

IHBI ADVANCES

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New insights into osteoporosis using advanced imaging and modelling

Science is shedding new light on aspects of bone tissue and the impact of mechanical forces, leading to a greater understanding of osteoporosis (OP). IHBI's Professor Peter Pivonka is collaborating with world leaders to build insights for prevention and effective treatment of bone diseases.

Professor Pivonka is interested in bone remodelling and its role in OP. Bone remodelling is a biological process involving osteoclasts, large bone cells that resorb bone tissue during repair; and osteoblasts, a different cell type that secretes the substance of bone as part of the building and formation process.

'In healthy people the process is balanced,' Professor Pivonka says. 'In people with OP, bone resorption is prevalent and minerals in bone are lost.'

The processes of bone resorption and formation come into conflict under conditions of changing mechanical forces applied when running, jumping or lifting heavy weights; and are also dependent on metabolism and nutrition — that is, the conversion of food to energy. Added to that are the different responses of different bones to increases or decreases in mechanical environment.

BIOMECHANICS AND SPINE RESEARCH GROUP

Professor Pivonka leads IHBI's Biomechanics and Spine Research Group, a collaboration between medical engineering researchers at QUT and spinal orthopaedic surgeons at the Lady Cilento Children's Hospital.

The group conducts research into paediatric spinal deformity and other spine conditions to improve treatments and understanding of spine disorders.

Expertise in mechanical testing, using state of the art facilities at QUT and computational simulation tools, underpins research to address paediatric spine deformity; osteoporotic fractures and the aging spine; and spine implant testing and analysis.

'Factors such as sex, age, genetic make-up, disease states, nutrient availability and drug use all affect bone's response to mechanical loading,' Professor Pivonka says.

'Building on existing research that used bone models developed to mimic the human body will help us understand the mechanism for controlling bone mass based on loading.'

Professor Pivonka is collaborating with Associate Professor David Cooper from the University of Saskatchewan, using recent funding from the Canadian Institute of Health Research, on 4D imaging of bone remodelling. Using sophisticated high-resolution microCT imaging methods, the team aims to show that it is possible to track bone remodelling processes in the dense outer surface of bone.

The collaboration is part of Professor Pivonka's global outlook and network, enabling him to build a comprehensive picture that includes understanding the role of muscles, blood vessels and the nervous system in OP.

Professor Pivonka edited the book *Multiscale Mechanobiology of Bone Remodeling and Adaptation*, capturing important findings shared at an international summer school. The school attracted researchers from around the world with expertise in applied mechanics and biomedical engineering, complex systems modelling, bone biology, mechanobiology and materials science.

'OP is a major health problem in society and requires a global and multi-faceted approach. Because bone loss occurs without symptoms, OP is often called the silent disease. New therapeutics are being developed and trials conducted, but many bone diseases including OP do not have a proven means of prevention or effective treatment.'

Professor Pivonka says progress is expected as advances are made in precision medicine, an approach that involves care being tailored to optimise the therapeutic benefit for particular groups of patients, especially through the use of genetic or molecular profiling.

Significant progress is also being made in material engineering, enabling models to be developed in laboratories to mimic human bone and show mechanical and biological responses with a high degree of accuracy. Cell-based models of bone remodelling are now being developed for predicting changes to bone mass and mechanical properties.

The ultimate goal is to predict the fracture risk of patients so interventions with either therapeutics or exercise programs can be introduced quickly.

OP affects 2.2 million people in Australia, with a lifetime risk of osteoporotic fracture after the age of 50 years at 42 per cent among women and 27 per cent among men. The spine, hip and wrist are particularly prone to OP-related bone fractures.

It is placed alongside diseases such as breast cancer, cardiovascular disease and diabetes when considering prevalence, lifetime risk and socio-economic impact.

Spotlight on efficacy and ethics of clinical cancer sequencing

Advances in genetic sequencing technology are having a major impact in healthcare, with improvements in diagnosis, treatment and recovery. Analysing people's DNA has gone from being a valuable research tool to actually being used in clinical settings.



Dr Aideen McInerney-Leo

Whole exome sequencing is the process of determining the DNA sequence of the coding region of a person's complete set of genes. The sequencing is being conducted at IHBI's Australian Translational Genomics Centre (ATGC) to enable rapid and comprehensive screening for cancer mutations and identify a patient's specific mutational profile.

ATGC genetic counsellor Dr Aideen McInerney-Leo says the sequencing can yield information about diagnosis, prognosis and predict responses to treatment.

QUT MASTERS IN DIAGNOSTIC GENOMICS

Dr Aideen McInerney-Leo has been working with IHBI Executive Director and molecular geneticist Professor Lyn Griffiths to establish Australasia's first Masters program in Diagnostic Genomics at QUT.

Australia has a workforce shortage in diagnostic genomics and many of those already working in the field want to update their skills.

The educational elements of the Masters program will be delivered entirely online and a six-month placement completed in a laboratory.

Program graduates will be eligible to apply for professional certification from the Human Genetics Society of Australasia.

Enrolments are accepted now, with merit-based, partial scholarships of \$5000 each available for 2018 and 2019.

The course will start in February 2018.

Visit www.qut.edu.au/study/courses/master-of-diagnostic-genomics

'Genetic sequencing for cancer has typically involved sequencing five genes or less, but cutting-edge technology can now sequence all 20 000 genes at once,' Dr McInerney-Leo says. 'It can selectively evaluate the 300 or so genes known to be involved in cancer development and progression.'

Work at the ATGC is conducted in partnership with Metro South Hospital and Health Service, Pathology Queensland and QUT under the leadership of IHBI Distinguished Professor Matt Brown. It aims to point the way to new cancer management processes based on the primary molecular causes of cancer.

The research takes a multi-faceted approach, with teams investigating biological and genetic aspects and understanding how to introduce research findings into clinical healthcare.

ATGC researchers also appreciate that it is people who will introduce the technology in hospitals and clinics and stand to benefit from the insights that DNA sequencing will provide. Dr McInerney-Leo's role at the ATGC is to assist with the introduction of a genetic testing service, in part by ascertaining the best ways to inform physicians and patients about cancer sequencing.

'My work involves assessing whether physicians perceive a value in genetic testing and how comfortable they feel with explaining the testing process and results,' Dr McInerney-Leo says. 'We can offer cutting-edge genetic testing, but we can only consider our services successful if physicians adopt them in hospitals and clinics.'

Another aspect of Dr McInerney-Leo's work involves understanding the ethical, legal and social implications of the technology.

'It is critical that patients are properly consenting to genetic testing. Our service will soon include assessing whether a person has inherited a genetic mutation which predisposed them to develop cancer. That will have clinical and psychosocial implications for the patient and for other family members. Such a result can generate feelings of anxiety or guilt.'

Dr McInerney-Leo is working with Professor Brown's team to develop a video to give patients enough information to decide whether genetic testing is appropriate for them.

'Genetic testing offers tremendous clinical value but also presents complex ethical, legal and social issues. I feel strongly that, given enough information and support, people can consider the pros and cons and make an informed decision about cancer genetic sequencing.'

ATGC researchers are also collaborating with IHBI's Professor Nick Graves to assess the clinical utility and cost effectiveness of genome sequencing for cancer patients. Clinical utility refers to the relevance or usefulness of the process in patient care.

The collaboration focusses on assessing whether expanded genetic sequencing for cancer patients has an impact on patient care and outcomes, while also determining whether it is cost effective. The research has the potential to have an impact on the standard of care for cancer patients in Queensland — and potentially around Australia.



Dr Indira Prasadam

Collaborative effort to tackle both obesity and osteoarthritis

Collaborating with clinicians ensures research is relevant and study results can be translated into better therapeutics, treatments, services or medical devices. IHBI researchers are working at the Prince Charles Hospital in Brisbane to prevent or delay progression of osteoarthritis.

Dr Indira Prasadam is leading a team of researchers investigating cellular, structural and molecular changes in joint tissue and the links to obesity. Her focus is on osteoarthritis (OA), with projects that aim to understand the genetic and biological processes, develop disease-modifying medicines and promote prevention strategies.

Dr Prasadam's team works with peers from other institutes, industry partners and patients, resulting in research that provides an evidence base for training future clinicians.

MAJOR RISK FACTORS FOR OSTEOARTHRITIS (OA) INCLUDE:

Diabetes

People with diabetes typically have high levels of insulin, a hormone that controls glucose levels. If glucose levels are high, the risk of OA rises.

High blood pressure

This can alter subchondral bone structure, a layer of bone just below the cartilage, causing issues with weight bearing that affects cartilage and leading to OA.

High lipid levels

Associated with cholesterol, lipids are carried in blood and suffocate cells, causing stress and cell death and changing the structure of cartilage.

Working with IHBI colleague Professor Yin Xiao, her team has been conducting research into the links between OA and diet, finding that certain types of saturated fat are a prime suspect in disease onset. The research group found saturated fat changed the composition of cartilage, particularly in the weight-bearing joints of the hip and knee.

Dr Prasadam is using a Prince Charles Hospital Foundation Research Fellowship Grant, with \$300 000 in associated funding, to analyse the knees of more than 180 patients scheduled for knee replacement surgery at the hospital. Assessments conducted as part of the research will cover insulin resistance, glucose tolerance, cholesterol and blood pressure.

'The aim is to identify metabolic factors involved in OA development and progression,' Dr Prasadam says, 'in order to develop effective prevention and treatments for metabolic OA.' Metabolic factors are common lifestyle aspects implicated in causing OA.

The research suggests that diet may be a bigger contributing factor than wear and tear in OA development, with particular emphasis on a 'junk food' diet containing saturated fatty acids found in animal fat and simple carbohydrates.

OA develops when factors such as ageing, obesity, sports injuries and inflammation cause injury or wear and tear, leading to chronic and painful defects in articular cartilage.

Arthritis is the most common cause of pain and disability in Australia, affecting 25 per cent of Australians — a number that is predicted to double by 2030. It is estimated that OA alone costs the health care system more than \$4 billion annually.

Knee or hip replacements are the most viable treatment options for people with late-stage OA, but they are expensive procedures. Artificial implants have a limited lifespan, after which revision surgery is often required.

Studies show that OA can be avoided in as many as 50 per cent of cases if a person's body mass index (BMI) is kept below 25 — the threshold for being considered overweight. Dr Prasadam says the studies point to the need to be healthy.

Dr Prasadam is working with collaborators in industry and healthcare in a multi-faceted approach to prevent OA, diagnose it early and treat it successfully. With industry partners, she aims to develop nutraceutical products, containing bioactive components from fruits, that can reduce obesity and keep joints in a healthy state.

In collaboration with clinicians, Dr Prasadam aims to tackle obesity through exercise and diet to prevent OA and introduce health policies for screening of metabolic factors that point to a risk of OA. She also aims to use her understanding of the mechanisms involved in obesity and joint degradation to develop treatments that delay OA progression.



PhD candidate
Yolanda Lovie-Toon

Filling in the blanks so chronic cough is effectively addressed

There is increasing recognition of the importance of chronic cough in children, including the need to intervene early to ensure the burden does not continue into adulthood. However, gaps remain about effective prevention strategies, improving treatment and the associated costs.

IHBI researchers are working with Aboriginal and Torres Strait Islander families and health services to better understand what is happening in their communities. The aim is to determine how the burden of respiratory illness can be reduced, while taking into account cultural safety and integrity, reciprocity, equality and respect.

PhD candidate Yolanda Lovie-Toon is conducting research informing the development and implementation of cost-effective, efficient, evidence-based guidelines and best practice standards of care.

The research recognises the significant national and international burden of acute respiratory illnesses (ARI) in childhood. It includes associated adverse clinical outcomes such as chronic cough and the development of chronic lung disease and the substantial costs that the family, community and healthcare system incur.

ARI is an infection of the upper and lower airways that may interfere with normal breathing. It can affect the upper respiratory system, starting at the sinuses and ending at the

vocal chords. It can also affect the lower respiratory system, starting at the vocal chords and ending at the lungs.

The illnesses range from the common cold to severe lung infections such as pneumonia. A doctor should be consulted if symptoms include fever, difficulty breathing, noisy breathing — including wheeze — and decreased levels of consciousness.

ARIs result in an estimated 1.6–2.2 million child deaths globally each year, with higher rates in low and middle-income countries. But Australia's burden is considered significant, with otherwise healthy children experiencing an average of 2–7 ARI episodes per year.

'Cough is symptomatic of a wide range of respiratory illness,' Ms Lovie-Toon says. 'Chronic cough is an adverse outcome of an ARI and a key indicator of chronic respiratory disease. Together, ARI and cough are associated with a high use of medical resources, hospitalisations, medication use, and time off work and school.'

Australian studies show that over-the-counter medications are used in the majority of childhood cases of ARI and coughs, a GP is consulted in half of the episodes and antibiotics are prescribed for one fifth of episodes.

Among Aboriginal and Torres Strait Islander children the incidence of ARIs and subsequent hospitalisation rate is considerably higher than the general Australian population and contributes to the high rates of chronic respiratory diseases in adulthood.

In some regions of Australia, the rates of pneumonia in Aboriginal children are higher than those in Sub-Saharan Africa. Reducing the ARI burden in childhood has the potential to improve respiratory health throughout the whole lifetime.

'There is a lack of comprehensive evidence on the costs of ARI and chronic cough among Australian children, and cost-effective interventions to prevent and manage the disease burden,' Ms Lovie-Toon says.

For example, studies estimating the cost per ARI episode show results varying significantly from \$241 to \$626. The studies show that patients and their families met 79–86 per cent of the costs associated with an ARI episode.

'Immunisation uptake and timeliness is lower among Aboriginal and Torres Strait Islander children than non-Indigenous Australian children,' Ms Lovie-Toon says. 'Interventions that seek to close this gap may be an effective way to prevent the development of ARIs in the population.'

Aiding Ms Lovie-Toon's understanding is her background as a research assistant at Caboolture Community Medical, where she saw the need to address gaps that prevented timely immunisation.

Her supervisors, including IHBI's Dr Kerry-Ann O'Grady, are involved in the National Health and Medical Research Council's (NHMRC) Centre for Research Excellence for Lung Health in Aboriginal and Torres Strait Islander children. An Indigenous Research Reference Group has oversight, with senior Indigenous academics, clinicians, community members, Elders and Traditional Owners guiding all research.

Ms Lovie-Toon's research includes collaboration with IHBI's Australian Centre for Health Services Innovation (AusHSI), tapping into expertise in integrating research into policy and practice to improve clinical care.

WHY IS CHRONIC COUGH IMPORTANT TO ADDRESS?

Without intervention early in life, it could cause permanent lung damage and cause health issues for the remainder of a person's life. It can place a burden on the family, community and health services.

WHY IS THIS RESEARCH IMPORTANT?

There is no clear picture of chronic cough because the burden and costs are borne by families. Hospital statistics do not provide a complete picture. Without it, it is difficult to come up with the most effective interventions to prevent chronic lung disease developing and to ensure children are immunised as early as possible.

Entrepreneurial mindset to push research into the real world

IHBI has strength in infection and immunity research, but the knowledge gained in a laboratory will not have an impact in the community without a commercialisation pathway. IHBI Professor Flavia Huygens is gaining skills to commercialise a diagnostic device for chronic wounds.



Professor Flavia Huygens

Professor Huygens has expertise in chronic wounds, with research that includes the investigation of venous, arterial, mixed and diabetic foot ulcers. The focus is to understand the microbiome of wounds and how changes impact on healing and on infection.

A microbiome is a collection of microorganisms found in a particular environment, creating what can be described as a mini ecosystem. It includes harmless commensal bacteria found on body surfaces and forming a mutually beneficial relationship with the human host.

An important outcome of the research Professor Huygens conducts is the association of specific bacterial species with wounds that heal versus those that do not. 'This is as a result of a prospective study in which we tested 80 venous leg ulcer patients and 120 diabetic foot ulcer patients for a period of three months,' she says.

The research involved collaboration with experts from 11 of Queensland Health's Metro North and Metro South Diabetic Foot Ulcer Clinics, QUT's Wound Clinic and the Royal Brisbane and Women's Hospital Wound Clinic. Funding was secured from the Wound Management Innovation Cooperative Research Council.

Data was used as a base for Professor Huygens and her team to develop a rapid DNA-based test that can detect wound infection at least four to six weeks prior to clinical signs and symptoms. The test is based on specific bacterial biomarkers associated with wound infection detection.

A major drawback with relying on clinical signs and symptoms of infection and inflammation is that patients with ischaemia, characterised by an inadequate blood supply to parts of the body, may suppress the signs as part of their immune response. A similar response can occur in patients with neuropathy, a dysfunction of peripheral nerves that typically causes numbness or weakness.

'Clinical signs of inflammation can also be seen in conditions not associated with bacteria,' Professor Huygens says. 'A critical need exists for a diagnostic test indicating wound infection early.'

Statistics show that 433 000 people have chronic wounds at any one time in Australia, costing the healthcare system \$2.85 billion a year. Every three hours, one person in Australia loses a lower limb as a result of diabetes-related foot disease. Globally, a person has a limb amputated due to a diabetic foot complication every 20 seconds.

The statistics bear out the need for early diagnosis, enabling effective treatment and improving the health and quality of life of patients. However, research excellence, clinical suitability and an unmet need do not guarantee success in commercialisation.

Professor Huygens is participating in the Bridge Program, involving a consortium of 15 pharmaceutical companies, universities and industry associations, providing training to enable successful commercialisation of Australian research.

'The program caters specifically for what I need — learning about commercialisation pathways and regulatory processes required to take a medical device to market,' she says.

'I've benefited from learning how to develop a value proposition that outlines the benefits my device will provide, who will benefit and how the product is unique compared to the current market.'

Professor Huygens has filed a provisional patent for the rapid molecular diagnostic test and is in discussions with an international wound care company about potential commercialisation options.

An additional benefit of being involved in the Bridge Program is the connections Professor Huygens has made. 'It's meant being connected to a diverse cohort of people across Australia with a shared interest in developing entrepreneurial skills and learning how to cross the bridge to commercialisation.'

THE BRIDGE TECH PROGRAM

The Medical Technologies and Pharmaceuticals Industry Growth Centre has announced \$300 000 in funding for two years to provide mid-career and senior researchers with commercialisation training for medical devices. It follows the success of this year's Bridge Program that involved 100 researchers in pharmaceutical research receiving training in commercialisation. QUT is leading the new project, with members from Siemens Healthcare, Stryker Australia, Cook Medical, Hydrix, IDE Group, Magnetica, Ellume, The Actuator, Immunexpress, Cicada Innovations and Flinders University.

Building resilience a key to curb teenage depression

A strength-focused program that builds resilience to address mental health in teenagers is being adapted to provide protection for adolescents with autism spectrum disorder. IHBI's Professor Ian Shochet is leading research that involves input from teenagers, parents and school staff.



Teenage mental health problems are prevalent, with about 20 per cent of people experiencing depression at some point in their teenage years. Depression during adolescence can result in a lifetime trajectory of symptoms.

Professor Shochet says even mild symptoms of depression are linked with reduced psycho-social functioning. 'Harmful effects in adolescents include increased likelihood of suicidal behaviour, social problems, poor academic performance, substance misuse, conduct problems and truancy,' he says. 'Depression impacts on your physical wellbeing. We need to alter the trajectory to prevent the course of depression into adult life.'

Depression involves having an overwhelming sense of sadness and having associated symptoms that may include tiredness, lack of energy, irritability, loss of confidence, poor self-esteem, feelings of guilt, difficulty concentrating and issues with short-term memory.

Risk of mental health problems increases in adolescents on the autism spectrum. Characteristics of autism spectrum disorder (ASD) include social and communication difficulties and difficulty with change and transition. The characteristics create a barrier to factors known for protecting teenagers from depression, such as having a sense of belonging and a capacity for self-regulation in the face of stress.

Professor Shochet says treatment for ASD has traditionally consisted primarily of prescribed medication that reduces symptoms such as irritability, impulsive aggression, repetitive behaviour and hyperactivity; and increases attention and improves sleep.

'We also need to address substantial social and adaptive functioning difficulties,' he says. 'Young adolescents are typically required to navigate increasingly complex peer relationships while dealing with the transition to secondary school. It involves larger schools, bigger classes, multiple educators and increasing academic demands.'

'Their vulnerability to significant decreases in self-esteem at this development stage may diminish their capacity to cope with such challenges.'

Professor Shochet led the development of the world's first successful trial of a school-based approach to preventing adolescent depression, the Resourceful Adolescent Program (RAP). The program promotes resilience, mental health and social and emotional wellbeing of adolescents, resulting in significant decreases in trials in student hopelessness and depressive symptoms.

RAP has since been implemented around Australia and in 19 other countries, including the US, UK, China, South Africa and Morocco.

Building on the success of RAP, Professor Shochet and colleagues from QUT's Faculty of Education, Dr Beth Siggers and Professor Suzanne Carrington, are introducing a whole-school intervention called the School Connectedness Conceptual Model as part of a proof-of-concept study. It uses funding from the Autism Cooperative Research Centre and involves more than 30 students aged 12–14 years from schools around South East Queensland.

A small committee is established at each of the participating schools, consisting of special education teachers, administrative staff, year-level coordinators, students, parents and researchers. Students and parents are also invited to attend RAP programs.

The program aims to build self-esteem among the students, promote their sense of connectedness and belonging, help them keep calm, generate positive self-talk, think resourcefully, solve problems, identify support networks, consider the perspectives of others and keep the peace.

'The whole-of-school intervention aims to trigger a shift in school culture, policy and practice,' Professor Shochet says. 'The aim is to assist school staff to foster a more inclusive school environment and to promote greater school connectedness and resilience in young adolescents with ASD.'

www.rap.qut.edu.au

AUTISM SPECTRUM DISORDER

Symptoms appear in early childhood and endure across the lifespan.

It affects 1 in 100 people.

Boys outnumber girls by a ratio of 4:1.

As a spectrum there is a wide variation of presentation.

Key features include social and communication problems, repetitive behaviours as well as limited interests or activities and heightened sensory awareness.



EXECUTIVE DIRECTOR'S REPORT

The laboratory is where we expect to find researchers, but their focus has to be wider than just their experiments and analysis to include the world around them. They have to understand how their research will improve healthcare for both clinicians who provide the treatments and patients who will benefit.

IHBI researchers work closely with end users — that is, doctors, nurses, therapists, carers, hospital administrators, patients and their families. These people will determine the success of our endeavours by choosing whether to use the treatments, medicines, medical devices and services flowing from our research.

Professor Ian Shochet has a clear understanding of the importance of collaboration with end users, involving teachers, administrative staff, students and parents in his research. He has led development of a school-based approach to preventing adolescent depression that has been implemented around Australia and in 19 other countries.

Dr Aideen McInerney-Leo is another, working at IHBI's Australian Translational Genomics Centre as part of a team that aims to use genetic sequencing technology to improve

diagnosis and prognosis and predict responses to a cancer patient's treatment. It involves partnering with Metro South Hospital and Health Service and Pathology Queensland to determine how to introduce technology into hospitals for healthcare professionals and providing patients with valuable information and support.

Dr Indira Prasadam works with peers from other research institutes, industry partners, clinicians and patients to understand and combat rising rates of osteoarthritis. Her projects aim to understand the genetic and biological processes, develop disease-modifying medicines and promote prevention strategies.

Similarly, Professor Peter Pivonka has his sights set on prevention and treatment strategies for osteoporosis. His research involves collaborating widely with experts from around the world to build a complete picture that includes understanding the role of muscles, blood vessels and the nervous system in osteoporosis.

Professor Flavia Huygens has used research involving patients with venous leg ulcers and diabetic foot ulcers to develop a

rapid DNA-based test that can detect wound infection before clinical signs and symptoms appear. Her next challenge is to use newly-acquired entrepreneurial skills to work with an international wound care company to commercialise the test, making it readily available for use around the world.

PhD candidate Yolanda Lovie-Toon works with families and health services to better understand the community needs and barriers to overcoming chronic cough in children. She has the support of senior IHBI researchers, guidance from an Indigenous Research Reference Group and a background in community health.

I would like to take this opportunity to thank the *IHBI Advances* readers who support important research through donations, enabling work that promises to enhance healthcare in the coming years and make steps to radically improve treatment in the future.

Since this is the final edition of *IHBI Advances* for 2017, I would like to take this opportunity to wish you a safe and healthy holiday period, a Merry Christmas and a Happy New Year.

Professor Lyn Griffiths
Executive Director, IHBI

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