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IHMRI researchers attract competitive grant funding

Several IHMRI-affiliated researchers have been successful in their National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC) grant applications this year.

In the first round of announcements, Dr Lyn Phillipson was awarded a $571,648 NHMRC-ARC Dementia Fellowship to investigate the impact of the Australian Government’s Home Care Packages (HCP), introduced on 1 July 2015 to allow people aged 65 and over to receive care in their own home.

Following this, the ARC announced the successful recipients of its grant program, with Professor Mark Wilson and Associate Professor Heath Ecroyd being awarded $452,800 to investigate how the human body defends itself against misfolded proteins which are causally involved in ageing and several neurodegenerative diseases, including Alzheimer’s disease.

Distinguished Professors Antoine van Oijen, Nick Dixon and collaborators also received a $355,000 ARC Linkage Infrastructure, Equipment and Facilities grant to purchase new and upgrade existing fluorescence imaging tools to facilitate the study of intracellular processes in microbial systems at maximum resolution to understand protein function inside living cells.

In the subsequent NHMRC grant announcement, IHMRI-affiliated researchers attracted another $3.3M in funding. Early-career researcher, Dr Amy Wyatt, received a $461,496 Project Grant to investigate the underlying cause of Alzheimer’s disease; in particular the harmful relationship that exists between inflammation in the brain and the accumulation of amyloid beta-a peptide with toxic properties.

Associate Professor Chao Deng received a $576,496 Project Grant to continue his well-established program investigating the obesity side-effects of second generation antipsychotics (SGAs). With this new grant, A/Prof Deng will turn his attention to the long-term effects of antipsychotics on the developing brains of children and adolescents and the underlying mechanisms of these side-effects.

Another exciting program to receive NHMRC Project Grant funding is in the realm of cancer drug development, with Associate Professor Michael Kelso, Professor Marie Ranson and an international team awarded $611,966 to develop a new class of breast cancer drugs based on a common diuretic, Amiloride, which is currently used to treat high blood pressure and heart failure in patients while maintaining normal blood potassium levels. This work builds on a successful research project conducted in Professors Ranson’s and Kelso’s labs by PhD candidate Benjamin Buckley.
A new Illawarra Shoalhaven Suicide Prevention Collaborative (ISSPC) has been formed by IHMRI-affiliated researchers as a vehicle to bring healthcare experts, educators and researchers together to tackle the suicide epidemic through a multi-pronged approach.

The project was initiated by IHMRI Mental Health and the Ageing Brain research theme leaders, Senior Professor Brin Grenyer (a leading psychologist) and Associate Professor Vida Bliokas (Head of Psychology/Principal Psychologist with the Illawarra Shoalhaven Local Health District) with Dr Alex Hains (Mental Health Manager of Grand Pacific Health).

The collaborative approach is based on recommendations outlined in the proposed Suicide Prevention Framework for NSW prepared by the National Health and Medical Research Council and Black Dog Institute for the NSW Mental Health Commission. It also references the recently-released Suicide Prevention Australia National Action Plan. Collectively these plans call for a systems approach to the implementation of evidence-based prevention strategies in local areas; the success of which relies on community support.

The first ISSPC meeting was held at IHMRI on the eve of World Suicide Prevention Day (9 September) and included (among others) the Director Lifeline South Coast, Grahame Gould, the CEO of Coordinaire, Dianne Kitcher, representatives of Grand Pacific Health and the ISLHD. With IHMRI-affiliated researchers Professor Lorna Moxham, Professor Frank Deane, Associate Professor Mitch Byrne and Dr Coralie Wilson (see page 12) the group discussed how they could work together to address the recommendations highlighted in the framework.

Dr Marco Petasecca from the IHMRI-affiliated Centre for Medical Radiation Physics received a $359,105 Development Grant to work in collaboration with Advanced Computer Systems Ltd., to further develop BrachyView – an imaging system that aims to bring 3D virtual reality into the quality assurance space and provide training to physicists using prostate cancer brachytherapy.

Congratulations also to Professor Brett Garner who received a highly-competitive five-year $687,975 Senior Research Fellowship to characterise new therapeutic targets for the prevention and treatment of Alzheimer’s disease (AD).

Professor Garner has previously been awarded an ARC Future Fellowship and this is the second time he has been awarded an NHMRC Research Fellowship. His team has already made important advances in the identification of pathways that contribute to AD and will now capitalise on their leading position in the field of brain lipid, apolipoprotein and ABC transporter function by translating these novel discoveries into therapeutic targets.

Several more IHMRI-affiliated researchers attracted funding through collaborative grants – with 2015 representing a good year for competitive grants overall.
We all know that being overweight and getting insufficient exercise increases our risk of developing chronic disease. However, we also know there can be complex emotional and psychological factors involved in following a ‘healthy lifestyle’ and that there are many barriers to good health.

In 2013 a group of IHMRI and Illawarra Shoalhaven Local Health District academics and clinicians representing the disciplines of medicine, dietetics, exercise science, psychology, nursing, statistics and public health got together to develop a novel interdisciplinary approach to weight loss and chronic disease risk.

Jump to 2015 and the HealthTrack Illawarra Shoalhaven Healthy Lifestyle study has been a major success in terms of recruitment, with 377 local residents now enrolled in the randomised controlled trial (RCT). Over the past 18 months these participants have received a tailored program of advice on diet and exercise as well as counselling to help them overcome these barriers.

The team behind the study, led by Senior Professor Linda Tapsell, are unable to tell us how successful they have been in helping participants improve their health and lose weight, but there are good signs in the journal *Nutrition and Dietetics* which has just published the results of the HealthTrack pilot conducted early in 2014.

The purpose of the pilot was to test the feasibility and acceptability of the intervention with 24 local participants over a three month period. Feasibility was assessed by determining how well the community responded to advertisements for the trial and how many of those people were able to participate. Acceptability was assessed by looking at the number of people who attended study visits. All the protocols that were to be conducted in the large trial were also tested to ensure they could be delivered on time and within the study resources.

Thirteen women and eight men participated in the pilot, with those in the intervention arm attending their appointments 100 per cent of the time, versus 83 per cent in the control group.

Although the researchers and participants were pleased to see favourable changes in body weight,
Personality Disorders conference

The 9th Annual Conference on the Treatment of Personality Disorders was held on the UOW campus in early November.

Hosted by the IHMRI-based Project Air Strategy for Personality Disorders and NSW Health, and based on the theme ‘Inside Borderline Personality Disorder’, the conference was opened by NSW Mental Health Commissioner, John Feneley, and brought hundreds of health professionals, consumers, family and community members together to discuss the treatment of personality disorders, as well as the latest research and innovative practices.

Keynote speakers included support worker, Sonia Neale (WA) who presented on ‘The importance of the BPD therapeutic relationship’ and Dr Dolores Mosquera (Spain) who gave a practitioner’s perspective on ‘Understanding BPD: insecure and disorganised attachment and the structural dissociation of personality’.

The conference also provided the Project Air team with the opportunity to launch their Parenting with Personality Disorder initiative designed to support parents with BPD – and their children.

Fellowship awarded to donor

Retired dairy farmer, Mr Richard Miller, is a community leader and philanthropist whose generous donations have given dozens of IHMRI Higher Degree Research students the opportunity to build their research skills and demonstrate their potential for future research work since the Miller Family Bridgewater IHMRI Summer Scholarships for Dementia Research were established in 2011-12.

Mr Miller’s support for the program, as well as the Miller Family Bridgewater Equity Scholarships for engineering, teaching and nursing students, was recently recognised at the UOW Alumni Awards.

Mr Miller was honoured with a Fellowship for his ongoing investment in education and research through his partnership with the UOW, executed through the John and Belle Miller Family Memorial Fund.

IHMRI congratulates Mr Miller and thanks him for his ongoing support.

body fat, waist circumference and blood pressure, Professor Tapsell said the results should be “treated with caution” because small studies such as these do not have the power to demonstrate generalisable effects.

This is now being tested with the main study.

“The good news is that the pilot study showed that HealthTrack works,” said Professor Tapsell.

“Not only was the interdisciplinary approach to lifestyle counselling feasible and acceptable to participants in the community, it got results for those who helped to test it out.

“These preliminary results give us a lot of confidence that the larger study will deliver evidence of potential benefits to the community.

“Importantly, the community has engaged with us and we have all worked together to make this happen. We hope this first publication will be one of many telling us more about ourselves, and how we go about improving the health of our community.”

The Nutrition and Dietetics paper is entitled: ‘Feasibility of a community based interdisciplinary lifestyle intervention trial on weight loss’.

Mr Richard Miller with his Fellowship documents and gown.
Neonatal abstinence syndrome or NAS is defined as a group of problems that occur in newborns exposed to addictive illegal or prescription drugs while in their mothers’ wombs.

These infants tend to be kept in hospital for longer than healthy children, but paediatricians wanting to know how these kids fare long-term find it difficult to gather information on them because they often come from chaotic communities.

IHMRI-affiliated researcher and Wollongong Hospital paediatrician, Professor Ian Wright, recently collaborated with a group of national researchers and healthcare professionals on an innovative study which has delivered new insights on the long-term health of NAS children, reported to the prestigious journal Paediatrics.

The team, led by paediatric prize-winning medical student Hannah Uebel from the University of New South Wales’ School of Women’s and Children’s Health, looked at the birth, hospitalisation and death records of all children registered in NSW between 2000 and 2011.

Of the 1,022,263 live born infants studied, 3,842 (0.38 per cent) were diagnosed with NAS during their hospital admission.

By linking the datasets, the team showed that NAS infants are more likely to be admitted to a nursery and be hospitalised for longer and in childhood they are more likely to be re-hospitalised, die during hospitalisation and be hospitalised for assaults, maltreatment, poisoning, mental/behavioural problems and visual disorders.

They also found that mothers of infants with NAS were more likely to be Indigenous, have no antenatal care and be socioeconomically deprived.

Even after accounting for prematurity, maternal age and Indigenous status, NAS appears to be the most important predictor of admissions for maltreatment and mental and behavioural disorders in childhood and adolescence.

“This research highlights the ongoing burden of risk for these infants and the need for evidence-based strategies to reduce these risks and improve the safety and outcomes of these vulnerable children,” said Professor Wright, who is also Professor of Paediatrics and Child Health Research with the UOW’s Graduate School of Medicine.

The paper is entitled ‘Reasons for Rehospitalisation in Children Who Had Neonatal Abstinence Syndrome’.

The authors were: Hannah Uebel (School of Women’s and Children’s Health, UNSW), Professor Ian Wright (ISLHD/IHMRI), Dr Lucy Burns and Dr Courtney Breen (National Drug and Alcohol Research Centre), Dr Lisa Hilder (National Perinatal Epidemiology and Statistics Unit, UNSW), Barbara Bajuk (NSW Pregnancy and Newborn Services Network), Professor Mohamed Abdel-Latif (Canberra Hospital and Australian National University), Dr John Feller (School of Women’s and Children’s Health, UNSW and Sydney Children’s Hospital), Janet Falconer and Sarah Clews (The Langton Centre, NSW), Dr John Eastwood (School of Women’s and Children’s Health, UNSW, Sydney Local Health District and School of Public Health, University of Sydney) and Dr Ju-Lee Oei (School of Women’s and Children’s Health, UNSW and Royal Hospital for Women).

Effects of neonatal abstinence syndrome are long-lived

Nontuberculous mycobacteria (NTM) are naturally-occurring organisms found in water and soil. However, when inhaled, a group of bacteria called Mycobacterium avium complex (MAC) can kick in causing serious lung infections requiring ongoing antibiotic treatment.

IHMRI’s Clinical Research and Trial Unit is currently conducting an NTM study with clinicians in the Wollongong Hospital’s Respiratory Clinic. The study will test the effectiveness and safety of an experimental antibiotic drug, Liposomal Amikacin for Inhalation (LAI), in people with lung infection caused by MAC (and not previously treated).

IHMRI and the hospital are sharing resources on the study, with IHMRI Clinical Trial Coordinator, Kim de Vries (pictured right with CRTU Director, Professor Wilf Yeo), given an honorary appointment at the hospital for the duration of the 21-month trial.

LAI will be given to participants once a day using an investigational device, known as the eFlow® nebulizer to see if it also improves the patient’s quality of life.
Infectious diseases research group leader, Dr Martina Sanderson-Smith, and a team of IHMRI-affiliated Higher Degree Research students were recently offered the cover of the Journal of Innate Immunity with their arresting image of a human immune cell interacting with group A streptococcal (GAS) cells.

The image was captured as part of a collaborative study looking at the way in which virulent forms of GAS change the way neutrophils (white blood cells) respond to GAS infection.

"Instead of the immune cells clearing the infection, the virulent GAS causes the cells to be killed in a way that increases inflammation and host tissue destruction at the site of infection," explained Dr Sanderson-Smith.

The research was conducted in collaboration with the Helmholtz Centre for Infection Research in Germany, which recently hosted IHMRI PhD candidate James Tsatsaronis (now Dr Tsatsaronis) on a German Academic Exchange Service scholarship. The image was captured by Dr Manfred Rohde.

The paper, entitled 'Group A Streptococcus Modulates Host Inflammation by Manipulating Polymorphonuclear Leukocyte Cell Death Responses' was co-authored by IHMRI-affiliated researchers Dr James Tsatsaronis, Diane Ly, Dr Aleta Pupovac, Dr Jude Taylor, Professor Mark Walker and Dr Martina Sanderson-Smith with Dr Eva Medina, Dr Manfred Rohde and Oliver Goldmann, Helmholtz Centre for Infection Research, Germany.

Image shows white blood cells which, in a healthy individual, digest bacteria to prevent or control infection.
A new game of tag for pre-schoolers

An innovative study led by PhD candidate Karen Tonge from the IHMRI-affiliated Early Start Research Institute (ESRI) uses radio-frequency identification (RFID) tags to provide insights on the extent to which teachers/educators influence the amount of physical activity that pre-schoolers get.

Previous research has identified the fact that Australian children in Early Childhood Education and Care (ECEC) services are not engaging in sufficient physical activity as recommended by the national guidelines, and levels of sedentary behaviours in ECECs are also not meeting recommended levels.

“Educators spend considerable periods of time with the children, so it’s important for us to understand their role,” said Karen.

“However, simply observing children’s activity would not provide the kind of detailed activity data we required.”

In this study, which commenced in 2014, the children and their educators are fitted with RFID wristbands and wear lightweight accelerometers around their waists. The wristbands transmit data to real-time location system (RTLS) readers which triangulate the tag’s movement to give Karen and other members of the ESRI team (including Professor Tony Okely and Dr Rachel Jones) information on the participants’ location and their proximity to each other while playing outdoors. The accelerometers measure the amount and intensity of physical activity.

“The technology locates and tracks the movements of participants and, in conjunction with the accelerometers, identifies the relationship between participants and how this may influence physical activity behaviours,” explained Karen, who also records observations and conducts educator surveys.

To date, she has been able to install the technology at eight preschools around Wollongong, but by the time the project finishes in 2017, it will involve 15 services across the Illawarra-Shoalhaven region and around 600 pre-schoolers and 100 educators.

While it is too soon to report on the findings, the potential of the technology in this context has been featured in the International RFID Journal and on several technology news sites.

“As far as we know, this is the first time that RTLS monitoring has been used to study how educators are engaging and interacting with children to influence physical activity,” said Karen.

“This research has the potential to influence ECEC policy and practice and have a positive impact on the health and wellbeing of young children in the region and beyond.”

Study links overweight and obesity to disadvantage

The SIMLR Cohort Study is emerging as one of IHMRI’s most important research studies with the potential to change how health services are delivered regionally.

Led by IHMRI Chronic Conditions and Lifestyle clinical theme leader, Professor Andrew Bonney, and Illawarra Shoalhaven Local Health District (ISLHD) Public Health epidemiologist, Darren Mayne, the study utilises Southern .IML Pathology’s large, longitudinal, community-derived database to analyse and identify health risk indicators and map where those risks are clustered geographically.

Recently the team, representing IHMRI, the ISLHD, Illawarra and Southern Practice Research Network, Sonic Healthcare and Southern .IML Pathology, demonstrated that this kind of data can be used to explore the relationship between area-level socioeconomic disadvantage and overweight and obesity.

While information on the rates of overweight and obesity and the probability of individuals accessing primary care is readily available nationally, body mass index (BMI) estimates are rarely available at regional levels.

In this study the team examined de-identified data from 91,776 adults in the Illawarra-Shoalhaven region who had their BMI objectively measured by Southern .IML between 1 July 2009 and 30 June 2011.

As reported in the highly-ranked journal PLOS ONE, the team extracted demographic data and BMI, matching them to 2006 national census socioeconomic data using geocoding.

The study demonstrated that the risk of obesity is higher in neighbourhoods of greatest disadvantage for both men
Every year around the world pharmaceutical companies spend billions testing therapeutic drugs on animals only to discover that, in human trials, the drugs have a different level of effectiveness. Researchers are unsure why the human brain differs from the animal brain, so the development of a ‘bench-top brain’ that accurately reflects brain tissue would not only allow researchers to explore the effects of different drugs, but investigate brain disorders like schizophrenia and dementia.

As recently reported in the journal *Biomaterials*, researchers at the IHMRI-affiliated ARC Centre of Excellence for Electromaterials Science (ACES) have made significant progress developing bench-top brain tissue which may provide critical information on how the brain functions.

The ACES team, led by Director Professor Gordon Wallace, used 3D printers to print a six-layered structure incorporating neural cells that mimic the structure of brain tissue.

To achieve this, they developed custom bio-ink containing naturally-occurring carbohydrate materials with properties allowing accurate cell dispersion throughout the structure while also protecting the cells. The bio-ink was then optimised for 3D-bioprinting and developed for use in a standard cell culturing facility without the need for expensive bioprinting equipment.

The result is a layered structure like brain tissue, in which cells are accurately placed and remain in their designated layer.

“We are still a long way from printing a brain, but the ability to arrange cells so they form neuronal networks is a significant step forward,” said Professor Wallace.

“This study highlights the importance of integrating advances in 3D printing with those in materials science to realise a biological outcome. It paves the way for the use of more sophisticated printers to create structures with much finer resolution.”

The research was funded through Professor Wallace’s Australian Laureate Fellowship.

*Story with thanks to the ARC Centre of Excellence for Electromaterials Science.*

*and women in the Illawarra-Shoalhaven region, with the risk of an elevated BMI being higher for women than men living in those neighbourhoods.

Professor Bonney said that, by capturing data on the risk of overweight or obesity at a neighbourhood level, targeted strategies towards preventing and managing disease could be tailored to those areas and may also potentially be used to address context-specific cultural and community factors.

“For example, in neighbourhoods with high disadvantage, health service providers may be able to integrate nutrition education with community-level activities to improve fresh food availability and the physical activity environment,” he said.

“Further research to investigate the clustering of BMI and associated health risks, as well as the proximity to community health services, could further support population health efforts in these vulnerable populations and regions.”

The PLOS ONE paper is entitled, ‘Area-Level Socioeconomic Gradients in Overweight and Obesity in a Community-Derived Cohort of Health Service Users – A Cross-Sectional Study’.

The authors were Professor Andrew Bonney (IHMRI/UOW), Darren Mayne (ISLHD), Bryan Jones (Sonic Healthcare), Dr Lawrie Bott (Southern JML Pathology), Clinical Associate Professor Stephen Andersen (IHMRI and Southern JML Pathology), Associate Professor Peter Caputi and Dr Kathryn Weston (IHMRI/UOW) with Professor Don Iverson (Swinburne University of Technology).*
Precise targeting to boost cancer drug activity

In adults, gliomas are among the most frequently found primary brain tumours. While new imaging techniques have made the early diagnosis of gliomas possible, the treatment of high-grade gliomas remains a major challenge for clinicians as these tumours are resistant to radiotherapy and chemotherapy often fails because of inadequate drug delivery inside the tumour. Consequently, treatment is palliative rather than curative.

To overcome these problems, researchers are attempting to optimise chemo-radiotherapy treatments by increasing both the chemotherapeutic drug concentration and the radiation dose while simultaneously seeking to minimise the effect on healthy tissue.

A team of IHMRI-affiliated researchers within the Centre for Medical Radiation Physics (CMRP)’s Targeted Nano-Therapies group recently reported on a new treatment option for gliomas in the journal *Physics in Medicine and Biology*. The research highlights the importance of linking drug activation to precise targeting of optimised energy x-ray beams.

Under the supervision of Dr Moeava Tehei, Associate Professor Michael Lerch, Professor Anatoly Rozenfeld, Dr Konstantin Konstantinov and Dr Stephanie Corde, Dr Sianne Oktaria pre-treated gliosarcoma cells with MTX, a commonly used chemotherapy drug and/or BrUdR, a radiosensitiser drug. The team then irradiated the cells with x-rays at energies ranging from 50 kVp (peak voltage) to 10 MV (millivolts) using a conventional orthovoltage unit and linear accelerator at the Prince of Wales Hospital in Sydney.

They found that the surviving fraction of the gliosarcoma cell was significantly reduced when MTX and BrUdR were combined together with photon irradiation, compared to irradiation alone, or either drug and irradiation.

“This combination led to a highly effective chemo-radiation therapy,” explained Dr Oktaria.

“This was achieved with a significant decrease in the dosage of both the required drug and the radiation dosage otherwise required for the same treatment outcome.”

The study also revealed that the enhancement in tumour cell killing activity had a strong dependence on the photon energy, with the greatest sensitisation enhancement ratio (2.3) being obtained using a 125 kVp x-ray beam.

“Our findings are potentially significant for two reasons. Firstly, the improved targeting reduces the toxicity applied to surrounding healthy tissue and secondly, the optimised x-ray energies are widely accessible in hospitals,” said Dr Oktaria.

The team envisage that, in clinical settings, the optimal approach will be to use tuneable quasi monoenergetic x-rays delivered to the deep-seated tumour.

“Pre-clinical evaluation of our radiation-induced chemo-beta therapy in small animal models is the next step in developing this method for eventual clinical application,” concluded Dr Oktaria.

The paper is entitled: ‘Indirect radio-chemo-beta therapy: a targeted approach to increase biological efficiency of X-rays based on energy’.
The number of nurses working in Australian general practice has increased exponentially over the past decade. The work that these nurses do has also evolved to meet the complex growing health needs of people within the community. Despite these advances, the current and potential role of nurses in general practice remains poorly understood.

The professional practice framework and Registered/Enrolled nurse practice standards developed by the Nursing and Midwifery Board of Australia define the generic role of nurses. However, clarity around the nursing role specifically in general practice has been lacking.

In 2013 the Australian Department of Health funded a project to develop new national practice standards for Australian general practice nurses. The project was managed by the Australian Nursing and Midwifery Federation (ANMF) in partnership with IHMRI-affiliated researcher, Professor Elizabeth Halcomb, from the UOW’s School of Nursing.

In 2013-14 Professor Halcomb conducted a series of 14 focus groups with over 200 nurses around Australia. Complemented by two online surveys and individual consultations, these activities ensured that clinical nurses, general practitioners and other key stakeholders had a say on the development of the new National Practice Standards for Nurses in General Practice, launched recently.

The new guidelines include 22 standards covering four key domains – professional practice, nursing care, the general practice environment, and collaborative practice, explained Professor Halcomb who presented the research at the Annual ANMF Victorian Branch conference in Melbourne.

“They articulate the nursing role within the unique context of Australian general practice, as distinct from nurses who work within other settings. This is important as, ensuring nurses work to the extent of their scope of practice not only optimises the quality of services, but promotes job satisfaction and workforce retention.

“We are happy to have made a contribution to these important standards.”

Australian nurses working in general practice are now covered by new standards underpinned by research.
Knowledge is power

in reducing youth suicide risk

Clearly ahead of its time, the Inspire Foundation launched the ReachOut initiative in 1998 believing that the internet could be harnessed as a tool for stopping youth suicide. ReachOut.com is now Australia’s leading online mental health information source for young people, providing a gateway to getting help for mental health issues and services.

IHMRI-affiliated researcher Dr Coralie Wilson has worked on several ReachOut initiatives over the course of her career as a specialist with an international reputation in help-seeking and suicide prevention research and the development of evidence-based interventions that promote effective help-seeking.

Over the past 12 months, Dr Wilson has been collaborating with researchers at the University of Melbourne and University of Sydney on a first-of-its kind study looking at the levels of depression, anxiety, stress and suicidal ideation among ReachOut.com users.

The team examined the online habits of 1,500 young people who used ReachOut.com over time, presenting preliminary data at the International Youth Mental Health Conference in Canada in October this year.

They found that, at baseline, 56 per cent of young people aged between 16 and 25 accessing ReachOut.com for the first time reported severe to extremely severe depression symptoms. Fifty per cent reported severe to extremely severe anxiety symptoms and 37 per cent reported severe to extremely severe stress symptoms.

Importantly, 28 per cent reported severe suicidal ideation and the proportion of those with severe levels of suicidal ideation who hadn’t yet talked to anyone about their thoughts was significantly higher than those reporting lower levels of suicide risk.

The team will soon report on some of the barriers to seeking help and the mechanisms underpinning these behaviours in peer-reviewed journals.

Dr Wilson also recently attracted Rotary Mental Health funding to refine models of suicide behaviour among young people with different levels and types of suicidal ideation and behaviour to inform national and regional intervention programs run by ReachOut to improve parent, teacher and gatekeeper’s capacity for identifying and supporting suicidal young people.

The project will be conducted with Professor Stuart Thomas, a forensic and mental health epidemiology researcher from the UOW and associate researcher, Sarah Furlong.

Preliminary work on the development of a comprehensive model of suicide prevention, led by Sarah, was recently selected by a panel of Australian suicide experts for presentation at the National Suicide Prevention conference in Hobart, Tasmania. IHMRI PhD student Tara Hunt (another member of Dr Wilson’s team) was also selected to present on gender-specific features of suicide presentation.

Dr Wilson, who was an advisor on the National Action Plan for Suicide Prevention launched by the Federal Minister for Health, Sussan Ley MP in September 2015, is a key member of the UOW-driven Mind the Gap project aiming to prevent regional suicides and is also participating in the Illawarra Shoalhaven Suicide Prevention Collaborative (see page 3).
Most of us know that having a good diet is one of the best ways to prevent illnesses such as heart disease and stroke, which according to the World Health Organisation accounted for a quarter of all deaths globally in 2012. We may know what’s good for us, but when we’re faced with making the ‘right’ choice while standing in front of a supermarket shelf stacked with delicious-looking food, this knowledge doesn’t always translate to positive action.

To improve our adherence to healthy eating patterns, experts are shifting their focus from simple messages to behavioural change interventions underpinned by models such as the Theory of Planned Behaviour (TPB) which asserts that our actions are determined by a process of conscious deliberation. The TPB model suggests that the most important determinant of eating a healthy diet is having a strong intention to do so. In turn, strong intentions to eating a healthy diet are more likely when we hold positive attitudes towards the behaviour, perceive social pressures from those whose opinions we value and feel capable of eating a healthy diet without difficulty.

A group of IHMRI-affiliated researchers led by Associate Professor Rajeev Sharma from the UOW’s School of Information Systems and Technology, recently conducted a systematic review and meta-analysis of 22 studies to understand the association between TPB variables and dietary patterns such as ‘eating a healthy diet’ or ‘eating a low-fat diet’.

The team, which included Associate Professor Peter Caputi, Professor Don Iverson, Associate Professor Eleanor Beck, Dr Máirtín McDermott, Thomas Sinnadis and Madalyn Oliver with Professor Tim Coltman from the UOW’s School of Management, Operations and Marketing, reviewed over 10,000 records before reaching their conclusions.

Their findings, reported in the journal Preventive Medicine, are broadly in line with previous reports. Overall, the team found that TPB variables had medium to large associations with both intention and behaviour, suggesting that the theory may provide a solid foundation for those seeking to increase adherence to health-promoting dietary patterns.

However, the authors conducted additional analyses which led them to point out that this recommendation needs to be accompanied by some important caveats. Primary among them was the finding that associations between TPB and behaviour were significantly weaker when more accurate assessments of food consumption were used. This suggests that the evidence in support of TPB and healthy eating behaviour may be less positive than it appears. The authors recommend that further research be undertaken using more precise evaluations of eating behaviour.

The paper is entitled: ‘The Theory of Planned Behaviour and dietary patterns: A systematic review and meta-analysis’.

Global conversation on health effects of Wi-Fi

The launch of a world-first study at IHMRI investigating the health effects of exposure to mobile phones, base stations and Wi-Fi captured worldwide attention after study leader Dr Sarah Loughran penned an article for The Conversation asking, “Can you be allergic to your Wi-Fi?”

The story was reproduced by the Sydney Morning Herald and Gizmodo UK (one of the world’s technology sites) with Dr Loughran, from the IHMRI-based Australian Centre for Electromagnetic Bioeffects Research, subsequently interviewed by the ABC’s Hack program, as well as 2SER and ABC Radio Darwin, among others.

The Conversation piece was also translated into French for the launch of the site’s new French portal.

With Dr Loughran’s permission, Research Matters has reproduced the article in full below for your interest (with details on how to participate in the IHMRI study).

Can you be allergic to your Wi-Fi?

Have you ever suffered from unexplained headaches, sleeping difficulties or nausea after a prolonged session on your laptop or phone? You could be suffering from electromagnetic hypersensitivity (EHS); a purported medical disability that has led to successful work compensation claims in court. Let’s take a look at the scientific evidence.

Electromagnetic fields are all around us. They are a part of our natural environment, produced by the Earth and the sun. But they are also becoming increasingly prominent with advancements in technology, such that we are surrounded daily by many different sources of electromagnetic energy.

Mobile phones, Wi-Fi, personal computers, smart meters, radio, television and even the TV remote control – they all emit this electromagnetic energy. Mobile phone base stations are continually being installed and Wi-Fi hotspots are increasing all the time.

Cafés and restaurants, libraries, hotels and even some city centres and parks now offer free Wi-Fi. But with all of this new infrastructure it is also getting harder to avoid exposure to the electromagnetic fields that these technologies emit.

continued p14
And the question often asked is, what does all of this exposure mean for our health?

It is an issue that has continued to gain exposure, culminating a court case in September that is being touted as a breakthrough case.

French woman Martine Richard, who suffers from what is called electromagnetic hypersensitivity (EHS), was granted disability payments due to claims that her symptoms, which she attributes to electromagnetic energy, prevent her from being able to work. This ruling was made despite the science saying that no relationship between exposure to these fields and symptoms exists.

So what is EHS, what do we know and what don’t we know about this condition? And what does this case mean for the future?

What is EHS?

EHS is a complex condition. It is characterised by sufferers reporting a variety of non-specific symptoms (for example, headaches, nausea and sleeping difficulties) when in the proximity of devices that emit electromagnetic fields. In severe cases it can have large and negative impacts, with people unable to work or function in modern society.

The prevalence of this condition varies widely. In general, the number of patients presenting with symptoms that they attribute to electromagnetic field exposure seems to be increasing.

There is no doubt that the symptoms experienced are very real. But the fact remains that there are no clear diagnostic criteria for this condition. It is a self-diagnosed disorder that currently has no medical or scientific basis.

What does the evidence say?

Research has consistently failed to find any association between electromagnetic field exposure and reported symptoms, or health more generally. This raises the question, if it is not the electromagnetic energy, then what is causing EHS and the symptoms that these people suffer from?

One possibility is the nocebo effect, or simply, the influence of a person’s expectations or perceptions of how something might affect them. In the case of EHS this would correspond to a misaligned belief that electromagnetic energy is harmful and, therefore, when around devices that emit such fields they expect to feel bad, and they do.

The idea of a nocebo effect makes even more sense when media coverage and vocal lobbying by those with EHS are considered. The vast majority of such accounts report EHS as being caused by man-made electromagnetic fields.

This constant misattribution serves only to perpetuate and reinforce the belief that electromagnetic energy from these devices is harmful, despite all of the scientific evidence to the contrary.

The research goes on

While controversy remains about the cause of EHS, it is clear that there also remains a need for more research to further consolidate that electromagnetic fields are not responsible for these symptoms and to provide evidence of a cause (such as the nocebo effect).

Such research is underway, including our own studies at the Australian Centre for Electromagnetic Bioeffects Research, which aims to combat some of the criticisms of past studies. Until a cause can be established, the treatment of this condition will remain a challenge.

But regardless of the science, what does this recent ruling in France mean and how will it impact future rulings in this area? What is important to note is that, despite compensation being awarded, the court did not actually declare EHS a legitimate condition.

However, the concern now is that this case will be used as a precedent and that the lack of scientific evidence will be overlooked by those wanting to legitimise EHS as a condition caused by electromagnetic energy.

Perhaps the real shame here is the potential impact a decision like this could have on the search for the truth. It provides fuel for the media and lobbyists to misinterpret the ruling as showing cause and effect, based on their own motivations.

This in turn has the potential to overshadow the research that is endeavouring to uncover the real cause of EHS. And sadly, without this research, the help and treatment needed by those suffering from EHS will likely remain elusive.

If you, a family member or friend are interested in participating in an EHS study, contact:

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Meet our new Executive Director
Professor David Adams

Following an extensive recruitment effort, the IHMRI Board recently announced that the Director of the Health Innovations Research Institute at the Royal Melbourne Institute of Technology University, Professor David Adams, had been appointed IHMRI Executive Director.

Professor Adams will take up his IHMRI role in mid-December, 2015. Research Matters asked him a few key questions by way of introduction.

Tell us a bit about your research background and passion? Where did it all start for you?

I studied science at the University of New South Wales, but to be honest I didn’t really know what I wanted to do. Things started to turn around in my third year when I attended lectures on membrane physiology with Professor Peter Gage, an inspirational lecturer and researcher who was at the forefront of ion channel research.

I did Honours in his lab in 1973 and was then conscripted to fight in Vietnam. I was able to defer this by undertaking a PhD with a Commonwealth Postgraduate Scholarship.

Under Professor Gage’s supervision, I had my first paper published in Science in 1976 and the output of my PhD also included two papers in Nature and four in the Journal of Physiology. Professor Gage went on to become Chair of Physiology at the John Curtin School of Medical Research, Australian National University. Peter was inspirational and many of the students he mentored have gone on to become leading scientists in their fields. I am indebted to him for the opportunity to have a career in medical research.

Tell us about your early career

When I first went overseas in 1978, I soon realised that the work I had been doing in Professor Gage’s lab was at the cutting-edge. I was able to attract a Muscular Dystrophy of America Postdoctoral Fellowship at the University of Washington (1978-80), then a Grass Fellowship in Neurophysiology at the Marine Biological Laboratory, Woods Hole Massachusetts (1980), followed by a Beit Memorial Fellowship for Medical Research at University College London (1981-84). I was then recruited by the University of Miami School of Medicine (US) as an Assistant Professor in the Department of Molecular and Cellular Pharmacology in 1984 with the aim of establishing an independent and productive electrophysiology laboratory. I was promoted to Associate Professor (tenured) in 1989 and then full Professor in 1993.

While there, I helped to establish and was Associate Director of the National Institutes of Environmental and Health Sciences Center for Marine Biomedical Research to investigate, for example, the impact that major environmental events such as Red Tide algal blooms had on human health.

I spent 18 years overseas and returned to Australia in late 1995 to take up the Chair of Physiology at the University of Queensland (UQ) bringing two postdoctoral fellows – and my family – with me.

It was an interesting time in Queensland. Peter Beattie was appointed Premier and the university was also changing, with new Vice-Chancellor, Professor John Hay, consolidating around 90 departments into 30 schools.

The Pro Vice-Chancellor (Biological Sciences) at the time was Professor Alan Pettigrew, who is now IHMRI’s Chair.

At UQ, I became Head of the Department of Physiology and Pharmacology (1997-2000), then Head of the School of Biomedical Sciences (2000-07) and then Director of the Neuroscience Program (2008-09).

Around that time, I was asked by the VC to write a proposal for what was to be the Australian Institute for Bioengineering and Nanotechnology and met American philanthropist Charles ‘Chuck’ Feeney. I was keen to build on the strength of neuroscience research at
UQ and approached the VC with regard to a neuroscience initiative. Donations from Atlantic Philanthropies, coupled with university and State Government funding, saw the Queensland Brain Institute (QBI) founded in 2003 with Professor Perry Bartlett as Director.

I spent a year as a Professoral Research Fellow with QBI until 2009 when I left to become Director of the Health Innovations Research Institute at RMIT University, Melbourne. I was also awarded an Australian Research Council (ARC) Australian Professorial Fellowship (2010-14) providing significant funding support and time for me to focus on my research interests.

Can you tell us a bit about your experience in building the Health Innovations Research Institute (HIRi)?

The opportunity to create a biomedical research institute from the ground up was appealing. I was given strong support and the freedom to shape the Institute from Vice-Chancellor, Professor Margaret Gardner (now President and Vice-Chancellor of Monash University) and Deputy Vice-Chancellor (Research and Innovation), Professor Daine Alcorn.

I focused on identifying research-active and externally-funded researchers in the biomedical sciences, establishing four programs based on critical mass: Biophysics and Bioengineering, Metabolism, Exercise and Disease, Traditional and Complementary Medicine, and Ion Channels and Transporters as Therapeutic Targets.

The Institute has been instrumental in building the research culture and infrastructure at RMIT’s Bundoora campus and now includes 38 core members, 80 affiliated members and 120 PhD candidates – many of whom have come from interstate and overseas.

I was then asked to act as Deputy Vice-Chancellor (Research and Innovation) at RMIT; a role I held from May 2013 to February 2014.

This was a great experience, giving me insights into university-wide challenges and initiatives. However, the frustration was that I had a National Health and Medical Research Council (NHMRC) Program Grant and two ARC grants and wanted to spend more time on research, so I relinquished the role.

What attracted you to the IHMRI role?

My interest was really sparked by talking to Professor Pettigrew, who first interviewed me back in 1995 at UQ and is now IHMRI’s Chair. Alan and I were recently involved in the review of the Australian National University’s College of Medicine, Biology and Environment.

I realised that this was a unique opportunity in that IHMRI is a partnership between the University of Wollongong and Illawarra Shoalhaven Local Health District.

There is a strong commitment from the partners to build on IHMRI’s strong foundations and I am passionate about research translation. My own research is in chronic pain, so the opportunity of working with clinicians, and the broader Illawarra community, is very exciting.

The IHMRI model also provides opportunities for research impact – that is, research excellence times relevance.

You will be bringing several major grants to IHMRI. Can you tell us a bit about these grants and the lab-based work you will be doing?

When I went to UQ in the mid-nineties, researchers in the Centre of Drug Design and Development were investigating peptides from the venom of marine cone snails. They were discovering new peptides and determining their structures but didn’t have the ability or capacity to study their function, so I started collaborating with them.

We then attracted a $2.5M five-year ARC Discovery Project grant, began publishing high impact papers and attracted an NHMRC Program Grant, which started in 2005 and has been renewed twice (2015-19). I also hold a NHMRC Project Grant and a five-year ARC Discovery Project Grant (2015-19).

My research involves the use of state-of-the-art electrophysiological and fluorescence imaging techniques to investigate the target(s) and mechanisms of action of analgesic peptides on membrane receptors and ion channels expressed in the sensory neurons of pain pathways.

The goal is to translate the basic discovery and development of these compounds into the clinic for the treatment of chronic neuropathic and visceral pain. That will be the focus of my work at IHMRI and I am eager to collaborate with clinicians with an interest in this area.

I will be establishing a lab in IHMRI’s headquarters and bringing four researchers with me. Most of them are from overseas and don’t know Wollongong well – I think they will be pleasantly surprised when they get here.

I am also collaborating with a team at Monash University and we are submitting an application to establish a NHMRC Centre of Excellence for Chronic Pain.

Tell us something about yourself away from work?

I was born in Goulburn NSW and went to high school and university in Sydney before travelling overseas.

I met my wife Trish Adams through a London tennis club. I used to be a keen tennis player, but now it’s more likely to be golf.

Trish is a visual artist who is an Adjunct Professor at the Queensland University of Technology and was a Research Fellow at RMIT from 2010 to 2013. She is an installation artist whose work is at the intersection of science and art.

We have two children, Brooke (30) and Matthew (28) and recently welcomed a grandson to the family.

In terms of personal interests, I enjoy travelling, reading, jazz; those more relaxing kinds of pursuits!

 Anything you would like to add?

Ask me after the first 100 days in the position of Executive Director, IHMRI!
Kidney health “angel” recognised

The Director of the Renal Service within the ISLHD, Professor Maureen Lonergan, has received an Operation Angel Award from Kidney Health Australia for her outstanding commitment and service to the kidney community.

The award recognises her dedication and willingness to go “beyond the call of duty” in ensuring patients are cared for and involved in decisions that will affect their health. She has also been instrumental in the development of area-wide services to ensure appropriate care is provided close to home for people with renal impairment.

“There are so few accolades and recognition for the people in the health frontline. It’s tiring work that requires enormous dedication and selflessness. It really is the work of angels,” said the CEO of Kidney Health Australia, Anne Wilson.

“The Operation Angel awards show our appreciation on behalf of Kidney Health Australia and the many families and individuals that are inspired and heartened by their efforts.”

New insights into Huntington's disease

Congratulations to IHMRI PhD candidate Fabian Kreilaus who recently had a paper accepted for publication in the journal, *Neuropathology and Applied Neurobiology*.

The paper, entitled, ‘Evidence for altered cholesterol metabolism in Huntington’s disease post-mortem brain tissue’, provides the first detailed report of cholesterol-related changes in human brains affected with Huntington’s disease (HD), a debilitating neurodegenerative disease that results in a gradual loss of cognitive thinking, physical and emotional function.

Cholesterol plays an essential role in membrane structure and function in the brain, and although altered cholesterol synthesis and metabolism has been demonstrated in several HD mouse and cell models, far less is known about these alterations in human tissue.

Under the supervision of Dr Andrew Jenner and in collaboration with Professor Brett Garner and Adena Spiros (IHMRI) and Professor Catriona McLean (Monash University/Alfred Hospital), Fabian quantified cholesterol synthetic precursors, metabolites and oxidation products in five regions of human post-mortem HD brains.

He was able to show that the human HD brain had significantly decreased cholesterol metabolism and disrupted cholesterol homeostasis, specifically localised to the striatum – the brain region severely affected in HD neurodegeneration.

The research also indicated that lipid oxidative stress accompanies HD pathology.

“Prior to our study it was unknown if cholesterol metabolic changes occurring in HD animal models were also present in human disease,” Fabian told Research Matters.

“We have confirmed a number of alterations are consistent. However, several important pathways are affected differently in humans and mice.

“This research is fundamental to identifying altered pathways in human HD for further investigation, as well as providing potential biomarkers of disease severity and progression. In addition, these findings have broader applications in other late onset neurodegenerative diseases, such as Alzheimer’s disease, which also exhibit cholesterol metabolic disturbances.”

Important paper on MND propagation

Congratulations to IHMRI PhD candidate, Rafaa Zeineddine, her supervisor Dr Justin Yerbury and a team of regional, national and international researchers who have just published a paper which shows how protein aggregates effectively trick neurons into allowing them to enter cells to propagate Motor Neurone Disease (MND).

Amyotrophic Lateral Sclerosis (ALS) is the most common form of MND and is typically characterised by the selective death of neurons in the motor cortex, brainstem and spinal cord. The specific causes of most cases of ALS are undefined, although around 10 per cent are inherited.

From this, a subset of ALS patients have mutations in the gene encoding the SOD1 protein, with previous studies showing that misfolded SOD1 can be repeatedly transmitted from cell to cell through the nervous system. The mechanism behind this is thought to be a form of non-specific pinocytosis (a process allowing small particles to be brought into cells).

In the *Molecular Neurodegeneration* paper, the team demonstrate that, in a manner similar to a virus entering neurons, protein aggregates interact with the cell surface, triggering the activation of signalling molecules and pathways of macropinocytosis (a process mediating the uptake of molecules and nutrients), permitting the engulfment of large protein aggregate particles.

“We also show that these protein aggregates can escape membrane bound compartments and are able to enter other parts of the cell to potentially cause more damage through aggregate propagation,” said Rafaa, who is listed as a lead author.

“Thus, we conclude that these mechanisms may help explain how neurons can take up such large protein aggregates and thus identify a possible target to halt the protein misfolding propagation.”

The paper is entitled: ‘SOD1 protein aggregates stimulate macropinocytosis in neurons to facilitate their propagation’.
UK visit advances promising yeast study

A PhD student in Dr Justin Yerbury’s lab, Isabella Lambert-Smith has just returned from a stint at the University of Cambridge (UK) where she worked on a promising research study with collaborators, Professor Steve Oliver and Dr Giorgio Favrin in the Department of Biochemistry.

The team are looking at amyotrophic lateral sclerosis (ALS), otherwise known as Motor Neuron Disease (MND), and the different pathways being disrupted in cells and how they are linked to the pathogenesis of MND.

“We are focused on understanding perturbations in protein homeostasis [proteostasis] mechanisms,” Isabella explained.

“Professor Oliver’s lab uses yeast as a disease model for studying genetic and protein-protein interactions in disease. Although yeast are a simple eukaryotic unicellular organism lacking the specialisation of neurons, the fundamental features of eukaryotic biology, particularly proteostasis mechanisms, are well conserved between yeast and mammalian cells, including human cells.”

Her aim in going to Cambridge was to develop and use a yeast model which she could then use to screen for specific genes. She came away with a “good list of gene hits” and an experience of a lifetime.

“Without a doubt, my 16 months in Cambridge were probably the best of my life. I fell in love with the city, the lifestyle, the history and made some really great friends – I didn’t want to leave.”

Isabella also presented a poster at the 25th International Symposium on ALS/MND and was selected from a field of around 400 posters to win a highly commended prize.

Poster presentation award

At the 9th General Meeting of the International Proteolysis Society (IPS) Meeting, held in Penang Malaysia in October, IHMRI PhD candidate Ben Buckley won the 2015 IPS Poster Presentation Award.

The meeting was attended by leading researchers in the proteolysis field and focused on therapeutics and novel technical developments.

Ben’s poster, entitled: ‘Developing potent uPA/NHE1 inhibitors with high selectivity over related TLSPs from the clinical drug Amiloride’, was one of four selected from the 80+ presentations to receive the award, which came with a cash prize.

He also participated in a ‘Practical Protease Kinetics’ workshop for early to mid-career researchers and presented his work as an invited oral speaker.

Ben is co-supervised by Professor Marie Ranson and Associate Professor Michael Kelso (see story page 2).

Prizes at protein meeting

Congratulations to IHMRI PhD candidates Dezarae Cox and Rebecca San Gil, who won student prizes at the East Coast Protein Meeting in Coffs Harbour (NSW) and Dr Amy Wyatt who took out the associated Queensland Protein Group-sponsored ComBio award for early career researchers. This gave her the opportunity to present her work at a combined meeting of several biological societies of Australia and New Zealand in Melbourne.

Dr Wyatt also recently took out the $8,000 UOW Pitch competition (with Professor Mark Wilson) with her presentation entitled: ‘Molecules for Healthy Ageing’.

Read more about Dr Wyatt’s work on page 2.
IHMRI PhD candidate, Blagojce Jovcevski, took home an ‘Oscar-style’ trophy for best poster presentation at the American Society for Mass Spectrometry (ASMS)’s Asilomar Conference, held in California in October.

The focus of the conference was on the use of native mass spectrometry (MS) to investigate large biomolecular assemblies ranging from small peptides to viruses.

His presentation was entitled, ‘Using native MS to delineate the structural heterogeneity and dynamics of small heat shock proteins’. It referenced a current collaboration between IHMRI-affiliated researcher, Associate Professor Heath Ecroyd (supervisor), and scientists at the University of Oxford (UK) looking at the role that small heat shock proteins play in neurodegeneration.

“As IHMRI is one of very few institutions in the country to use native MS to interrogate protein structure, the conference allowed us to showcase how we utilise MS to provide a structural rationale for protein function,” explained Blagojce, whose work is funded by an Australian Rotary Health scholarship.

“It was an amazing experience to be able to present my work to world leaders in the field of native MS. It also highlighted how it is being used to investigate a wide range of biological systems.”
Dr Kara Perrow, a cancer researcher and former Vice-Chancellor Postdoctoral Research Fellow based at IHMRI, regularly participates in community engagement and fundraising activities run by local organisations such as Illawarra Cancer Carers, whose donations have supported her and other IHMRI-based cancer researchers with grants and vital pieces of equipment.

Dr Perrow recently gave a ‘thank-you’ community talk to a group of Can Too supporters whose donations are funding her current two-year Cure Cancer Australia Foundation grant. The foundation’s aim is to transform lives through fun, fitness, friends and fundraising, with participants being given professional coaching to run or swim and bike in sporting events. In return, they raise valuable funds for innovative cancer research.

“My talk was given on the track at Beaton Park in Wollongong,” said Dr Perrow.

“And the supporters I spoke to were training for the Blackmores Sydney Running Festival Half Marathon and fundraising for cancer research at the same time – absolutely amazing given the time and commitment required to train for such an event and that most of them were working women with young families.

“In my opinion it is critical that we, as researchers, meet and thank the dedicated individuals who put in the hard work, sweat [and tears] to raise such valuable funds for us. The money that the Can Too supporters have raised has been vital financially in enabling me to continue developing new targeted anticancer drugs. Research is a costly venture and without continued support and fundraising efforts, none of this would be possible.

“As a young researcher, the funding has also been instrumental in allowing me to build my career, become an independent researcher, employ other young scientists and teach and inspire research students who will hopefully one day contribute to finding a cure for cancer – and for that I am truly grateful.”