

IHBI ADVANCES

IN THIS ISSUE

Developing new materials to overcome age-related disease
 Business acumen a key aspect in advancing tissue engineering
 Bid to target treatment for cancer prevalent in the young
 Personalised approach to aid facial fracture treatment
 Implant design to accelerate recovery of limb use
 Executive Director's report

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Dr Paige Little

Research bid to optimise new scoliosis treatment in children

Idiopathic scoliosis is a deformity of the spine which typically develops in adolescence. For some, the best possible treatment is surgery. A new technique aims to use the patient's own growth to correct the deformity while preserving post-operative spine motion through use of a flexible implant.

The new technique is called vertebral body tethering (VBT) and involves screws securing a flexible polyethylene-terephthalate (PET) tether that can be tailored to a patient's anatomy. Before securing the tether to the spine, it is tensioned between the screw heads along the spine to correct the deformity.

IHBI's Biomechanics and Spine Research Group senior research fellow Dr Paige Little says the technique shows much promise, but there are still various biomechanical aspects of the surgery that would benefit from further investigation. The aspects include improved knowledge of the forces that should be applied to a patient's spine to optimise their deformity correction.

There are no clear guidelines regarding the force required for optimal correction and surgical results may depend on a surgeon's expertise.

Dr Little conducts research at the Centre for Children's Health Research, enabling collaboration with Dr Geoffrey Askin and Dr Robert Labrom, senior spinal consultants at the adjacent Queensland Children's Hospital.

Dr Little is using patient-specific spine modelling software to simulate the proposed surgery and predict deformity correction as part of planning for VBT.

A recent study used the software to reconstruct the spine and ribcage of an unidentified 10-year-old patient. The software was used to investigate different combinations of tether tension forces.

'Drawing on these preliminary results, further investigations of different tether tension magnitudes, different screw configurations and screw orientations will be investigated to optimise the post-operative deformity correction,' Dr Little says.

'Our studies will consider the balance between providing a favourable environment for correcting growth asymmetry while not risking bone overload at the screw-bone interface.

'We are taking great strides in understanding how best to plan for surgery and aiding surgeons in providing their patients with the best outcomes.'

Dr Little says VBT suits younger adolescents who are still growing because the PET tether is flexible and can move with the patient, letting the body aid the spinal correction.

'One of the key benefits of VBT surgery is that it allows for continued growth and mobility of the spinal joints after surgery, which is favourable when considering the implant system will remain in place permanently.'

Advantages of the surgery also include reduced blood loss and faster recovery time than existing posterior fusion surgery.

In comparison, spinal fusion uses inflexible metal rods, hooks and wires to correct the spinal curve and secure the spine in a straightened position, making it suitable only for older adolescents.

Idiopathic scoliosis is the most common type of scoliosis and has no definite cause. It tends to run in families but the origins are multi-factorial, with idiopathic scoliosis being 10 times more common in girls than boys. Although idiopathic scoliosis can occur at any age, it frequently becomes an issue during pre-adolescence and adolescence when children are growing rapidly.

During a growth spurt, signs of idiopathic scoliosis often become more noticeable, such as uneven shoulders, one shoulder blade protruding more than the other, ribs more prominent on one side, an uneven waistline or a difference in hip height.

Idiopathic scoliosis is often diagnosed at a paediatric check-up or following a school screening, particularly in children who wear loose-fitting clothes that might cover up the symptoms.

Dr Little is part of IHBI's Centre for Biomedical Technologies, aiming to improve treatment of complex medical cases stemming from injuries, infection and age-related issues. Centre researchers use approaches of regenerative medicine, robotics, artificial intelligence and advanced manufacturing to expand surgical possibilities and reduce complications.

Many of the centre's researchers also collaborate with orthopaedic surgeons and industry as part of the Queensland Unit for Advanced Shoulder Research to improve knowledge of the shoulder's biomechanical functions and anatomy using computer modelling, virtual and augmented reality and biofabrication.

WHAT IS SCOLIOSIS?

The most common spinal disorder in children and adolescents, with characteristics such as side-to-side curvature of the spine, usually combined with a rotation of the vertebrae.

DO ALL PATIENTS NEED SURGERY?

No. Children with mild scoliosis are typically monitored at regular doctor visits. Children with moderate scoliosis typically have bracing, keeping the spine in a straighter position. Children with severe scoliosis usually need surgery.

QUEENSLAND UNIT FOR ADVANCED SHOULDER RESEARCH

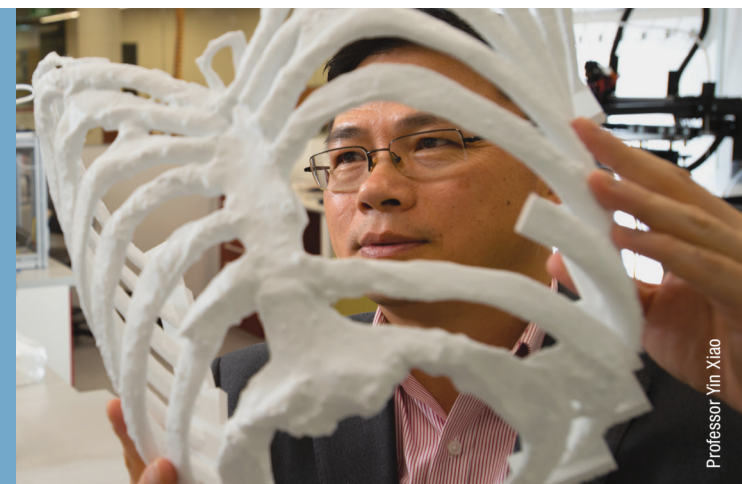
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Developing new materials to overcome age-related disease

3D printing will ultimately enable the fabrication of human tissue and implants to restore function when age-related disease causes damage. Researchers first need to develop new bio-inks that can be manipulated during 3D printing to ensure specific implant properties.



Professor Yin Xiao

Professor Yin Xiao is working with researches and industry partners in Queensland and Shanghai in China to develop, manufacture and validate the next generation of biomaterials and bio-inks.

He is the Queensland leader and centre director of the Joint Research Centre for the Development of Functional Biomaterials in Advanced Manufacturing of Human Tissues and Organs, established late last year with of \$300 000 in support from the State Government.

The centre will focus on living tissue replacements to restore the functions of damaged tissues and organs in the treatment of bone and joint disorders including osteoporosis, osteoarthritis and fractures, and soft tissue trauma including wounds.

WHAT IS A BIOMATERIAL?

A biological or synthetic substance which can be introduced into body tissue as part of an implanted medical device or used to replace tissues or an organ.

WHAT CAN A BIOMATERIAL DO IN A HUMAN BODY?

Replicate the characteristics of tissues and even organs, restore function and encourage tissue regeneration.

WHAT IS TISSUE REGENERATION?

Introduction of an implant with special properties, and potentially populated with a patient's own cells, enhancing the opportunity for one cell type to populate an area while providing contact guidance to the functioning cells. It also ensures stability while the regeneration takes place.

'The ultimate goal is to generate mature biomedical products for bone and cartilage repair, skin regeneration and blood vessel reconstruction to fulfil the huge demand in clinical treatment with advanced biofabrication techniques,' Professor Xiao says.

'Patients will no longer suffer because there are limited suitable donors—or because they are experiencing organ rejection.

'Personalised implants with delicate designs will deliver vastly improved treatment through use of high-performance biomedical product options for soft and hard tissue disorders. It will reduce the burden on the healthcare system and increase quality of life for patients.'

Queensland's older population is expected to grow by 68 per cent in the next 10 years, and about a third of China's population will be over 60 by 2050.

New materials being developed as part of the centre include bio-ceramic 3D bone grafts, cartilage constructs made using ceramics, polymers and hydrogels, and biomimetic skin and blood vessel grafts.

Biomimetics, also known as biomimicry, is the imitation of models, systems and elements found in nature to solve complex human problems.

Professor Xiao says the research will take inspiration from nature in the development of the biomaterials, such as

introducing properties that encourage self-healing when implanted in a human body.

A significant challenge for the researchers is overcoming very narrow 'fabrication windows'. There is a limit to present 3D printing resolutions, speeds and the ability to reproduce the exact same shapes—known as shape fidelity.

'We must overcome the limits to improve process outputs and end product quality—an outcome that can only be achieved through the development of functional biomaterials with tailored biological, rheological and biomechanical properties.'

Establishment of the new joint research centre is largely the result of six years of successful collaboration between QUT—specially through Professor Xiao's Australia-China Centre for Tissue Engineering and Regenerative Medicine—and Shanghai researchers. They include researchers from East China University of Science and Technology and Shanghai Institute of Ceramics—Chinese Academy of Sciences. Researchers from The University of Queensland are also part of the centre.

A number of Queensland-based and Chinese biotechnology companies are involved in the development and potential commercialisation of the products stemming from the centre's research.

The world market for biomaterials is expected to almost double by 2024 to \$308 billion.



Dr Laura Bray

Business acumen a key aspect in advancing tissue engineering

Translation is key to ensuring that research goes from a scientific pursuit in a laboratory to an impact in the community, producing medical devices, products and services for better diagnosis and treatment—and ultimately improving lives.

Researchers are increasingly partnering with industry and employing an entrepreneurial mindset to ensure advances in medicine and healthcare.

IHBI's Dr Laura Bray is part of an initiative developing world-class training programs and enhancing industry partnerships to overcome barriers in manufacturing processes and encourage investment in cell-based and tissue engineering therapies.

She says regenerative medicine, tissue engineering and cell therapies are promising new technologies to overcome the health burden associated with ageing populations and increasing chronic disease incidences. Yet they often remain in early development phases or early clinical trials because of a lack of investment.

Dr Bray is Deputy Director of the Australian Research Council (ARC) Training Centre for Cell and Tissue Engineering Technologies. It has been established with close to \$5 million in Federal Government funding as a collaboration between Monash University and QUT to produce industry-ready graduates and early career researchers with innovative, translational and entrepreneurial mindsets to underpin growth in the industry sector.

THE AUSTRALIAN RESEARCH COUNCIL (ARC) TRAINING CENTRE FOR CELL AND TISSUE ENGINEERING TECHNOLOGIES

'Our government is strategically investing in partnerships between universities, industry and government to drive the commercialisation of research leading to new jobs, new business opportunities, productivity gains and benefits for society.'

~ Federal Minister for Education Dan Tehan

Using a background in 3D tissue engineering and culture techniques, Dr Bray is leading research to improve cell purity and viability for research, as well as for the manufacture of cell therapies.

She is also involved in an IHBI research project developing 3D-printed implants, called scaffolds, that encourage cell growth and tissue regeneration following a mastectomy. The scaffolds degrade safely in time as human tissue replaces it. The research will involve studying the scaffolds in the laboratory for 12 months to ensure long-term growth of normal breast cells and tissues.

'We need to confirm the potential of the scaffolds as a 3D tissue engineering construct, and to investigate normal mammary processes are occurring so that we can be confident of their potential as a future breast implant technology,' Dr Bray says.

Other research areas in which Dr Bray is taking a lead at IHBI include leveraging smart technologies for pre-operative planning and customisation in orthopaedic surgery, and enhancing nanomaterials used in cancer treatment.

Nanomaterials show potential as vehicles for targeted anti-cancer therapeutics, overcoming key limitations of conventional chemotherapy.

Chemotherapy works on cells that are dividing rapidly. Cancer cells divide and multiply rapidly but so do some healthy cells, such as those in a person's blood, mouth, digestive system and hair follicles. Side effects occur when chemotherapy damages the healthy cells.

Dr Bray will use 3D models that mimic human tissue to screen and identify chemotherapy-loaded nanoparticles that target cancer cells effectively.

'The cancer microenvironment is influenced by many mechanical, chemical and cellular processes which can't be depicted in 2D,' Dr Bray says. 'We are developing highly sophisticated 3D models of the cancer microenvironment to more accurately mimic interactions during cancer development.'

'Our lab is developing 3D models of breast cancer, prostate cancer and acute myeloid leukaemia. The models can be used for therapeutics testing and studying therapeutic targets for cancer patients.'

IHBI researchers collaborating as part of the ARC centre include biomedical engineer Distinguished Professor Dietmar W Huttmacher, molecular cancer geneticist Associate Professor Jyotsna Batra and polymer chemist Associate Professor Tim Dargaville.

Nine other IHBI researchers add critical mass to the centre, as well as QUT colleague Professor Uwe Dulleck—a leading behavioural economist from QUT's Centre for Behavioural Economics, Society and Technology—who will contribute expertise to ensure optimal consumer uptake of the technologies developed within the centre.

PhD candidates and researchers will be provided opportunities to participate in professional development programs, building skills and demonstrating effective navigation in medical technology development and commercialisation.



Dr Jacqui McGovern

Bid to target treatment for cancer prevalent in the young

Osteosarcoma (OS) is a common type of bone cancer, often diagnosed in teenagers or young adults and typically requiring both chemotherapy and surgery. IHBI researchers are developing a model to better target the treatment, reduce side effects and improve a patient's quality of life.

IHBI researcher Dr Jacqui McGovern is developing specialised 3D-printed implants capable of delivering chemotherapy to the surgical site, preventing OS recurrence and subsequent metastatic spread, as well as saving the limb.

Dr McGovern is using \$197 556 in funding from Cancer Australia and My Room for pre-clinical osteosarcoma studies, involving surgeons and research experts in biomaterials, tissue-engineering and regenerative medicine.

She will lead development of a tissue-engineered microenvironment, a laboratory model that will closely mimic a patient's surgical site, seeded with bone tissue sourced through a collaboration with the Prince Charles Hospital.

'The project will pave the way to develop an effective pre-clinical model to study new therapeutics, their target cells, as well as therapeutic delivery systems and complex surgical and tissue regeneration techniques,' Dr McGovern says.

OS surgery—called a tumour resection—involves removing the bone tumour as well as surrounding bone and muscle to ensure no cancer or tumour traces are left behind. A bone graft—a piece of bone from another part of the body—or a prosthesis replaces the removed bone.

Cancer recurrence is typically difficult to detect and may result in metastasis. The five-year survival rate is estimated to be 25 per cent following metastasis.

Chemotherapy initially increased patient survival in the 1970s, but there has been no enhancement of overall OS patient survival since then. Many new therapeutic candidates appear effective in preclinical studies but up to 80 per cent prove ineffective during human trials.

Dr McGovern says targeted chemotherapy will decrease the impact on patient quality of life by circumventing systemic chemotherapy in young OS patients—and with it the potential for long-term side effects such as secondary malignancies.

Specialised 3D-printed implants called scaffolds will be introduced in Dr McGovern's tissue-engineered micro-environment to deliver chemotherapy, and a specialised bone graft will be used to regenerate the bone defect.

'The specialised scaffold will help guide the bone regeneration and ensure the correct positioning of the bone graft material,' Dr McGovern says.

An important collaborator is Adjunct Professor Boris Holzapfel, a renowned orthopaedic surgeon based in Germany who has performed cutting-edge surgery on patients with bone tumours such as OS.

Professor Holzapfel has shown that a defect site can be filled with a bone cement following a tumour resection until a patient is ready for the next surgical procedure.

After six weeks, the bone cement can be removed and patient-specific tissue-engineering methods employed to regenerate a bone defect using a bone graft from the patients' own healthy femur.

'That tells us that an OS surgical site is ideal for grafting and capable of regeneration,' Dr McGovern says. 'The research has the potential to change the way OS patients are treated and improve their surgical outcomes.'

FACTORS LINKED TO BETTER OSTEOSARCOMA PROGNOSIS

Being younger

Being female

The tumour being on an arm or leg, as opposed to the hip bone

The tumour being completely removable

Normal blood alkaline phosphatase and LDH levels

The tumour having a good response to chemotherapy

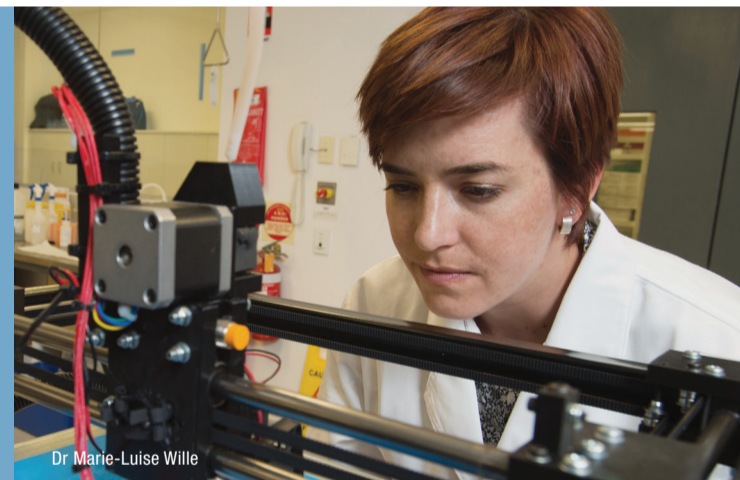
LIMB-SPARING SURGERY

Also called limb salvage. A treatment for malignant bone tumours and soft tissue tumours, referred to as sarcomas.

Unlike many types of surgery for malignant bone and soft tissue tumours, limb-sparing surgery provides a patient with a chance to keep the limb with the tumour.

Personalised approach to aid facial fracture treatment

People with facial injuries involving eye socket damage routinely require cheekbone implants, often made of silicone. IHBI researchers are working on a 3D-printed replacement that overcomes the risk of rupture or misalignment.



Dr Marie-Luise Wille

Assaults and car accidents are the most common causes of eye socket fractures—called orbital fractures—and together account for up to 70 per cent of all facial fractures.

Silicon implants are used to restore aesthetic appearance in such cases, as well as following tumour excisions for cancer therapies. Subsequent ruptures or misalignment may result in a secondary operation. Silicone implants also come with a risk of a negative foreign body response.

IHBI's Dr Marie-Luise Wille is leading the development of a 3D-printed implant—called a scaffold—that will improve a patient's experience, enable a surgeon to provide a tailored approach and avoid re-operation.

'Orbital fractures may differ in their presentation when patients are admitted to hospital and in their clinical management, necessitating a patient-specific approach,' Dr Wille says.

'We are looking to make regenerative, resorbable scaffolds that are as clinician-friendly as possible. Surgeons tend to prefer a product which can be cut or moulded to shape in the operating theatre.'

The scaffolds are made using a medical grade biocompatible polymer, already used in the clinic for more than 20 years, and populated with a patient's own cells that encourage the body to regenerate damaged tissue.

As the patient's tissue grows, the scaffold provides a support matrix and is then slowly and safely absorbed.

Dr Wille says the patient-specific approach that is at the core of the new generation of orbital fracture treatment brings challenges for the research team.

'We will develop a novel 3D printer for this purpose, which does not have a flat print bed and is able to print curved surfaces on all sides. Further, we will design and test the implants. IHBI is unique in providing facilities where the implant can be printed, mechanically tested and research involving actual human tissue can be performed.'

Additional challenges include ensuring the implant is fit for purpose, aligns with established surgical techniques and meets regulatory requirements.

Collaborators on the research include Chief Technology Officer Dr Mohit Chhaya, Head of Design Sara Lucarotti and

Head of Research and Development Dr Navid Khani from medical technology manufacturer BellaSeno in Germany, with expertise in biomedical engineering and additive manufacturing technologies.

Dr Wille is the Deputy Director of the Australian Research Council (ARC) Training Centre for Multiscale 3D Imaging, Modelling and Manufacturing, working with researchers from around QUT and the Australian National University.

The centre has been established with \$3.98 million in Federal Government funding, with research, industry and clinical collaborators in Canada, Germany, Norway and the US.

Among the IHBI researchers are Distinguished Professor Dietmar W Huttmacher, with expertise in biomaterials, biomechanics, medical devices and tissue engineering, and Professor Prasad Yarlagadda, with expertise in artificial intelligence in manufacturing, prototype manufacturing, tool design and non-traditional manufacturing.

Dr Wille says the centre's research has application in industries as diverse as oil, gas and energy, medical technologies, and advanced manufacturing.

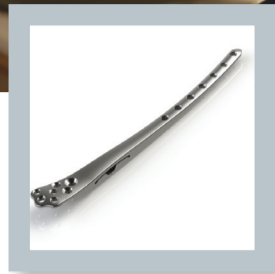
The centre aims to produce industry-ready graduates and early career researchers with innovative, translational and entrepreneurial mindsets to underpin growth in the industry sector.

PhD candidates and post-doctoral researchers will be given an opportunity to participate in professional development programs such as BridgeTech, training researchers and entrepreneurs to effectively navigate the medical technology commercialisation pathway.

Implant design to accelerate recovery of limb use

People with fractures of the thighbone—or the distal femur—have better recovery when they move soon after surgery. But movement that prevents joint stiffness must be balanced with precautions to avoid overloading.

Associate Professor Devakar Epari inset below: the biphasic plate



IHBI Associate Professor Devakar Epari is collaborating with engineers from the AO Research Institute (ARI) Davos in Switzerland to develop the biphasic plate, improving fracture stabilisation and promoting fast, robust healing.

Associate Professor Epari is a co-inventor of the plate, along with ARI Focus Area Leader Markus Windolf.

‘Our invention addresses the clinical dilemma of plates that are too rigid or too flexible, leading to suboptimal movement of the fractured site,’ Associate Professor Epari says.

The knee is the largest weightbearing joint in the body and is vulnerable to injury. The distal femur makes up the top part of a knee joint, with cartilage cushioning the bone and strong muscles at the front and back of the thigh providing support and enabling bending and straightening.

Fractures of the thighbone just above the knee joint—called distal femur fractures—are often the result in younger people of high-energy injuries, such as falls from significant heights or car accidents. Elderly people with distal femur fractures typically have poor bone quality.

Regardless of age, people with such fractures have the best recovery when they can move soon after treatment, such as walking. Treatment allowing early motion of the knee lessens the risk of stiffness and prevents problems resulting from extended bed rest, such as bed sores and blood clots.

Because traction, casting and bracing do not allow for early knee movement they are used less frequently than surgery.

Surgery may involve fixing a plate at the end of the fracture but does not usually include piecing small fragments of fractured bone together. The fixed plate keeps the shape and length of the bone correct while it heals. Individual fragments will fill in with new bone, called a callous.

‘We know that a certain degree of motion is advantageous and promotes the callus formation essential to fracture stabilisation,’ Associate Professor Epari says.

‘In contrast to conventional plates, the biphasic plate—due to its specific design—enables defined motion of the fractured site while avoiding overloading.’

The concept took shape in 2014 and 2015 when Dr Windolf had a research sabbatical at QUT, where he collaborated with Associate Professor Epari on fracture healing research. ‘It started with an idea: Let’s make a slot in the plate,’ Dr Windolf says. ‘This evolved to detailed discussions about how we could build a plate with enhanced features.’

The biphasic plate concept was proven using mechanical testing and preclinical experiments at ARI from 2016 to 2018. With support from the AO Development Incubator, the plate is undergoing a clinical proof of concept process ahead of possible certification for introduction in the European market.

The plate standardises a bone-healing environment, increases implant strength for full early weight bearing and prevents implant fatigue failure. It also enables standardised surgical procedures, makes it easier for surgeons to apply, reduces risks and improves patient outcomes.

Associate Professor Epari and Dr Windolf are confident of the plate’s success following engagement with—and input from—physicians. ‘At the AO Davos Courses 2018, we had feedback from 150 surgeons who were enthusiastic and saw a need.’

‘Our aim is to get it CE marked within the next two years, and then getting it to users and building its reputation.’

DISTAL FEMUR FRACTURES

A US STUDY FOUND:

293 patients were treated for 302 fractures between 2005 and 2010.

The mean age at the time of fracture was 62.2 years: 44 years for males and 71.6 years for females.

33.4 per cent were males and 66.6 per cent were females.

After the age of 60, a rapid increase in fracture incidence was observed in both genders, with a large female predominance.

A UK STUDY FOUND:

Records at Major Trauma Centre in London identified 219 patients with distal femoral shaft fractures between December 2010 and January 2016.

Male patients had a median age of 65.6, and females a median age of 71.

Injury through high-energy mechanisms were more common in men, with 70.5 per cent.

Women sustained injuries mainly from low-energy mechanisms, with 82.7 per cent.



EXECUTIVE DIRECTOR'S REPORT

IHBI has long had a focus on research that combines expertise across disciplines with clinical collaboration, industry engagement and leveraging of the latest technology. Now, we have taken a major step towards delivering better health in our lifetime with establishment of the Centre for Biomedical Technologies and the appointment of its Director, **Associate Professor Travis Klein**.

The centre aims to improve how we treat complex medical cases stemming from injuries, infection and age-related issues. Regenerative approaches, robotics and artificial intelligence, and advanced manufacturing are used to expand surgical possibilities and reduce complications. Ultimately, the research is conducted to provide better patient treatments and quality of life into the future.

It is part of a recent move to establish QUT research centres representing high-quality and focused research activity aligning to the university’s key research strengths. The purpose of the centres is to develop critical mass in research capabilities that are nationally and internationally leading.

This edition of *IHBI Advances* showcases the research conducted as part of the Centre for Biomedical Technologies,

bringing together multi-disciplinary experts, developing and translating new medical technologies and increasing capacity. Centre activities will also improve training to enable better career opportunities for PhD candidates and early career researchers.

The centre has leadership and significant input in four Australian Research Council (ARC) training centres, producing industry-ready graduates and early career researchers with innovative, translational and entrepreneurial mindsets to underpin growth.

Distinguished Professor Dietmar W Huttmacher mentors and oversees a training centre in additive biomanufacturing and professors **YuanTong Gu** and **Peter Pivonka** lead investigations in joint biomechanics.

Dr Laura Bray is Deputy Director of a training centre for cell and tissue engineering technologies, collaborating with Monash University. **Dr Marie-Luise Wille** is Deputy Director of a training centre for multiscale 3D imaging, modelling and manufacturing, working with researchers from QUT and the Australian National University.

Shoulder research represents a significant centre capability through the Queensland Unit for Advanced Shoulder Research. Professor Pivonka is a QUASR director, alongside **Adjunct Associate Professor Ashish Gupta**, a Brisbane orthopaedic shoulder surgeon with an interest in biomedical research.

Surgeons are significant stakeholders in the centre’s research, ranging from bioengineering and computer modelling that is involved in implant design and post-surgical healing, to nanotechnology, with textured surfaces being developed to lower the risk of bacterial infection in implants.

Dr Jacqui McGovern collaborates with surgeons and research experts to develop specialised 3D-printed implants capable of delivering targeted chemotherapy following bone cancer surgery, with the aim of preventing recurrence.

With such a breadth of research activity across the Centre for Biomedical Technologies, we are confident of being able to deliver better health in our lifetime.

Enjoy this edition of *IHBI Advances*.

Professor Lyn Griffiths
Executive Director, IHBI

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