2016

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Message from the Pro Vice-Chancellor

Professor Michael Berndt
Pro Vice-Chancellor
Faculty of Health Sciences

The Faculty of Health Sciences is internationally recognised for its leadership in health research, policy and practice. We are engaged in developing practical solutions to global health challenges, preparing our students for leadership roles in healthcare, and working with our partners and communities to advance health and wellbeing both locally and globally.

This publication provides a snapshot of the diverse range of research being undertaken by the Curtin Health Innovation Research Institute, as well as other research groups and schools in the Faculty. It showcases projects across medical microbiology, immunology, vaccines, biomolecular interaction and drug discovery in chronic conditions that burden Australia. This important research focuses on translating findings from discovery, to translational research programs to include applications and adoption in the clinical context.

In this issue we present articles on:
- an innovative microcapsule delivery of insulin
- the link between asthma and allergy
- how nutrition contributes to neurodegenerative disorders
- a natural protein used to target cancer stem cells
- how microorganisms can be used to help make mineral processing more sustainable
- and more

I invite you to read about the innovative, integrated and collaborative approaches that our health sciences researchers and academics are committed to, which will ultimately make a significant impact on improving the health and wellbeing of people and communities.

Professor Michael Berndt
Pro Vice-Chancellor
Faculty of Health Sciences
What is the connection between the ‘Western’ lifestyle, allergies and asthma? Why is it that English speaking countries such as Australia have a significantly higher incidence of asthma than most other countries? For example, the difference in asthma and allergy rates between Australia and China is massive – there is about a tenfold variation between the two countries.

Some people suggest that the presence of bacteria in food has some bearing on the development of allergy and asthma. However it may be some other element, such as exposure to pathogens and pollutants, changes in lifestyle, or some other unknown influence. But clearly, something in the Western environment is altering the function of the human genome, and it is these genomic changes that most likely cause higher allergy and asthma rates in countries like Australia.

While several epidemiological studies have reported an increased susceptibility to allergies among Chinese migrants to Australia, until recently, no studies had reported on the molecular changes in the genome of Chinese migrants to Australia. Three years ago, Dr Brad Zhang, Associate Professor at the Curtin School of Public Health, embarked on a unique study involving recently arrived migrants from China, comparing the genomic profiles of that group to those of Chinese migrants who had been here for more than two years, to determine the change in their immune function.

He presented some findings of those studies at the Annual Scientific Meeting of the Thoracic Society of Australia and New Zealand in April 2015. The study is looking deeply into the effects that the Western environment has on the human genome, by utilising advanced molecular analysis techniques to characterise millions of molecular changes in the genome of CD4+ T cells such as DNA methylation and gene expression. Investigating these genomic changes using high-throughput molecular techniques, such as the Illumina 450K and Human HT-12 v4 techniques, may hold the key to understanding why asthma and allergy are more common in Western countries.

The work is ongoing, and while it has confirmed some global, overall trends, specific findings require the comparisons of millions and millions of epigenetic markers. However, the study has already determined that incidence of hay fever and levels of the inflammatory molecule interleukin-10 (an indication of allergy) both increased with increasing length of time in Australia, and that the DNA of longer-resident immigrants was found to have undergone more structural changes known as methylation, which in turn reduced the global gene expression in these longer-resident immigrants.

Dr Zhang plans to expand the study to investigate nasopharyngeal and gut microbiome profiles in Australian Born Chinese (ABC) and Chinese Born Chinese (CBC) children living in China. “We are investigating the whole genome methylation changes in ABC children in relation to dietary patterns, compared with CBC children.

The ongoing project provides a unique opportunity to investigate the microbiome mechanisms underlying the development and precipitation of asthma and allergy in ABC children. We hypothesise that the western diet has changed the upper respiratory airways’ and intestinal microbiome pools in ABC children, thus causing a higher incidence of asthma and allergy in Western countries,” he said.

As the projects proceed, our understanding of the causes, and the effects, of genomic change related to environmental change is expected to increase, and eventually to lead to effective prevention strategies, focusing on modifying the environment, to minimise allergic diseases.

Dr Zhang’s team is being supported by four Telethon Perth New Hospital Research Funds grants, one Princess Margaret Hospital research grant and two fellowships: BrightSpark and Thoracic Society of Australia and New Zealand fellowships. He has a strong collaboration with Professors Peter LeSouef and Jack Goldblatt from the University of Western Australia. He also has extensive collaboration with researchers at Telethon Kids Institute and Princess Margaret Hospital for Children.
Innovative microcapsule delivery of insulin heralds new promise.

Curtin-based biomaterial research is challenging the long-held use of injected insulin with a new discovery that may offer better and safer control of blood glucose in the long-term, complementing or even replacing the need for insulin administration in diabetes patients.

Since the 1920s, continuous use injected insulin has been the mainstream treatment for type 1 diabetes. But its limitations remain – from strict storage temperatures to dose control sensitivity. Imprecise control of blood sugar levels can lead to long term complications such as eye disease, kidney and nerve damage, and can be fatal in certain instances.

Type 1 diabetes is a life-long disease, in which cells that make insulin are destroyed by our own immune system. As a chronic disease in children, it affects more than 122,000 in Australia alone (Juvenile Diabetes Research Foundation, 2014) with rates increasing every year.

Insulin is used by all type 1 diabetic patients and over 30 per cent of type 2 patients, as well as more than half of pregnant women with gestational diabetes. Diabetes remains difficult to treat and all types have significant complications arising from substantial inflammation that develops throughout the disease.

As rates of type 1 and type 2 diabetes continue to rise every year, and considering the widespread health and social impacts on patients, their families and the community at large, finding a safer and more precise insulin delivery mechanism remains critical.

At Curtin University, Dr Hani Al-Salami is researching and making significant progress on a unique approach that has the potential to change the face of diabetes treatment. His innovative insulin delivery system is based on the use of special microcapsules.

Dr Al-Salami worked in the laboratory where the microencapsulation was pioneered by Professor Thomas Chang at McGill University (Montreal, Canada). Now, he and his team have made an exciting new discovery. “Collaborating with The University of Western Australia, my lab at Curtin was the first in the world to engineer a special capsule. This capsule is made using polymers and available bile components that are safely and naturally produced in our gut.”

Dr Al-Salami explains the new method further: “Our robust, efficient, and novel method uses engineered microcapsules, pioneered in my lab in 2014, incorporating unique bile acids and containing cells that have the potential to permanently and continuously release insulin, reducing the need to inject insulin, and so controlling diabetes symptoms.”

Furthermore, Dr Al-Salami and his team at the Curtin lab have achieved two standout features in their capsule’s engineering, enabling them to overcome the key obstacles encountered in other studies carried out in Canada, the USA and Australia.

“Firstly, we have engineered bile acid-based microcapsules. This and other biocompatible components with improved anti-inflammatory properties means our capsules may not trigger a significant overgrowth of tissue around the capsule that previous studies experienced, and which causes inflammation and destroys cells.”

“Secondly, we’ve used refined micro-encapsulating methods to be able to produce exceptionally small size microcapsules, with a high cell-load/mass ratio and a higher surface area.”

Bile acids are already known to have potential benefits in diabetes, as they’ve been shown to maintain insulin secreting cells in an incubator. But apart from the Curtin group, to date no one has trialled bile acid-based microcapsules with potential transplantation of insulin-producing cells.

The microcapsule has shown a good safety profile, and Dr Al-Salami explains they aim to test the method by possibly transplanting insulin-producing living cells, using microcapsules, into diabetic animals.

“The project will measure the physiological response (blood glucose and inflammatory biomarkers) of diabetic mice, after being transplanted with our cell-containing biomaterials-based microcapsules. The ultimate goal is to replace dead β-cells with newly transplanted cells that can control blood glucose, and function as host-own cells.”

The potential for developing a single delivery system to complement or even replace the use of insulin in diabetes is certainly exciting. Achieving a method that will mimic normal insulin delivery will go a long way to alleviating many diabetic complications.

“Being able to grow cells in vitro, using unique bile acid-based microcapsules for transplantation, is a significant step towards innovating therapeutics using functional living cells, rather than manufactured drugs as a continuous source of treatment for diabetes.”
UNDERSTANDING THE HUMAN MICROBIOME

In a fast approaching post-antibiotic era, understanding how to protect the human microbiome and ultimately our health, will depend on the discovery of targeted, selective antimicrobial therapies.

The discovery of the antibiotic, penicillin, and follow on drugs to treat human infections and diseases was a landmark event, and the successes led society to view microorganisms largely as ‘bad’ bugs that must be eradicated to protect our health.

However we’ve learned that antibiotics are not currently selective, so although they target ‘bad’ bugs or pathogens, they also affect beneficial microbial communities in our bodies, often reducing or wiping them out.

It’s now becoming apparent that human health is inextricably linked to the presence of beneficial microorganisms colonising our systems, that can act as a barrier to the entry of unwanted pathogenic ‘bugs’.

The microbiome is the collective term for microbial communities and their genes that colonise different parts of our bodies. Their composition can be unique to individuals, and microbiomes have been likened to an extra ‘organ’ capable of providing additional functions that contribute to our health.

Under the direction of Professor Fergal O’Gara, Curtin’s Human Microbiome Program is helping to progress worldwide understanding of microbiomes. “Our program is based on understanding how alterations in the make-up of the microbiome in different parts of the body can shift the balance between health and disease. And the more we understand, the more we need to look for targeted therapeutic options to conventional antibiotics.”

One of the program’s most noteworthy research projects is focused on finding innovative strategies to protect and maintain the microbiome population. The team has developed an extremely promising approach that has been shown to target and block the formation of potentially damaging ‘biofilms’ in the human body.

Biofilms are breeding grounds for maintaining multi-drug resistant pathogens, so together with the overuse and misuse of antibiotics, they contribute to a dramatic reduction in almost all antibiotics’ ability to fight infections. It is also suspected that biofilms in the gut microbiome may act as ‘bio-factories’ capable of producing harmful substances linked to cancer initiation events.

Prof O’Gara explains: “We are already approaching the perfect storm in which the rapid decline in new antibiotic production is being met by an equally rapid increase in multi-drug resistant organisms. Clearly, blocking biofilm formation is a key strategy for future human health and wellbeing.”

Collaborating with researchers in Ireland, Europe and several Perth hospitals and research institutes, the Curtin School of Biomedical Science has made an exceptionally promising breakthrough.

“We have recently been successful in developing next-generation, antimicrobial strategies for the control of microbial biofilms. We’ve developed innovative bioactive compounds that selectively disrupt the signalling pathways involved in biofilm formation. This approach has key advantages over conventional antibiotics that are designed to kill invading microorganisms, but are not selective, and may wipe out beneficial organisms.”

This synthetic biology approach has enabled the isolation of a suite of compounds that selectively block the formation of biofilms. Some have been optimised synthetically. These ‘smart’ biofilm blockers mimic natural signals and possess the critical hallmarks of effective therapeutic anti-microbial molecules.

What makes this breakthrough even more exciting is the origin of these compounds. “Our novel bioactive compounds have been mined from previously uncultured marine derived microorganisms and metagenomic libraries. The enabling technology of incorporating the vast genetic diversity of uncultivable marine microorganisms is particularly exciting for drug discovery.”

The Curtin developed technology offers access to the complete biodiversity of the ocean environment, free from the ‘culturable bottleneck’ that limits the effectiveness of other more traditional approaches. The marine environment is now recognised as a relatively untapped and major source of organisms that produce novel biological materials as well as unique metabolic processes.

In the context of global microbiome research, this approach holds immense biotechnological and biopharmaceutical potential. “We’re faced with the challenge of developing targeted pharmaceuticals that can protect beneficial microbial populations in our bodies, while selectively eliminating pathogens. So we are particularly excited about the potential our new prototype bioactives are displaying in providing this selectivity.”
While the world makes strides in developing therapies for malaria – as evidenced in the 2015 Nobel Prize for Medicine that recognised the discovery of artemisinin by Chinese scientists – there is still a way to go to ensure optimum dosage regimens are carefully determined, especially for vulnerable patients such as young children and pregnant women.

Performing drug assays to do this has traditionally been by the use of blood plasma samples. But collecting, storing and transporting samples presents multiple problems in tropical countries and remote locations, including rural Australia.

Meeting this challenge is an innovative research project at Curtin’s School of Pharmacy. Researchers have developed assay techniques to measure drug concentrations in dried blood spots, offering a novel, reliable option for collecting important data.

“Our research is supported by an NHMRC Project Grant and has a focus on optimisation of artemisinin-based antimalarial and other antimicrobial therapy in young children in Papua New Guinea,”

Professor Batty’s laboratory at Curtin is responsible for assay development and validation, to produce the pharmacokinetic data from clinical studies. This data is being used in sophisticated pharmacokinetic-pharmacodynamic models to inform clinical decisions on dosage regimens for antimicrobial therapy.

“A particularly exciting aspect of our work has been the development of assay techniques to measure these drugs in dried blood spots, which solves a number of problems associated with traditional plasma samples, particularly storage and transportation in tropical climates and remote areas.”

Being able to collect and use dried blood spots has several advantages for pharmacokinetic studies. The volume of blood required is considerably smaller and can be collected from venous blood samples, finger pricks, or heel pricks in young babies. The blood is placed onto sample cards, air-dried and stored in moisture-free envelopes.

When the cards reach the laboratory, analysts punch out a disk (approximately the same size as a standard office paper punch) and extract the drug from the disk. Analysis is then performed by high performance liquid chromatography with mass spectrometry detection (LC-MS/MS).

While dried blood spot assays are being reported for a range of drugs, from research groups in several parts of the world, according to Professor Batty, the technique developed at the Curtin lab is significant for several reasons.

“Here, we are developing and validating techniques for some drugs where no methods have been reported, and for the challenging purpose of obtaining pharmacokinetic data. This necessitates the detection of low concentrations of drug and metabolites, as well as validating the storage and transportation requirements of the dried blood spots. Furthermore, the stability studies are important because of the logistical challenges of research in tropical countries and remote locations in Australia.”

This technique clearly has important potential applications globally. Being able to measure drug concentrations in dried blood spots is an innovation that could improve clinical research and patient care, especially in babies and young children.

“Our research to date shows that we can use this technique for pharmacokinetic studies, and we envisage these assays being valuable for this and other research where determining drug concentrations in the blood is important. Indeed, we have established a new collaboration with clinicians at King Edward Memorial Hospital, Perth, to further develop this research technique, with the aid of a grant from the Telethon - Perth Children’s Hospital Research Fund,” says Batty.

Professor Batty says the groundbreaking technique has exceptional potential to improve health care in Australia.

“Although our research has important potential applications in children and vulnerable patient groups in any clinical setting, the Australian context is that care of patients in rural and remote locations could be improved by the use of dried blood spot assays as part of medication management strategies.”
MICROBES AND MINING

Research is showing how microorganisms can be used to help make mineral processing a more sustainable operation.

The mining and minerals industry is facing serious future challenges on a number of fronts. In addition to declining ore grades and increased concentrations of impurities in ores, environmental regulations on processing of the ores are becoming ever stricter. Conventional mineral processing and extractive metallurgy often use energy intensive processes with aggressive chemicals to solubilise the metal of interest. However, by exploiting biological pathways, more subtle and selective technologies may be used to extract the metals, with the potential to generate less hazardous waste.

One of the most innovative extraction methods is to use microorganisms to solubilise metals from ores. Curtin’s Associate Professor Elizabeth Watkin and Professor Jacques Eksteen, from the Western Australian School Mines, Curtin University, are leading several key research projects in this area.

“With an overarching theme of my research being the microbial ecology of environmental systems in mineral resource recovery, my team investigates biotechnological processes for environmental and industrial applications.”

“Essentially our research projects focus on the use of microorganisms to help leach metals from ore. We aim to demonstrate new ways in which biotechnology can drive more sustainable processing operations, transforming previously or perceived uneconomic resources into reserves.”

A major area of research under the direction of Associate Professor Watkin and Professor Eksteen is the use of phosphate solubilising bacteria for the extraction of rare earth elements.

Rare earth elements (REEs) are essential to modern technology and renewable energy applications. Historically, China has controlled most of the world’s REE production. To diversify supply of REEs and not be beholden to a single source of supply, the world has been looking at alternative sources and processing routes to extract REEs. The REEs are mostly mineralised in low-grade phosphates, of which Australia has numerous sizable resources.

However, current processing approaches are expensive, generates large amounts of waste and use aggressive chemicals. Finding cost-effective and selective processing alternatives is therefore important.

The research team is achieving good results using phosphate solubilising bacteria, by solubilising the matrix in which the minerals are found.

The typical rare earth elements that can be extracted using this future-focused technology include lanthanum, cerium, yttrium and neodymium. These elements are necessary for many modern devices including medical imaging equipment requiring magnets, mobile phones, LCD and plasma screens, superconductors and electric batteries for hybrid vehicles.

This project aims to provide information to determine the commercial viability of using phosphate solubilising bacteria in the extraction of rare earth elements, thereby providing a viable alternative to conventional methods. This will provide the option of being able to extract important and much-used minerals while avoiding an environmentally harsh process.

This promising research is being conducted in collaboration with the Western Australian School of Mines and is funded by the Minerals Research Institute of Western Australia. The project is also funded by the Lynas Corporation, with whom researchers collaborate.

Associate Professor Watkin cited another major project her team is running, investigating the use of microorganisms to solubilise metals from sulfur based ores. “This technology has been successfully applied to a number of ores, however it is compromised by high levels of chloride that mining in Australia contends with, along with a lack of fresh water.”

“It’s an enormously costly problem to manage in processing, so a new approach would be extremely positive on economic and environmental fronts. Right now, we are one of the very few projects actively focusing on the impact of chloride on acidophilic iron and sulfur oxidising bacteria.”

Although microbes and mining may seem unlikely allies, Associate Professor Watkin’s work is highlighting how their crucial partnership promises to bring greater sustainability to mineral processing.
A/Professor Patricia Price joined Curtin’s School of Biomedical Sciences in 2015 as a principal research fellow. She designs and conducts studies investigating individual differences in responses to infectious agents, such as HIV, cytomegalovirus (CMV) and non-tuberculous mycobacteria. This includes studies of the pathological effects of CMV on individuals infected with HIV. CMV is a common virus that is relatively benign to healthy individuals, but far more severe for those whose immune system has been compromised by HIV. A/Professor Price has primarily been conducting these studies in a developing world setting, where co-infection with HIV and other viruses frequently occurs. Her most recent project, called JakCCANDO (Jakarta CMV, Cardiovascular, Antiretroviral, Neuropathy, Dental, Ophthalmology), is based in Jakarta and has been organised in collaboration with the University of Indonesia. The project examines 82 HIV patients, testing their oral health, neurocognitive status, cardiovascular system and retinal health as they respond to antiretroviral therapy. The aim of the project is to detect CMV reactivation in HIV patients and to compare the state of their immune systems to healthy individuals. The project is scheduled to continue for three to four years. A/Professor Price’s research into cases of HIV could lead to improved care for HIV patients in Indonesia and countries with a similar patient profile, including the early identification of patients likely to have oral health, neurocognitive or cardiovascular problems as they respond to HIV therapy. As part of her research, she also trains Indonesian doctors and scientists so they can design locally relevant research projects. A/Professor Price has received funding from the Goodeve Foundation, AbbVie and the University of Indonesia for JakCCANDO, while her Australian research investigating the role of CMV in the long-term outcome - including the development of cardiovascular disease – in healthy ageing and renal transplant patients, has received National Health and Medical Research Council funding and support from the Medical Research Foundation of WA. A/Professor Price received her PhD in immunology from The University of Western Australia (UWA) and has published over 200 papers in peer-reviewed journals. Prior to taking up her position at Curtin, she was employed at UWA, teaching the undergraduate immunology course and coordinating the honours course and masters degree for the School of Pathology and Laboratory Medicine.
BEATING DRUG-RESISTANT TUBERCULOSIS

Killing around 1.2 million people annually, tuberculosis ranks alongside HIV as a leading cause of death worldwide. Drug-resistant strains of the disease present a significant challenge, but Curtin researchers are exploring promising new treatment methods.

In spite of the fact that it is curable, tuberculosis remains a significant global health problem. It is thought that up to a third of the world’s population has been infected with the bacillus that causes the disease, Mycobacterium tuberculosis, with an estimated 9.6 million new cases of tuberculosis in 2014. Without treatment the death rate is high, with the global death toll in 2014 estimated at 1.5 million.

One of the primary issues associated with the control and treatment of tuberculosis is the ongoing emergence of various drug-resistant strains of the bacterium, and co-infection with HIV. Even the recent addition to the arsenal of anti-tubercular drugs in late 2012, bedaquiline, is known to be associated with adverse side effects leading to fatalities. Clearly, there is a need for new, more effective drugs with different mechanism of action to combat the disease.

A multidisciplinary research team led by Dr Hendra Gunosewoyo of Curtin University has brought the skills of Dr Shichun Lun and Professor William Bishai from Johns Hopkins’ Center for Tuberculosis Research (USA) together to find new ways of attacking the bacteria. The team is concentrating on mycolic acids – fatty acids found in the cell walls of bacteria including M. tuberculosis – the presence of which makes tuberculosis difficult to treat. These mycolic acids increase the cells’ resistance to chemical damage and dehydration, and prevent the action of hydrophobic antibiotics. Further, mycolic acids can help to hide the tuberculosis bacterium from the host’s immune system.

“Our objective is to develop chemical probes capable of inhibiting the transport of essential mycolic acid across the cell wall of Mycobacterium tuberculosis, rendering it more vulnerable to antibiotics,” said Dr Gunosewoyo.

Utilising cutting edge techniques such as high throughput screening and elucidation of the mechanism of its action via whole genome sequencing, the team has developed a new way of inhibiting the action of the mycolic acid transporter Mycobacterial membrane protein large 3 (MmpL3). They have found that certain indoleamide-based compounds can exhibit powerful growth inhibitory effects against drug-susceptible and drug-resistant strains of Mycobacterium tuberculosis.

“Having published our findings regarding indoleamidnes in peer reviewed journals such as Nature Communications, the current focus is to improve the bioavailability of these compounds. Utilising rational drug design principles and chemical intuition in tandem with in vitro and in vivo screens, our goal is ultimately to yield anti-tubercular compounds that could be advanced to the clinic. The bioavailability of the indoleamidines, combined with their ability to kill tubercle bacilli, indicates great potential for translational developments of this structural class for the treatment of drug-resistant tuberculosis.”
FOOD ON THE MIND
Researching how nutrition contributes to neurodegenerative disorders

As the global population ages, the incidence of neurodegenerative disorders associated with ageing will increase. It is therefore essential that we enhance our understanding of the origins and progression of diseases such as Alzheimer’s disease and vascular-dementia, Parkinson’s disease, multiple sclerosis and epilepsy, amongst others, to facilitate the development of safe, effective treatments.

The central issue in beating these disorders is in decoding how the brain works, and utilising that understanding to develop strategies to prevent or delay disease onset, or slow progression. An award-winning team led by the Director of the Curtin Health Innovation Research Institute, Professor John Mamo, and Research Fellow Dr Ryusuke Takechi, is at the forefront of this essential work.

In 2014 the Australian National Health and Medical Research Council (NHMRC) awarded the team the Marshall and Warren Research Award, which recognises the most innovative and potentially transformative project grant application from approximately 4,000 grants applications submitted to the NHMRC in the previous granting year.

“Our research was highlighted because we are the only group globally investigating ‘restoration’ of brain capillary function,” said Professor Mamo. “Our aim is to generate evidence-based targeted lifestyle interventions for the prevention and treatment of capillary-based central nervous system disorders.”

THE BRAIN, THE CAPILLARY NETWORK AND THE BLOOD BRAIN BARRIER

Every 24 hours, approximately 1,000 litres of blood flows through the brain, delivering up to several kilograms of glucose to support activity. The main agent of this delivery is a network of microscopic vessels, the capillaries, which combined represent up to 30m2 of surface area in humans.

One of the crucial actions of the capillary network is to provide a barrier or check-gate function - the blood brain barrier (BBB) - which strictly limits what gets into the brain from the bloodstream. Increased permeability of the capillaries due to factors such as diet, chemical exposure and other environmental influences that affect the integrity of the vessels, may result in leakage of compounds and agents that promote inflammation from blood into brain.

Disturbances in BBB function that allow infection and inflammatory responses that may occur elsewhere in the body to enter the brain, are associated with a range of neurodegenerative disorders, and emerging evidence suggests that even subtle alterations in brain capillary function may have effects on mood, behaviour, depression and anxiety.

Animal model studies indicate that persistent, BBB-dysfunction may trigger or accelerate neurodegenerative conditions. Restoring blood-brain barrier impermeability, and otherwise ensuring its integrity, may be critical in avoiding, minimising and treating neurodegenerative disorders.

A UNIQUE AREA OF RESEARCH

“Our research focuses on potential environmental factors regulating brain capillary integrity and function,” said Professor Mamo. “Several promising agents are being studied in a unique animal model of natural human-ageing. The animal model studies are used to inform novel clinical studies in subjects at risk of selected neurodegenerative disorders.”

With a strong emphasis on diet, the team has made several remarkable findings describing how particular nutrients modulate brain capillary integrity. Among the findings is evidence that any dietary or environmental insult that compromises brain capillaries will have an accumulative effect. Binge exposures with poor diet (saturated fats, alcohol, processed meats or foods laden with sugar) may be as harmful as chronic, constant exposures.

“These findings may be critically important in identifying modifiable risk factors for significant neurodegenerative disorders or mental health conditions that have a capillary axis, and have substantial potential in the context of reducing disease burden.”
A promising new understanding of how type 2 diabetes may trigger dementia onset in the brain offers hope for early intervention to reduce the disease burden.

Rates of dementia and Alzheimer’s disease (the most common form of dementia) are increasing dramatically, with 46.8 million cases worldwide currently. In 2015 alone, 9.9 million new cases, or one every 3 seconds, have been reported (2015 World Alzheimer Report) and this number is expected to almost double every 20 years. Dementia is currently Australia’s second leading cause of death (Australian Bureau of Statistics) with 340,000 sufferers and predictions for over 1 million by 2050. The financial impact on our community is more than $6 billion a year, and the emotional and physical strain on families and loved ones of sufferers is immeasurable.

However, current treatments for age-related neurodegeneration, Alzheimer’s and dementia only improve the symptoms somewhat. They do not delay or halt disease progression. Yet delaying disease onset by just 5 years would be dramatic, giving Australia potential savings of $56.7 billion by 2050. Clearly, there is an urgent need for research to develop appropriate disease modifying strategies, so that early intervention (before symptom onset occurs) can halt this growing health crisis.

At Curtin University, A/Professor Giuseppe Verdile and his research team are making notable inroads towards this goal. They’re investigating the poorly understood process by which type 2 diabetes, known to double the risk of developing dementia, promotes the onset of dementia. Collaborating in Australia and internationally, the team is working to better understand the underlying molecular mechanisms linking type 2 diabetes with Alzheimer’s disease. And it may be that an innovative mouse model known as T2D-AD, will help provide answers, leading to new drugs that may target diabetes in slowing down dementia onset.

A/Professor Verdile explains: “In type 2 diabetes there is reduced action of the hormone insulin on target tissues (insulin resistance) and as the disease progresses the pancreas fails to produce enough insulin. The brain requires insulin for normal neuronal function. In our research, we propose that impairments in this neuronal function for insulin could trigger the events that lead to the development of Alzheimer’s disease pathology, neuronal loss and ultimately brain atrophy.”

Although human studies provide some insight, studies in animal models (traditionally mice) are required to drill down into what is happening in the brain. Because mice do not develop Alzheimer’s themselves, they are genetically engineered to exhibit the disease, and may be used to evaluate drugs before human trials. But they do not show neuron loss to the same extent as human Alzheimer’s brains, so have limits in research.

“Our research is going a promising step further. Our collaborator, Professor Paul Fraser (University of Toronto) has developed novel mouse models that, for the very first time, more closely mimic events occurring in the Alzheimer’s brain, and the impact that progression of type-2 diabetes has on the brain.”

“What’s even more exciting” says A/Professor Verdile, “is that our findings so far suggest type 2 diabetes can exacerbate loss of synapses (junctions transmitting signals between neurons) and can promote accumulation of another Alzheimer’s-related protein called tau, which together with beta amyloid, is thought to be the driver of neuronal loss in the Alzheimer’s brain.”

Because the T2-AD mice are more clinically relevant, they’re ideal for investigating how type 2 diabetes may trigger neuronal loss. Furthermore, these mice may also provide a more clinically relevant model for evaluating drug therapies or interventions to slow and prevent progression of Alzheimer’s disease.

The collaborative group includes Professors Philip Newsholme and Erik Helmerhorst from the School of Biomedical Sciences at Curtin, Professor Paul Fraser from the University of Toronto and Professor Ralph Martins from Edith Cowan University. The team was recently awarded an NHMRC project grant to commence in 2016 to substantially extend this promising preliminary data, and provide further insight into how type 2 diabetes may trigger dementia. The work will also evaluate, in mouse models, known and novel drugs targeting diabetes, for their ability to prevent or slow neuronal loss.

A/Professor Verdile emphasises why urgent, innovative research is critical for this global health crisis. “In addition to looking at pre-symptomatic and early stage diagnosis, we must understand the disease mechanisms further, and how risk factors, like type 2 diabetes, exacerbate progression. This is essential to the ultimate goal of developing effective therapeutic and preventative strategies to delay onset, slow progression or prevent Alzheimer’s disease.”
FINDING THE CONNECTION

Diabetes, insulin and neurodegenerative disease.

Investigating the role of insulin in protecting the body from disease, and how a loss of insulin dependent protection can promote disease progression.

The range of factors that have an influence on our likelihood of disease are well documented: genetic background, gene modification by environment (epigenetics) and lifestyle factors such as lack of exercise and poor diet. What’s less understood is the effect that a less-than-optimal diet has on the progression of disease.

Gaining an understanding of how malnutrition and the conditions it can trigger contribute to disease progression is critical to developing optimal treatment strategies for afflictions such as cardiovascular conditions, impaired immune responses and inflammatory diseases, reproductive health, liver function, diabetes and neurodegenerative diseases.

The School of Biomedical Sciences at Curtin University has brought together researchers from diverse backgrounds, such as molecular and cellular metabolism, nutrition, molecular genetics, neurosciences and clinical intervention studies, to address this issue.

A team including Head of School - Professor Philip Newsholme, Associate Professor Giuseppe Verdile, Dr Prashant Bharadwaj and PhD student Ms Joanne Rowles, together with researchers from Edith Cowan University and The University of Toronto, are investigating the molecular links between diabetes and neurodegenerative disease. The research is funded through grants from the NHMRC and the Curtin School of Biomedical Sciences.

THE LINK BETWEEN DIABETES AND ALZHEIMER’S

Insulin resistance, which is common in cases of Type 2 Diabetes (T2D), leads to a reduction of insulin available in the brain. At the same time, disruption of insulin signalling, which is involved in a range of brain functions, results in the impairment of neuroprotective properties supported by normal insulin activity. The team is investigating how this loss of insulin dependent protection may instigate a sequence of events that lead to the synaptic failure and neuronal loss associated with Alzheimer’s disease.

THE LOSS OF INSULIN DEPENDENT PROTECTION AND THE DEVELOPMENT OF DIABETES

A similar loss of insulin dependent protective properties may occur in the pancreas in T2D, affecting pancreatic beta cell dysfunction. So the team is also investigating the process in relation to the development of diabetes pathology.

Specifically, they are investigating the toxicity induced by two peptides (Amylin and Abeta) when they are allowed to combine. Amylin is produced in the pancreas and is normally associated with diabetes, while Abeta is produced in the brain and is usually related to Alzheimer’s disease. However, recent evidence has demonstrated the presence of Abeta in the pancreas and Amylin in the brain. The team is binding these two peptides together to investigate the strength of the bond, and to establish the toxicity of the changed molecule. Exposing the bound peptides to pancreatic cells outside the body has indicated that they can produce significant dysfunctional effects including dysfunctional energy metabolism.

Professor Newsholme says that while almost all of the current research is based on studies in cells or animals such as mice, the findings may be translated to benefit human health in the future. “It is the critical application of the understanding of regulation in metabolism coupled with an understanding of protein binding and function that sets our research apart from other work in this area,” he says.

“Our research is expected to lead to strategies that will facilitate discovery of novel therapeutics which, when coupled with optimal nutrition and lifestyle choices, will impact positively on metabolism and disease-related outcomes. By working closely with clinical researchers, especially those that will be based at the new Sarich Neuroscience Research Institute at the QEII Medical Centre, we expect significant translational outcomes based on our findings.”
STEMMING THE TIDE

Targeting cancer stem cells with a natural protein.

Researchers at Curtin University are investigating the potential of a naturally secreted protein in the fight against cancer recurrence.

The work of Professor Arun Dharmarajan is an exciting breakthrough in cancer treatment and will address the challenge that cancer stem cells pose for its recurrence. It presents a unique and differentiated therapeutic strategy that is potentially applicable to a broad range of cancers, both independently and in synergy with existing therapies.

Cancer stem cells are the bane of medicine’s efforts to prevent cancer recurring. They are resistant to chemo and radiotherapy, so they remain the major reason for treatment failure, leading to many cancers – including breast, lung, gastrointestinal, prostate, and ovarian cancers – growing back, even after surgical removal of malignant tumours.

At the Curtin Health Innovation Research Institute, Professor Arun Dharmarajan and his team are focusing on the therapeutic potential of a naturally secreted compound that impedes tumour growth driven by cancer stem cells. Their results to date are exciting.

The protein is known as ‘Secreted Frizzled-Related Protein 4’ or sFRP4 (SC201), and Professor Dharmarajan has shown it to prevent blood vessel formation in cancerous tissue. This significant finding builds on his already important work.

Professor Dharmarajan originally discovered sFRP4 in a number of human tissues and organs. He cloned sFRP4, and has dedicated the majority of his scientific career to understanding its biology and relevance to cancer.

Now the Drug Discovery Program at Curtin University, which is founded on a unique therapeutic strategy to treat cancer, has taken the research another step forward. Led by the expertise of Professor Dharmarajan, the team has derived peptide fragment drug candidates from sFRP4, which have shown enormous potential.

The program includes a granted method patent covering the therapy, peptide drug candidates, and exciting proof-of-principle data, showing this strategy holds significant potential for treating cancers often considered hard to treat, including through synergy with existing chemotherapeutics.

Professor Dharmarajan’s revolutionary work on sFRP4 shows how exploiting this protein in treatment provides it with multiple anti-tumour effects. This innovation underlines the work as being particularly important and noteworthy. The team’s WNT antagonist strategy incorporates an unprecedented three different and effective mechanisms of action to kill tumours: shutting down blood supply to the tumour, inhibiting cellular signalling pathways in order to stop cell division and inducing cancer cell and cancer stem cell death.

For Professor Dharmarajan, the results to date are nothing short of astounding. “Our findings show significant promise in reducing tumour growth by using sFRP4 and its peptides, not only by themselves but along with existing chemotherapeutic agents. In some cases, the reduction in tumour growth has been almost 80 per cent.”

“We have generated large in vitro and in vivo data sets, including peer-reviewed and published data demonstrating potent and effective anti-tumour activity.”

This project has attracted a number of high-calibre researchers and PhD students to Curtin over the past three years, as the area of cancer stem cell research expands within the School of Biomedical Science.

“Looking at sFRP4, I would like to take this protein to the next level of excellence and establish industry partnerships to further support our cancer stem cell research. The sooner we can get this work into clinical trials, the sooner it may become a useful mode of treating so many people who are suffering from this devastating disease.”
Pancreatic cancer currently offers sufferers little hope of survival, but a Curtin research team is making inroads, by focusing on ways of blocking lipid signalling.

Pancreatic cancer is one of the most lethal diseases in Australia today. Although it is currently the eleventh most prevalent cancer diagnosed in the country, it is difficult to detect in the early stages, and once established, is highly aggressive and results in a high mortality rate. Resistant to both chemo and radiotherapy, a pancreatic cancer diagnosis presents the physician with few, if any, effective treatment options. Of around three thousand new cases of pancreatic cancer diagnoses nationally in 2015, only 6 per cent of sufferers will survive to five years following diagnosis.

There is an urgent need to understand more about how this disease is initiated and proliferates, in order to develop treatments and cures. Professor Marco Falasca of the Curtin University School of Biomedical Sciences, a highly regarded expert in human metabolism and pathologies associated with altered metabolism such as diabetes and cancer, is heading a team committed to finding cures and treatments for patients with chronic diseases, in particular challenging to finding cures and treatments for patients with chronic diseases, in particular, pancreatic cancer.

His current focus is on the role of metabolism in diseases in Australia today. Although it is an aggressive disease, pancreatic cancer is one of the most lethal illnesses, such as pancreatic cancer.

In recent years, our work on proteins involved in LPI mechanism of action, such as ABC transporters and G-protein coupled receptors, has received much attention for these proteins in cancer progression and cell signalling. LPI is a bioactive lipid that is able to activate signalling cascades relevant to cell proliferation, migration, survival and tumourigenesis. The enhanced understanding of the pivotal role that LPI signalling and its effect on G-protein coupled receptors play in the progress of cancer uncovered by Professor Falasca and his team, has advanced to the point where they have been able to test various drug combinations aimed at breaking that nexus, and perhaps halting the proliferation of cancerous cells.

“We are paying particular attention to lipids known as phosphoinositides, such as Lysophosphatidylinositol (LPI), that can themselves act as, or be converted into, messengers, ultimately regulating several cellular functions.”

The research into the causes and possible cures of cancer is almost as broad and far reaching as the disease itself. Cancer killed almost 47,000 Australians in 2015, and there were over 125,000 new cases diagnosed. It is a massive and growing problem, particularly as Australia’s population ages.

The older a person gets, the more likely they are to be diagnosed with any of almost 100 different diseases that come under the term ‘cancer’. By the time they reach 65 years of age, one in two men and one in three women will be diagnosed with cancer.

In spite of this, the great majority of preclinical studies of anti-cancer therapies are conducted in young adult animals with intact immunity. The reason for this is that the older the subject becomes, the greater their susceptibility to the toxicity of the treatment itself. The challenge for researchers looking to unlock the secret of treating cancer in older patients is to reduce toxicity, yet kill cancer. Curtin University’s Dr Delia Nelson has been conducting research into the role of the immune system in the development and treatment of cancer for many years, and she and her team believe that their work may lead to the capacity for a patient’s own immune system to combat cancer.

“We have recently discovered a very promising drug combination that is currently under evaluation for testing in clinical trials,” said Professor Falasca.

“The reason most cancers occur in older people is not fully understood,” said Dr Nelson. “One possibility is that the immune system does not function as well when a person ages, so that the ability to prevent tumour growth decreases as time goes on.”

It is understood that the immune system is aware of the presence of cancer in the body, and for many years researchers have been seeking a way to compel the immune system to attack the cancerous cells. Dr Nelson and her team, which includes collaborators from the University of Western Australia, the Institute of Technology in Sligo, Ireland, University College Dublin and the University of Southampton, have been tackling the problem with a specific focus on older people.

This includes examining the problem of immunosenescence – the aging and gradual deterioration of cell functionality, which affects the cell’s ability to produce lymphocytes, the white cells critical to the proper functioning of our immune systems.

They have found that a key compartment of the immune system is different in elderly people, and this difference may be a factor in the higher incidence of cancer in older people. This raises the possibility of developing immune based therapies that may be of use in treating older people with cancer, which is the subject of current studies.

The team’s research is funded by the NHMRC and the Cancer Council of Western Australia, and their work has been recognised by several Australian and international awards. These include an ‘Outstanding Merit Award’ by the international editorial board as the best paper published in 2008 in the journal International Immunology. The article was also rated as exceptional by the Faculty of 1000 Biology. Another award was the Australian Lung Foundation Mesothelioma Research Award presented at the Thoracic Society for Australia and New Zealand annual scientific meeting in Canberra in 2006. In 2013 the research group was awarded the Faculty Publication Category 1 Highest Impact Factor Paper Award.

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