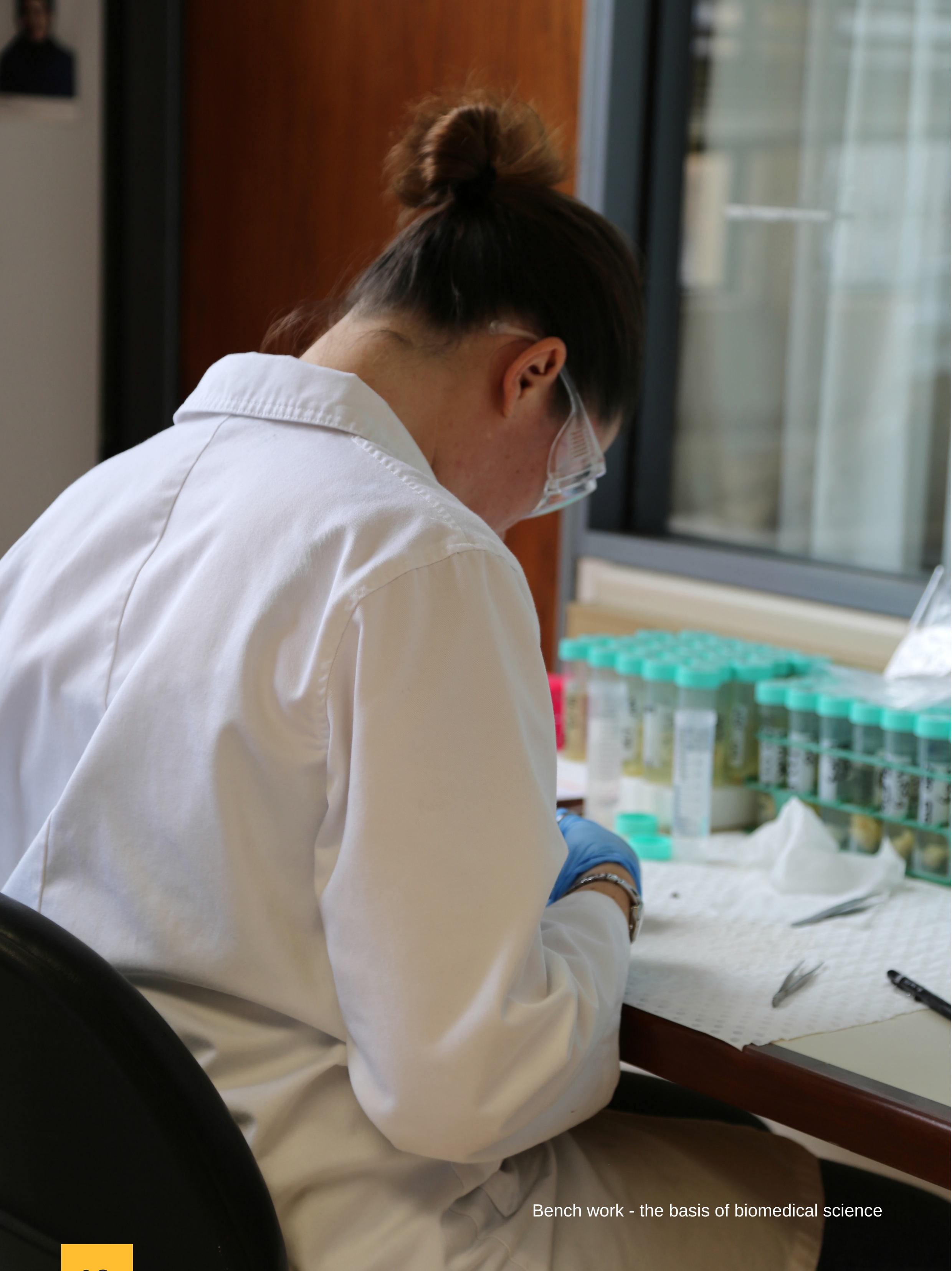


Professor Hala Zreiqat is a Professor of Biomedical Engineering. Hala has been awarded a prestigious Radcliffe Institute Fellowship at Harvard University. She is a National Health and Medical Research Council Senior Research Fellow, and is Head of the Biomaterials and Tissue Engineering Research Unit in the Faculty of Engineering at the University of Sydney. Hala holds a Bachelor of Science from Jordan University, Amman and a PhD from the University of New South Wales.

Millions of people worldwide suffer bone loss due to injury, infection, disease or abnormal skeletal development, and treatment frequently requires regeneration of new bone. Since each patient has only a limited amount of bone available for grafting, the demand for synthetic bone substitutes is high. Those currently available are far from optimal. Professor Hala Zreiqat has developed a unique ceramic material that acts as a scaffold on which the body can regenerate new bone. This ceramic material gradually degrades as it is replaced by natural bone. It can withstand the loads that will be applied to it. It also contains

pores that allow blood and nutrients to penetrate it. The ceramic scaffold is designed to encourage normal bone growth, and over time to be replaced by natural bone in the body. This scaffold is far superior to other available materials as it 'kick starts' the process of bone regeneration. Hala's investigations have also shown that the body will not reject the ceramic scaffold. Her discovery has the potential to positively affect the quality of life of millions of people globally, and she is hoping to see the ceramic scaffold in use clinically within the next 10 years.

DISCOVERY | BONE REGENERATION



Bench work - the basis of biomedical science



SUPPORTING OUR RESEARCH PROGRAMS

As you have seen from the preceding pages, a lot has been achieved to further our understanding on a number of diseases, as well as to progress managing and treating the impacts they have on our bodies. This crucial work comes at a high price with equipment and facilities for this specialist work costing into the millions.

Our commitment at the Bosch Institute is to provide these dedicated and talented scientists with the best possible tools to help achieve their goals of solving the complex puzzles that are disease, and the impact they have on the human condition. In doing so, we help each other and humanity to live better, stronger and more fulfilled lives.

We therefore encourage you to support these efforts in any way you can. All donations, even small ones, make a huge difference to the institute and the work our team carries out. Below are some of the ways you can pledge your support.

On behalf of the Bosch institute Board, I thank you for your continued interest in our work and look forward to celebrating many new milestones and discoveries over the coming years.

Paul Fegan

Chairman

The Bosch Institute for Medical Research

Care to Donate?

Please contact the Bosch Institute by email at coo@bosch.org.au or by telephone on +61 2 9114 0567. If you prefer to write, the address is:

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