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QUT ihbi
Institute of Health and Biomedical Innovation

IHBI ADVANCES

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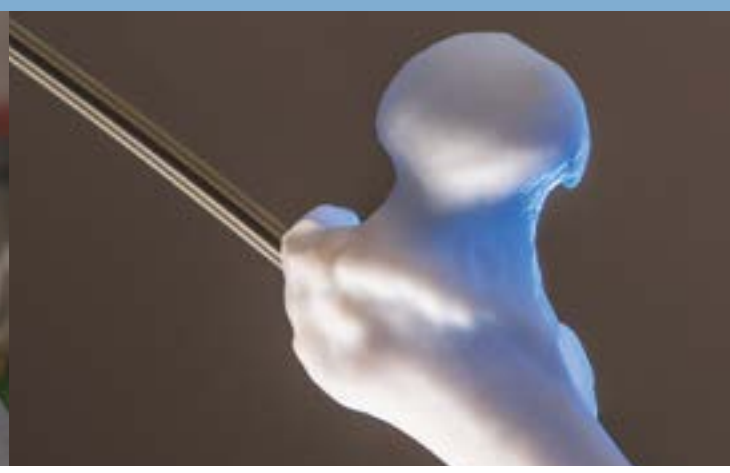
Dr Beat Schmutz



3D modelling at the core of improved hip fracture implants

Hip and femur fracture treatments require expert surgical skills and an implant shape that closely matches the patient's anatomy when inserted into the canal of the thigh bone, called the femur.

IHBI's Dr Beat Schmutz is an expert in implant shape design and optimisation and understands the pressure to get it right, as the implants need to fit a global patient population with a wide range of bone shapes and sizes. 'This is a very complex process that has to take into account clinical and regulatory requirements, anatomical patient variabilities and logistical and commercial factors,' he says.

Dr Schmutz has worked with product development groups from global orthopaedics company and industry partner DePuy Synthes (DPS), part of Johnson & Johnson, in the US and Switzerland on the design and validation of new implant shapes for the development of two nails. The first, the TFN-ADVANCED (TFNA) Proximal Femur Nailing System has been in use in surgery since 2015, while the Femoral Recon Nail (FRN) has been used since June 2018.

HIP FRACTURES

The incidence of hip fractures is rising and projected to further increase in Australia as the population ages.

Cases of hospitalisation are numerous and heavily concentrated in older age groups, with more than 90 per cent of patients aged 65 years and above.

There are significantly more female than male patients, with an age-adjusted rate of 107 per 100 000, compared with 65 per 100 000 for males.

The work builds on a collaboration with DPS stretching back 10 years and involving IHBI input from Professor Michael Schuetz and members of the Trauma Research Group in the development of several implants for fracture treatment. Under the leadership of Dr Schmutz, the research associated with nail fit has attracted awards at four international conferences, notably the prestigious Wilhelm-Roux Prize at the 2009 Annual Meeting of the German Society for Orthopaedics and Trauma in Berlin.

Factors that determine differences in bone properties such as shape and size include age, gender and ethnicity. Older people are likely to have weaker bones and signs of bowing, while women commonly have smaller bones. Ethnicity is linked to differences in bone curvature and length, in part based on a person's height.

Surgeons have several implant options, with each nail similar in shape but having varying lengths, diameters and different angles for hip screw fixation.

More than 1.6 million people sustain a hip fracture globally every year and an estimated 6.3 per cent of patients undergoing surgical treatment require revision surgery. Revision surgery is a second surgery that takes place if the original implant fails and needs to be replaced.

'Fracture treatment with a nail inserted into the femur is highly effective, with successful outcomes for the majority of patients,' Dr Schmutz says. 'However, there are studies that show certain design elements of the nails sometimes lead to complications during or after surgery.'

Dr Schmutz says there have been reports of misfits between a patient's anatomy and nail designs, leading to complications such as the nail tip impinging on, or protruding from, the internal bone surface. While impingement often results in knee pain, nails that protrude require revision surgery.

Traditionally, design validation of the nail shapes involves surgically implanting nails in the lab using anatomical specimens, and the fit being assessed using 2D x-ray images. However, the images generated contain distortion and do not necessarily indicate the true fit between the nail and the bone.

Dr Schmutz has overcome the limitations through use of a customised nail fit tool, using computer graphical 3D modelling, developed in collaboration with Professor Schuetz. The software that drives the nail fit tool was developed at IHBI as part of Jayani Amarathunga's PhD project, under the supervision of Dr Schmutz, Professor Schuetz and Professor Prasad Yarlagadda.

An important consideration has been the nail's radius of curvature (ROC), the bend in the nail that enables it to fit the natural bow of the patient's femur when inserted.

Dr Schmutz conducted 3D computer graphical anatomy studies in collaboration with DPS, showing that a 1.0m ROC nail would more closely match the average anatomy of the target patient populations than the present 1.5 m ROC nails. 'This helps to reduce nail tip impingement in the canal,' he says.

'Using our nail fit tool along with 3D bone and nail models, we have been able to contribute to the development of anatomically better fitting nails for an age and ethnically diverse patient population. This would not have been possible with traditional methods.'

Evaluating pharmacist delivered vaccination a step to wider roll-out

Globally, vaccination is estimated to save between 2 and 3 million lives annually. Yet low immunisation rates are a significant public health concern. IHBI researchers are part of a solution involving pharmacists that started in Queensland and has spread across Australia.

Professor Lisa Nissen

IHBI Professor Lisa Nissen has led research as part of a Queensland collaboration that implemented and evaluated pharmacist vaccination through the Queensland Pharmacist Immunisation Pilot (QPIP). The collaboration involves QUT, the Pharmaceutical Society of Australia, the Pharmacy Guild of Australia, James Cook University and Queensland Health.

The collaboration partners recognise that better access to vaccination services through community pharmacies could influence immunisation rates. Pharmacists are readily accessible and have competency in managing medications, including vaccines; managing deteriorating patients; and understanding the importance of keeping vaccines in a temperature-controlled supply chain.

PATIENT STATISTICS

13.7 per cent of people would not have had a flu vaccine if the QPIP service was not available.

67 per cent were 65 years of age or older.

5 per cent were living with a chronic illness.

99.4 per cent would be happy to receive their vaccination from a pharmacy in the future.

99.5 per cent would recommend the service to other people.

Professor Nissen says the research identified the physical administration of injections as a competency gap for the Queensland pharmacists. It found training could be developed with involvement from Canadian collaborators who had been vaccinating patients in pharmacies for more than a decade. The training was adapted for Australia and delivered to an initial cohort of more than 300 pharmacists.

'After completing the training, the participating pharmacists felt highly confident about injecting patients,' Professor Nissen says.

Pharmacists were trained across all common vaccinations, with the initial Queensland program focusing on influenza and expanded to include delivery of measles and whooping cough vaccinations in subsequent years.

During the two-year QPIP, pharmacists immunised more than 35 000 people, with more than 99 per cent saying they would be happy to return to a community pharmacy for vaccination in the future.

'QPIP has demonstrated the effectiveness of equipping pharmacists with the knowledge, skills and competencies to administer injections and to establish and deliver a successful immunisation service in community pharmacies,' Professor Nissen says.

The pilot's success led the Queensland Government to approve legislation to enable pharmacists to administer vaccinations to the public in a community pharmacy setting.

Pharmacist-delivered vaccination in the community has been a solution for increasing vaccination uptake for influenza in countries such as the UK, the US, Canada and New Zealand.

Professor Nissen says there is evidence from Canada and the US that national immunisation programs involving pharmacists positively affect immunisation rates.

'QPIP has paved the way for legislative changes to allow pharmacist-administered vaccinations across the whole of Australia,' she says. 'Because of QPIP, the value of pharmacists as immunisers is now acknowledged across the country.'

Many universities in Australia have also incorporated immunisation training in their pharmacy programs.

Associate Professor Jyotsna Batra

Genetics showing promise in predicting prostate cancer risk

In Australia, 17 729 men are estimated to have been diagnosed with prostate cancer in 2018, with a loss of 3500 lives. The majority of prostate cancer tumours are not life-threatening but present diagnostic processes are unable to accurately predict which men require treatment.

IHBI Associate Professor Jyotsna Batra has an interest in using genetics to identify cancer early and to distinguish between slow growing prostate cancer and aggressive forms of the disease. She aims to identify tiny changes in DNA, called Single Nucleotide Polymorphisms (SNPs), and establish their link to the cause, development and progression of prostate cancer.

The research has the potential to detect cancer early and discriminate between forms of the disease at an early stage, so oncologists can determine the best treatment options.

Not all cancer medicines benefit all cancers—or patients. Insights into the form and severity of a specific patient's cancer could eventually save them from receiving a cocktail of ineffective medicines.

PROSTATE CANCER

An estimated 3000 Australian men die from the disease each year, making prostate the second leading cause of cancer mortality in Australian men.

Early detection and treatment is essential for a good prognosis.

If appropriate treatment is started while the cancer is still solely in the prostate gland, a cure is possible.

AUSTRALIAN PROSTATE CANCER RESEARCH CENTRE – QUEENSLAND

A transdisciplinary team of IHBI researchers driving the development and translation of new therapeutics and biomarkers for prostate cancer to improve clinical management for patients.

www.australianprostatecentre.org

'I can feel patients' anxiety in the initial stages of diagnosis,' Associate Professor Batra says. 'Affected men are keen to find out whether they should wait and watch, or start aggressive treatment as soon as possible.'

Associate Professor Batra is part of an international prostate cancer consortium called PRACTICAL that is taking major strides in discovering genetic variations that predispose men to prostate cancer risk. From 3 billion base pairs of DNA modules, the consortium has been able to drill down and focus on about 150 genetic variations of interest.

`By analysing the DNA of about 100 000 people, half of which belongs to prostate cancer patients, we've identified more than 150 genetic variations associated with prostate cancer risk,' she says. 'They can collectively explain about 30 per cent of the inherited component of the disease.'

Collaborating with IHBI colleagues at the Australian Prostate Cancer Research Centre – Queensland and the Australian Prostate Cancer Bioresource, based at the Translational Research Institute, Associate Professor Batra is also studying the effects of SNPs on proteins encoded by a person's DNA. The research has resulted in Associate Professor Batra being named Cure Cancer Australia's Researcher of the Year 2018.

DNA is the molecule found in every cell, containing a person's genetic code and instructing cells what proteins to make.

Proteins form enzymes, responsible for much of the work in cells, and are also an important building block in tissues. They are made in the main body of the cell.

But DNA is only in the nucleus of the cell. A copy of the DNA is made, called a messenger RNA (mRNA), capable of moving through pores in the membrane to the main body of the cell. When DNA is copied, mistakes are sometimes made, called mutations.

Associate Professor Batra is also studying the SNPs in the KLK3 protein, commonly called prostate specific antigen (PSA). The protein is an important clinical biomarker, potentially pointing to the presence of disease in a patient.

Recent research shows that the SNPs can change the PSA levels in men and thus the interpretation of the PSA results can be influenced by the presence of the SNPs.

'I am conducting genetic analysis to broadly define genes that define disease risk. One gene discovered through genome-wide association studies involving my laboratory is already proposed as a clinical biomarker for prostate cancer diagnosis and prognosis.

'Present diagnosis is unable to predict the presence of high risk, aggressive disease so many men proceed to biopsy and treatment unnecessarily,' she says. 'Research tells us that large numbers of patients will undergo treatment that will not benefit them. It will only make them sick and adversely impact on their quality of life.

'I would like to avoid such scenarios and ensure that patients have the best quality of life.'


Professor Ross Young

Understanding the physical impacts of PTSD

Research suggests that between 5 and 20 per cent of ex-service personnel will develop post-traumatic stress disorder (PTSD) at some point in their lives. IHBI researchers aim to better understand the factors influencing veteran health and physical symptoms associated with PTSD.

PTSD is a disabling mental health condition that can develop following exposure to a traumatic event. People with PTSD experience a range of psychological symptoms, including intrusive memories, significant changes in mood, arousal and reactivity, as well as persistent avoidance of reminders of the traumatic event.

IHBI clinical psychologist and QUT Faculty of Health Executive Dean Professor Ross Young says PTSD can pose a significant burden, including challenges to maintaining employment, relationship issues and self-care.

POST-TRAUMATIC STRESS DISORDER

People with PTSD often experience feelings of panic or extreme fear, such as:

- **Re-living the traumatic event: The person relives the event through unwanted and recurring memories, often in the form of vivid images and nightmares. There may be intense emotional or physical reactions, such as sweating, heart palpitations or panic when reminded of the event.**
- **Being overly alert or wound up: The person experiences sleeping difficulties, irritability and lack of concentration, becoming easily startled and constantly on the lookout for signs of danger.**
- **Avoiding reminders of the event: The person deliberately avoids activities, places, people, thoughts or feelings associated with the event because they bring back painful memories.**
- **Feeling emotionally numb: The person loses interest in day-to-day activities, feels cut off and detached from friends and family, or feels emotionally flat and numb.**

Treatment usually involves cognitive behaviour therapy, antidepressants or eye movement desensitisation reprocessing.

In addition to the psychological burden, there is increasing awareness of the negative impact of PTSD on physical health.

Gallipoli Medical Research Foundation (GMRF) in partnership with the Returned and Services League of Australia (Queensland Branch) led a large study investigating both the long-term psychological and physical consequences of PTSD. The study was part of a collaboration involving key clinical investigators at Greenslopes Private Hospital (GPH) and research teams at QUT and the University of Queensland, with Professor Young as one of the chief study investigators.

It demonstrated significant physical disease associated with PTSD including liver disease, decreased lung function and gastrointestinal problems.

More than 300 Vietnam veterans, aged 60 to 88 with and without PTSD, took part in the study. With in-kind support from GPH, Queensland X-Ray and Sullivan & Nicolaides Pathology, participants underwent extensive medical and psychological assessments including MRI scans, abdominal and cardiac ultrasonography and fasting blood pathology.

With about 20 per cent of Vietnam veterans experiencing PTSD, Professor Young says the study is important in providing further evidence about the association between PTSD and broader health status.

'The veterans were typically among the most fit members of the community and our work indicates that they may end up with multiple health issues. We need to do all that we can to understand why.'

Taking into account typical disease risk factors such as age, obesity, smoking and alcohol intake, veterans with PTSD were two to three times more likely to be suffering from gastrointestinal problems including irritable bowel syndrome and associated symptoms, stomach ulcers and reflux. They were also more likely to have a significantly increased risk of obstructive sleep apnoea, fatty liver, and are four times more likely to have suffered a heart attack in the past.

Results from the PTSD Initiative published last year in the *Medical Journal of Australia* have been developed into a national health education program by GMRF and RSL (Queensland Branch).

Professor Young says the findings emphasise the importance of viewing PTSD more holistically while recognising the significant implications for how chronic stress can influence overall health.

'We need integrated healthcare strategies directed at both the psychological and physical health of patients with PTSD,' he says. 'The strategies, as well as risk factors, are likely to improve their quality of life and their survival. This also has important implications for other members of society who have been exposed to trauma.'

The collaborating team from QUT including Dr Joanne Voisey, Dr Dagmar Bruenig, Professors Bruce Lawford and Phil Morris, Dr Divya Mehta and Dr Wole Akosile are continuing to look further into the PTSD Initiative data investigating epigenetic markers of associated disease to establish which individual genes may be implicated in PTSD, offering hope for more targeted interventions in the future.

Genetic study casts doubt on iron overload's link to arthritis

Chronic progressive arthritis is a symptom in a significant number of people with haemochromatosis, also called iron overload disorder. But new IHBI research is throwing into doubt the long-held belief that too much iron is the direct cause of arthritis among people with haemochromatosis.


Dr Daniel Wallace

IHBI researchers Dr Daniel Wallace and Professor Nathan Subramaniam are part of a study that aims to understand the genetics underlying haemochromatosis and the different genetic causes between people.

They are part of a study that used data from 1140 people with haemochromatosis to make comparisons between two distinct cohorts. The study involves researchers and clinicians from IHBI, the Prince Charles Hospital, the Royal Brisbane and Women's Hospital, QIMR Berghofer and the University of Queensland.

HAEMOCHROMATOSIS

A common autosomal recessive disease that affects Caucasian populations at a rate ranging from one in 200 to one in 500.

HAEMOCHROMATOSIS AND ARTHRITIS

Chronic progressive arthritis, predominantly affecting joints of the fingers and wrists, is the presenting complaint in about half of the cases of haemochromatosis.

FERROPORTIN

A protein that transports iron from inside to outside of a cell and into the bloodstream.

HEPCIDIN

A small peptide hormone responsible for regulation of body iron homeostasis.

IRON HOMEOSTASIS

The maintenance of stability that prevents iron overload or deficiency.

THE STUDY

www.bloodjournal.org/content/132/1/101

Dr Wallace brings to the collaboration expertise in the molecular basis underlying iron associated disorders; and Professor Subramaniam brings an interest in characterising the consequences of genetic mutations that cause liver disease.

Dr Wallace says the study has a very large cohort of people with a gene that is most frequently mutated in haemochromatosis, HFE. For haemochromatosis to be passed on, both mother and father must have one copy of a mutated HFE gene. People who have two copies of the C282Y mutation, referred to as homozygous C282Y, have a greatly increased risk of iron overload.

A smaller cohort of 156 people involved in the study have a genetic iron overload condition in which one of three other genes is implicated.

The cohorts share a defect affecting the hepcidin-ferroportin axis. Ferroportin represents the only known mechanism for iron export and excretion from a body's cells.

Haemochromatosis involves the body absorbing too much iron from the diet, storing it in organs such as the liver, heart, skin, joints and pancreas.

Treatment for haemochromatosis involves phlebotomy, the removal of blood from the body similar to what is done when donating blood, to reduce iron levels. Initially blood may be drawn once or twice a week but draws can usually be reduced to every three to four months once iron levels are normal.

Yet the study, published in the journal *Blood*, suggests that the treatment does not relieve joint symptoms in people with haemochromatosis.

'Arthritis can often progress even after iron levels have been normalised,' Dr Wallace says. 'This suggests that factors other than body iron stores may be contributing to joint disease in haemochromatosis.'

'Iron may be distributed differently so that it has more damaging effects in the joints of people with genetic mutations in HFE, compared to those with mutations in the other three genes.'

Dr Wallace says there is no known treatment for joint pain among people with haemochromatosis. 'It could be that in the early stages of iron build-up in people with haemochromatosis, something happens that cannot later be reversed.'

The findings open the door to closer collaboration with IHBI researchers in arthritis and wound healing, including Dr Indira Prasadam, who has an interest in genetic signalling pathways and the role of micro RNAs in osteoarthritis. Dr Kathleen Finlayson has expertise in wound healing and chronic disease management while Dr Karsten Schrobback brings an interest in cell and tissue stability in healthy and osteoarthritic cartilage.

Research to build a picture of gut health and link to depression

Gut health is increasingly being recognised as important in improving digestion, boosting the immune system, physical health and even brain and mental health. IHBI researchers are investigating the link between gut health and the management of depression.

Dr Esben Strodl (pictured) is a clinical psychologist, leading IHBI research in improving the health of people with major depressive disorder.

His research involves examining changes in measures of mental and physical health in at least 150 adults with severe depression in response to taking either probiotics or a placebo.

At the core of the research is evidence suggesting that an imbalance of colonies of bacteria, collectively known as a microbiome, may, in part, create systemic inflammation which may be associated with depression.

The imbalance in the gut microbiome, called dysbiosis, involves normally dominating species of bacteria underrepresented and normally contained species increasing in number to fill the void.

Dr Strodl says the research aims to investigate how effective a combination of probiotics and magnesium with orotic acid is to treat depression. The research will also determine if changes in dysbiosis and blood levels of markers of inflammation are associated with improvements in symptoms of depression.

The research will involve recruiting adults with severe depression and monitoring them for eight weeks, and taking blood and fecal samples before and after the intervention.

In addition, the research will take into account the severity of depression, anxiety and stress levels; health behaviours such as sleep, diet and activity levels; and other factors such as medication, mental health history, significant life events and general health issues to build a complete picture.

Non-invasive electrodes will be used on the skin of study participants to monitor activity of the vagus nerve, linking with the parasympathetic nervous system and responsible for regulating the unconscious actions of the heart, lungs and digestive tract. The electrodes will measure variation in the heart rate, reflecting activities of the nervous system.

'Vagus nerve activity is understood to be one of the main mechanisms by which microbiome activity in the gut communicates with the brain,' Dr Strodl says.

'We will evaluate the symptom response and maintenance of people in the study, as well as monitor for side effects,' Dr Strodl says. 'Importantly, we will also measure changes in life satisfaction and engagement in interpersonal relationships and life roles as a way of determining quality of life.'

Collaborators include clinical psychologist Dr Matthew Bambling from the University of Queensland, with expertise in mental health and behavioural medicine, and clinical epidemiologist Professor Luis Vitetta from the University of Sydney, with expertise in the human microbiome and probiotics. QML Pathology will collect participant samples, while industry partner MedLab Pathology will conduct the testing in Sydney.

Dr Strodl brings to the research expertise in health psychology, psychological factors associated with chronic disease and the relationship between physical and mental health.

'We anticipate a significant improvement in a range of mental health measures in participants diagnosed with depression. We also expect an enhanced management of depressive symptoms will favourably impact on quality of life,' he says.

About 30 per cent of people with depression respond well to either medications or psychotherapy, while another 40 per cent have a mixed response. The remaining 30 per cent stay unwell regardless of the intervention.

DEPRESSION

Involves low mood and/or loss of interest and pleasure in usual activities, as well as other symptoms that interfere with all areas of a person's life, including work and social relationships.

BEHAVIOUR

- **Not going out; not getting things done; withdrawing from close family and friends; relying on alcohol and sedatives; not doing usual enjoyable activities; either moving and thinking slower or being agitated.**

FEELINGS

- **Overwhelmed; guilty; irritable; frustrated; feeling a lack of interest or pleasure in things that previously were fun and enjoyable; unhappy; indecisive; disappointed; miserable; sad; feeling hopeless.**

THOUGHTS

- **Thoughts of being a failure; everything being your fault; nothing good ever happening; being worthless; life not being worth living; people being better off without you.**

PHYSICAL

- **Tired; difficulty concentrating; poor short term memory; not sleeping enough or sleeping a lot; loss or change of appetite; significant weight loss or gain.**

EXECUTIVE DIRECTOR'S REPORT

IHBI researchers are working with international collaborators, industry, support organisations and patients to better understand disease and injury and improve healthcare.

The research is already having impact, with improvements being made in hip implant designs and the roll-out of a community vaccination program. Other research is casting doubt on long-held beliefs and providing an evidence base to draw links between diseases.

Dr Beat Schmutz has a long-standing collaboration with industry partner DePuy Synthes, using his expertise in implant shape and 3D modelling to design and validate nails for hip and femur fractures. The research is having an impact, with two different nails now in use in fracture treatments around the world.

Dr Lisa Nissen has also been working closely with collaborators as part of the Queensland Pharmacist Immunisation Pilot that involved more than 35 000 people being immunised in the state's pharmacies and paved the way for legislative changes.

The research of **Dr Esben Strodl** has the potential to manage depression in an innovative new way, unearthing a link to gut health and studying the potential role of probiotics. Importantly, Dr Strodl will consider both physical and mental health issues, with expectations that the research will have a major impact on improving people's quality of life.

Similarly, **Professor Ross Young** has research that covers mind and body, adding to the increasing awareness among researchers and clinicians of the impact of post-traumatic stress on physical health. He is working with support organisations, clinicians and Vietnam veterans to better understand links to liver disease, decreased lung function and gastrointestinal problems and ensure a holistic view of the disorder.

Dr Daniel Wallace and **Professor Nathan Subramaniam** are challenging the long-held belief that too much iron is the direct cause of arthritis among people with iron overload disorder. Their research suggests that normalising iron levels may not necessarily prevent arthritis from progressing.

Using genetics to identify tiny changes in DNA, **Associate Professor Jyotsna Batra** aims to distinguish between slow growing and aggressive forms of prostate cancer to assist clinicians in predicting which men need treatment.

Our endeavours in each of these areas adds significantly to the knowledge gap and combines collaboration, use of the latest technology and innovative thinking to advance research from the laboratory to use in healthcare and the community.

Enjoy this, our first *IHBI Advances* for 2019. I trust it will be a good year ahead, with exciting scientific discoveries; new collaborations with experts from around the world; and support for our researchers to translate and innovate.

Professor Lyn Griffiths
Executive Director, IHBI

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