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QUT ihbi
Institute of Health and Biomedical Innovation

IHBI ADVANCES

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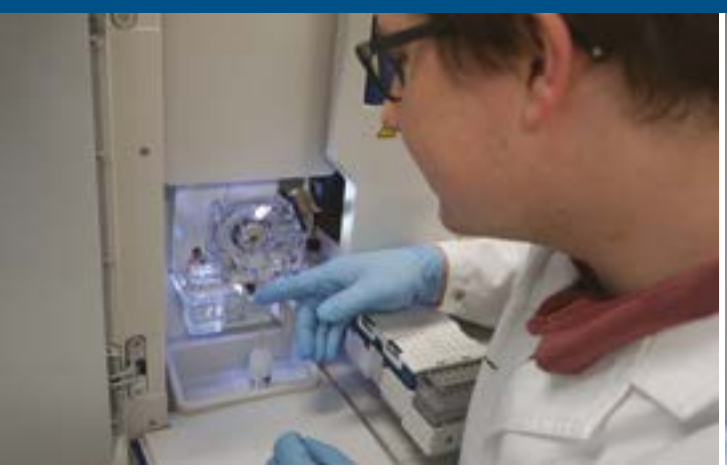

Paul Dunn

Research focuses on genetic causes of poorly understood brain disease

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopthy (CADASIL) is a poorly understood small vessel disease affecting the brain that can cause strokes, vascular dementia, cognitive decline, migraine, severe depression and even epilepsy.

IHBI research aims to understand the genetic causes of CADASIL, leading to better diagnostic, prognostic and treatment options for patients.

Paul Dunn is working to identify gene mutations predicted to cause CADASIL as part of his PhD studies at IHBI's Genomics Research Centre (GRC).

'CADASIL is a major contribution to disease burden in Australia and around the world,' Mr Dunn says.

'It is a progressive neurodegenerative disease which often doesn't present until between the third and fifth decade of life. Due to the severe spectrum of symptoms, which have limited treatment options, it can often have a devastating impact on quality of life with an associated increased caregiver burden.'

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopthy (CADASIL)

An inherited disease of the blood vessels that occurs when the thickening of blood vessel walls blocks the flow of blood to the brain.

Primarily affects the small blood vessels in the white matter of the brain.

Identified and named by French researchers Marie-Germaine Bousser and Elisabeth Tournier-Lasserve in the 1990s.

Common clinical manifestations are migraines or strokes, which usually occur between 40 and 50 years of age.

No specific treatment for CADASIL is available. Instead, doctors carefully manage the symptoms of CASASIL, as common treatments for symptoms including migraine can increase the risk of stroke.

Exact prevalence of CADASIL is not known. A study from Scotland found the disease prevalence was 1.98 per 100 000 people. The figure could underestimate the true prevalence because of frequent CADASIL misdiagnosis.

CADASIL is typically diagnosed as a result of unexplained ischaemic events, in which blood supply is restricted to tissues causing a shortage of oxygen, such as a stroke.

Characteristic migraines and multiple strokes progress to dementia, with other symptoms including white matter lesions throughout the brain, cognitive deterioration, seizures, vision problems and psychiatric problems such as severe depression and changes in behaviour and personality.

Symptoms of CADASIL usually progress slowly. By the age of 65, most people will have severe cognitive problems and dementia. Some lose the ability to walk and most become completely dependent on the care of others as the result of multiple strokes.

The disease is inherited in an autosomal dominant manner, meaning that having a mutation in only one copy of the responsible gene in each cell is enough to cause CADASIL. In most cases, an affected person inherits the mutated gene from an affected parent.

In rare cases, CADASIL may result from having a new mutation in the gene, meaning it is not inherited from a parent.

When a person with an autosomal dominant condition has children, each child has a 50 per cent chance of inheriting the mutated copy of the gene.

Mr Dunn says mutations in the *NOTCH3* gene were traditionally believed to cause CADASIL.

The GRC has conducted National Association of Testing Authorities, Australia accredited diagnostic testing for *NOTCH3* mutations using next generation sequencing. The testing was unable to detect potential disease-causing mutations in 78 per cent of patients with CADASIL symptoms.

'That suggests there are additional genes and mutations responsible for CADASIL that are yet to be discovered,' Mr Dunn says.

Using a National Health and Medical Research Council (NHMRC) scholarship, Mr Dunn aims to identify mutations and genetic risk factors that cause CADASIL in patients who do not have the *NOTCH3* mutation.

Blood from patients with CADASIL symptoms has been sent to the GRC clinic for diagnostic testing using neurologists in Australia and New Zealand.

Mr Dunn's research is being conducted under the supervision of IHBI Executive Director and molecular geneticist Professor Lyn Griffiths. The GRC is conducting whole exome sequencing and bioinformatics analysis and is validating novel genes most likely to be responsible for mutating and causing CADASIL.

'The research will provide a better understanding of the mechanisms behind CADASIL, likely leading to better patient management, giving rise to new pharmaceutical targets for improved treatment options and enabling a better care and quality of life for affected people and their families and carers,' Mr Dunn says.

Studying the role of bone cells to drive prostate cancer progression

Prostate cancer is a complex disease, with a variety of processes and body cells involved at different stages. For example, early disease onset involves different cells and treatments to later stages when therapeutic resistance is evident and the disease is disseminated to other organs, such as bone.


Dr Nathalie Bock

Patients with therapeutic resistance and cancer metastasis have more serious symptoms, complicated treatment regimens and a poorer prognosis.

Metastatic castrate-resistant prostate cancer (CRPC) is incurable in 90 per cent of cases when it metastasises to the bone. The metastasis affects the structural integrity of bone and causes pain, debilitating skeletal-related issues and ultimately claims the lives of a significant number of patients.

PROSTATE CANCER

More than 16 600 new cases diagnosed in Australia in 2017.

3400 deaths in Australia in 2017.

METASTASIS

Prostate cancer often metastasises to bone. In such cases, the five-year survival rate drops from 56 per cent to 3 per cent.

The only present treatments are palliative.

THERAPEUTIC DEVELOPMENT

Cancer research is typically performed using 2D flat surfaces, lacking the specific microenvironment in which metastasis occurs.

Clinical trials for the development of new therapeutics, based on such research, fail 80 to 90 per cent of the time.

IHBI's Dr Nathalie Bock has taken a step towards understanding the role of various cells in the bone, including osteoblasts and osteocytes.

Osteoblasts are the cells that form new bone, originating in a person's bone marrow and working in teams on the building process. They work in tandem with osteoclasts, cells that break down bone tissue as part of critical processes to maintain, repair and remodel bones.

Some osteoblasts turn into osteocytes while the new bone is being formed, becoming surrounded by new bone and sending out long branches that connect to the other osteocytes. The cells can sense pressures or cracks and assist in directing osteoblasts and osteoclasts where to lay down new bone and dissolve old bone.

Dr Bock says osteoblasts produce several factors known to promote prostate tumour growth in bone, but there are gaps in the knowledge because many of the factors have not been identified. Gaps also exist in understanding the mechanisms behind cancer transition to therapeutic resistance in bone.

Dr Bock is recreating direct and indirect cell-to-cell interactions in 3D laboratory models that more closely replicate the human bone microenvironment than traditional 2D research models. By using 3D printers to create a matrix that is populated with a patient's cells, 3D osteoblasts and tumour tissue are being studied in a more relevant setting – without the use of animal models.

'Using the 3D models, we have been able to study the bone microenvironment and see cancer cells partly displaying the same functional and molecular features that have been observed in real bone,' she says.

'While some cancers, such as breast cancer, produce over-activity of osteoclasts, prostate cancer progression in bone is characterised by a dominant role of osteoblasts.

'There are potentially more gaps we will be able to bridge if we separate the bone formation process from the bone resorption process in our 3D models.'

Ultimately, the research aims to understand the roles of both osteoblasts and osteocytes in CRPC in the bone microenvironment and build a predictive platform that features patient-specific cells for testing therapeutics as part of a personalised medicine approach to treatment.

The research involves IHBI experts at the Australian Prostate Cancer Research Centre – Queensland, based at the Translational Research Institute, and 3D model production at the IHBI-based ARC Industrial Transformation Training Centre in Additive Biomanufacturing. IHBI facilities supporting the research include the Cell Analysis Research Facility and the Histology laboratory.

Dr Bock says the research has the potential for major impact in healthcare, with prostate cancer known to be one of the most commonly diagnosed cancers and the second most common cause of cancer-related deaths among Australian men.


Dr Anjali Jaiprakash

Step towards personalised, preventative eye care

Up to 80 per cent of visual impairment, estimated to affect 280 million people worldwide, is preventable or curable with regular monitoring and timely treatment. IHBI is developing technology and investigating barriers to screening in a bid to lower the rates.

Dr Anjali Jaiprakash and her co-investigators are developing a patient-specific 3D retinal diagnostic camera to improve rates and accuracy of retinal screening, enabling early diagnosis of eye disease.

The camera also has the potential to ultimately diagnose and monitor conditions such as diabetes, Parkinson's and Alzheimer's, as well as elevated risk of cardiovascular disease.

AUSTRALIAN RESEARCH COUNCIL CENTRE OF EXCELLENCE FOR ROBOTIC VISION

Vision

Creating robots that see and understand for the sustainable wellbeing of people and the environments in which they live.

Mission

To develop new robotic vision technologies to expand the capabilities of robots.

About the centre

An Australian research centre that leads the world in the new discipline of robotic vision, applying computer vision to robotics. While robotics is about machines that interact with the physical world, computer vision is about analysing and understanding the world through images. Robotic vision expands the capabilities of robots, allowing them to see and understand the world in which they are working. It is the key technology that will allow robotics to change the way people live and work.

The centre's researchers

Researchers are looking to apply technologies to solve challenges in the monitoring and protection of the natural and built environments, the provision of healthcare in hospitals and in the home, sustainable food production and efficiently harnessing natural resources.

The website

www.roboticvision.org

Dr Jaiprakash is part of the Australian Research Council Centre of Excellence for Robotic Vision and works with researchers from QUT and IHBI, the University of Queensland and the Southern Queensland Centre of Excellence in Aboriginal and Torres Strait Islander Primary Health Care.

The collaboration enables a multidisciplinary approach that will consider multiple aspects of disease, diagnosis and the disadvantages that flow from living in rural and remote communities.

Dr Jaiprakash says rates of blindness are six times higher in Aboriginal and Torres Strait Islander people.

The researchers will work with healthcare providers to understand eye screening processes, she says. They will also work with Aboriginal and Torres Strait Islander people living with diabetes to gain insights into their experiences in the healthcare system.

'That will enable us to forecast future screening services that integrate people's needs, policy changes, technology innovations and result in enhanced patient and clinician experiences.'

Researchers will also develop a 3D retinal diagnostic camera that is affordable, reliable and portable, so it can easily be used in rural and remote communities.

'Taking a high-quality image of the retina, suitable for accurate diagnosis, presently requires precision equipment that is bulky, expensive, difficult to transport and needs sophisticated technical training to operate,' Dr Jaiprakash says.

The camera Dr Jaiprakash is involved in developing will remove moving parts found in present technology, eliminating the need for constant calibration and technical specialists and reducing ongoing costs as well as the need for a sensitive operating environment.

Capturing 3D retinal images in all possible focal planes means the technology will be able to track structural changes to the retina, a thin layer of tissue that lines the back of the eye.

'The retina is like our fingerprint, unique even between identical twins,' Dr Jaiprakash says. The retinal features also indicate the health of your heart and brain.'

The camera can be applied to understand early Parkinson's, Alzheimer's and cardiovascular risk and monitor disease development so that medical interventions are timely.

Future research will also involve using machine-learning to develop accurate automated diagnosis of retinal conditions.

Another strand of the research will investigate how computer vision can be incorporated into a surgical robotic platform to improve the speed and safety of procedures such as a specific cataract surgery called phacoemulsification.

Other surgeries that may benefit include retinal vein cannulation, a challenging procedure for delivery of therapeutics into very small retinal veins.

Alison Farrington

Hospital clinicians join research focusing on end-of-life care

Advances in medicine enable clinicians to extend lives, yet some treatments have little chance of providing meaningful benefits to a patient at the end of life. IHBI is part of a collaboration that aims to reduce such treatments at three southeast Queensland hospitals.

Alison Farrington is the Research Project Manager with IHBI's Australian Centre for Health Services Innovation and has oversight of the InterACT study.

The study will involve researchers from IHBI, QUT's Australian Centre for Health Law Research (ACHLR), the University of Adelaide, Bond University and clinicians from the Royal Brisbane and Women's Hospital, Prince Charles Hospital and the Gold Coast Hospital. Health policy partners include Palliative Care Australia and the Deeble Institute for Health Policy and Research.

WHY HOSPITAL PATIENTS RECEIVE NON-BENEFICIAL TREATMENT AT END OF LIFE

Clinician factors: such as an orientation towards curative treatment; discomfort and inexperience with death and dying; concerns about legal risk; poor communication skills.

Hospital factors: such as high degree of specialisation; ready availability of routine tests and interventions.

Patient or family factors: such as requests or demands for further treatment; prognostic uncertainty; lack of information about a patient's wishes.

THE STATISTICS

Research shows 33–38 per cent of patients received non-beneficial treatment at the end of life.

One study found the mean duration of non-beneficial hospital treatment is 15 days.

One third of the time is spent in an Intensive Care Unit.

Ms Farrington says Australia's healthcare system operates in a challenging climate, with an ageing population, an increasing number of people living with chronic disease and, most relevant for the study, an increase in elderly people living with frailty and physical and cognitive disabilities.

The elderly population is also more likely than previously to be hospitalised, she says, with hospitalisation rates for people aged 85 years and above increasing by 35 per cent for women and 48 per cent for men in the decade to 2011.

'Clinicians providing end-of-life care are often tasked with preparing patients and families for a transition to less active treatment. However, they can frequently experience a range of barriers in providing that care pathway.

'The barriers are likely to lead to an increase in treatment provided that is actually not beneficial to the patient. Further, they can cause moral distress to clinicians and prolong or increase patient suffering.'

The InterACT study has been designed to increase awareness among clinicians of the extent of non-beneficial treatment at end of life and stimulate action to reduce it.

`We expect to improve the capacity of clinicians to choose alternative treatments and increase institutional support for better end-of-life care for a group of vulnerable patients,' Ms Farrington says. 'Rather than blaming or judging clinical practice we will promote education, awareness and the use of objective data.'

Each of the participating hospitals will have five clinical teams enrolled in the study and stages rolled out for more than a year. Clinical teams may include cardiology, geriatrics, internal medicine, oncology, respiratory and post-surgery.

Advisory groups will be formed at each hospital, palliative care services enhanced in expectation of increased referrals and education sessions provided to hospital staff.

Patients included in the study will be those aged 75 years and above, with persistent symptoms despite optimal treatment, with multiple unplanned hospital admissions, or with unexpectedly long stays.

Ms Farrington says the study will address a complex issue that is sometimes called futile care, with support from Metro North Hospital and Health Service and the Gold Coast Hospital and Health Service.

'The complexity of non-beneficial treatment means it is not feasible for a single intervention to address all its causes.

'For the clinician, the InterACT study addresses concerns about legal risk, poor communication skills and discomfort and inexperience with death and dying. For the hospital, it addresses organisational barriers to stopping a curative pathway.'

Researchers involved in the study include IHBI expert statistician Professor Adrian Barnett and ACHLR experts in end of life decision-making Professor Lindy Willmott and Professor Ben White.

Nanotechnology approach to lower implant infection risk

Orthopaedic surgery comes with a risk of bacterial infection, prolonged antibiotic therapy and revision surgery. IHBI researchers are using expertise in nanotechnology to develop implant surfaces that minimise the risk of bacterial infection, taking inspiration from nature.

Professor Prasad Yarlagadda

Professor Prasad Yarlagadda is interested in nanotextured surfaces that are designed to mimic the bactericidal properties, capable of killing bacteria, of some animal, plant and insect species.

He has published articles in peer-reviewed scientific journals that investigated the surface structures of cicada, dragonfly and butterfly wings, shark skin, gecko feet, taro and lotus leaves. The research emphasised the relationship between nanostructures and surface contact angles on self-cleaning and bactericidal properties.

Using the findings from that research, Professor Yarlagadda and Dr Jafar Hasan are focusing on developing implant surfaces that not only overcome bacterial infection but support osseointegration.

TITANIUM ALLOY

Metal containing titanium and other chemical elements.

Has high tensile strength and toughness, even at extreme temperatures; is lightweight; has extraordinary corrosion resistance.

High cost of raw materials and processing limits use to military applications, aircraft, spacecraft, bicycles, medical devices and jewellery.

NANOSTRUCTURED IMPLANTS

Have significant scope in medical science and dental implants.

Nanoscale surface features provide significant potential for addressing medical problems through the use of better biomaterials, improved implant design and surface engineering techniques such as coating, patterning and molecular grafting.

THE PUBLICATION

https://eprints.qut.edu.au/128130/

Osseointegration is the direct structural and functional connection between living bone and the surface of a load-bearing artificial implant.

The research needs to incorporate a titanium alloy implant's favourable mechanical and biomedical properties and corrosion resistance with physical and chemical properties in nanomaterials that prevent bacterial adhesion.

Professor Yarlagadda says nanotechnology enables precise surfaces to be developed, closely mimicking the roughness of natural bone and improving an implant's integration in the body.

'Introducing structures similar to the natural bone minimises possible implant rejection and improves osseointegration, bone regrowth, implant lifespan and the body's ability to develop capillaries and transport nutrients,' he says.

Previous research from Professor Yarlagadda's group found that nanofibres of about 300 nanometres improve growth of a person's osteoblasts, cells that form new bone.

In the new research, the same nanofibers were found to accelerate the death of the bacterium *Staphylococcus aureus*.

'From images obtained of the bacteria cells in contact with the nanostructure surfaces, piercing of the cell walls was clearly observed,' Professor Yarlagadda says. 'The piercing led to the disfiguration and collapse of the bacteria cells, resulting in bacteria death and highlighting this as the possible mechanism of bacteria killing.'

He says the nanostructured surface was efficient in inhibiting bacterial adhesion and preventing infection on implant surfaces.

The new research involved varying and studying the nanostructured surface's properties, such as roughness, mechanical properties, contact angle of the nanofibers and bactericidal effects, as well as cellular activity in surrounding tissue.

'Our findings are significant and can assist in future implant design, improving osteoblast cell activity and impacting bacterial attachment.

'It could lead to reductions in orthopaedic surgery recovery time and improve osseointegration, bone remodelling and implant fixation.'

Professor Yarlagadda leads a team with expertise that straddles IHBI, QUT's Science and Engineering Faculty and the Institute of Future Environments. The team's expertise covers design, modelling and simulation, engineering, computer control, artificial intelligence, image processing, tool design and non-traditional manufacturing.

The team collaborates with the IHBI-based ARC Industrial Transformation Training Centre in Additive Biomanufacturing, bringing together leading researchers, industry partners and end-users to develop next-generation manufacturing technologies. The technologies are geared towards clinical application, industrial scale biomanufacturing and multi-material manufacturing processes.


Dr Elke Hacker

Cricket fans embrace stickers as part of sun protection study

Australia has one of the highest rates of skin cancer in the world, making sun protection an important health prevention strategy. Yet research shows sunscreen is often not applied or reapplied sufficiently to provide protection.

IHBI's Dr Elke Hacker has recruited 428 people to what is believed to be the first study showing the benefits of UV detection stickers in ensuring adequate sun protection using sunscreen.

She provided the stickers to people at the Ashes Test at the Gabba in Brisbane in November 2017, with 72 per cent of participants being men and 63 per cent having fair or very fair skin.

The stickers contain UV-sensitive ink that changes colour to warn people when the effect of their sunscreen is wearing off and it needs to be reapplied. They are typically placed on exposed body parts such as people's hands.

Dr Hacker has analysed the study results and found 80 per cent of the participants were prompted to reapply protective sunscreen and 86 per cent reported that they would like to see stickers included with tickets to outdoor events.

WHAT A STUDY PARTICIPANT SAYS:

'I am your typical red hair equals fair skin. I think anything that makes people more aware of sun safety, especially when you are outside all day, is a great idea.

'I had prepared for the cricket. I had a hat, sunglasses and sunscreen and had chosen to sit under cover. I had the UV detection sticker on the back of my hand and when it changed colour it reminded me to put on more sunscreen.

'I teach sun safety to my students, so I am keen to share the results of this study with them.'

Shaun Griggs, 53, high school physical education teacher

'The results tell us that the stickers are effective reminders to reapply sunscreen throughout the day when people are outside for long periods of time in Queensland,' Dr Hacker says.

'The high rate of use of the stickers indicates this type of technology resonates with people. The stickers are small, simple to use and provide personalised information.'

New technologies assist people in determining how long they can safely stay in the sun after applying sunscreen, she says, including several mobile phone apps with sunscreen volume calculators and re-application reminders. However, the apps will not provide feedback on whether the correct amount of sunscreen has been applied. Research into the apps found no improvement in sunscreen use.

Previous studies have also investigated sunscreen reapplication prompts via SMS or mobile app platforms, finding the technology increased sunscreen use to 56 per cent of participants – significantly short of the 80 per cent achieved in Dr Hacker's study.

Sun protection behaviours were high among Dr Hacker's study participants, with 84 per cent bringing a hat and a similar percentage wearing sunglasses, while 64 per cent brought sunscreen.

While the stickers were effective as a reminder, she says, 41 per cent of study participants reported a mild sunburn, mostly on their face and neck. Most said they had applied and reapplied their sunscreen.

`This suggests that perhaps people may not have applied enough sunscreen or did not apply it in a way that gave them full protection from sunburn. Previous studies have shown that people sometimes apply only half the recommended thickness to cover the skin. This is something to look at in future studies.'

Statistics show Australia has one of the highest rates of melanoma in the world, at least double those of high-risk countries such as the US and UK.

In Queensland during 2015–16, almost 54 per cent of adults reported being sunburnt in the previous 12 months. A nationwide survey in 2016–17 found 17 per cent of adults reported being sunburnt on an average summer weekend.

All skin cancers together in Australia are more common than all other cancers combined. 'There is also a large societal impact from skin cancer,' Dr Hacker says. 'Many people are affected by multiple skin cancers, which need to be managed as a chronic disease.

'Skin cancer prevention initiatives are very important for Australia and have been shown to be highly cost effective, with every dollar invested in sun protection programs returning an estimated $2.30 to $3.20 in cost savings.'

EXECUTIVE DIRECTOR'S REPORT

Technology has the potential to significantly improve our healthcare into the future, including through the use of robotics, 3D printing, nanotechnology and genetic analysis. Advances will ultimately pave the way for increasingly personalised, precision medicine, benefiting patients with disparate health concerns such as cancer, eye disease and neurological conditions.

Often technology is not the only key, with researchers being challenged to consider people's needs, behaviours and motivations to deliver effective, fairer and more equitable care for all Australians, including people in rural and remote communities and those at the end of life.

Dr Anjali Jaiprakash is conscious of both developing technology and understanding people's needs to ensure a patient-specific 3D retinal diagnostic camera will have the desired impact on high rates of preventable or curable visual impairment.

She collaborates with experts in robotics, works closely with clinicians and liaises with Aboriginal and Torres Strait Islander people who stand to benefit from her research.

Dr Nathalie Bock also works in an emerging area of medical research, with 3D printing providing laboratory models that closely resemble a human bone, embedded with prostate cancer patient cells to mimic disease metastasis.

The 3D models enable screening of therapeutics for efficacy without having to be prescribed to patients – potentially saving them from receiving a cocktail of ineffective drugs. They also have the potential to one day replace testing conducted on animals.

Dr Elke Hacker has been working with large numbers of cricket fans to ensure sun protection strategies have the best chance of being widely adopted – and skin cancer rates decrease as a result.

A technology as simple as a sticker containing UV-sensitive ink is showing promise, with far higher numbers of people being prompted to reapply sunscreen when compared to use of mobile phone apps or SMS prompts.

Professor Prasad Yarlagadda is interested in another promising technology, investigating nanotextured surfaces that are designed to mimic properties found in nature capable of killing bacteria.

His research has significant potential in developing implant surfaces that overcome bacterial infection and risk to patients of prolonged antibiotic therapy and even revision surgery.

PhD candidate **Paul Dunn** is part of a team using blood from patients with the most common hereditary stroke disorder, CADASIL, and working with neurologists in Australia and New Zealand to understand genetic causes to aid in developing diagnostic, prognostic and treatment tools.

Ultimately, the insights that flow from the whole exome sequencing and bioinformatics analysis conducted in the laboratory will enable better care and quality of life for affected people, their families and carers.

Similarly, **Alison Farrington** has a focus on people's needs as part of research into end-of-life care and the elimination of treatments that cause suffering and have little chance of providing meaningful benefit.

IHBI researchers are embracing technology that has the potential to deliver improvements to many areas of healthcare and wellbeing; and are also working to understand people's needs, reservations and experiences to ensure a fairer and more equitable care for all Australians.

Enjoy this edition of *IHBI Advances*.

Professor Lyn Griffiths
Executive Director, IHBI

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