

Translational research into osteoporosis wins NSW health award

Professor Markus Seibel, Dr Kirtan Ganda and Dr Anna Lih have won the prestigious 2012 NSW Health Award for their ongoing translational research into cost effective ways of treating osteoporosis patients.

Significantly, their research has led the Sydney Local Health District to establish an innovative integrated Fracture Liaison Service at Concord Hospital's Department of Endocrinology and Metabolism.

The Hon. Jillian Skinner, Minister for Health, presented the award to the members of the ANZAC Bone Research Program and the hospital's Department of Endocrinology at a ceremony in October.

The project had its origins in 2003 when Markus Seibel and an Honours student initiated an audit of patients admitted to Concord Hospital with osteoporotic fractures and discovered that although the fractures were repaired by surgery, there was no investigation of how the fracture occurred and no treatment to minimise the risk of another similar injury.

"Everyone had an X-ray but only 3% of patients got a bone mineral density scan which is an excellent test to define future fracture risk," Prof Seibel recalled.

"Osteoporosis was basically ignored. So in May 2005 we established a Fracture Liaison Service with the purpose to identify, investigate and properly manage patients who presented to Concord Hospital with a recent minimal trauma fracture."

In 2010 Drs Lih and Ganda and Prof Seibel analysed data from about 250 patients and compared the results to those



Markus Seibel, Kirtan Ganda and Susan Maree receive the award from Health Minister Jillian Skinner

from some 160 patients who had not taken up the opportunity, but were otherwise similar.

"While this was a non-randomised study and certain biases would naturally exist, our results were clear enough - re-fracture rates were 20% in the unmanaged group and only 4% in the managed group," says Prof Seibel.

"Effectively, proper management of osteoporosis reduced the risk of re-fracture by up to 80%. Not only that, but we found the service and its interventions were highly cost efficient.

"A well-managed Fracture Liaison Service costs money. Our service is run by a doctor with some input from nursing staff, and we do blood tests, X-rays and a bone mineral density scan to identify those patients who require treatment, which usually consists of calcium,

vitamin D and an anti-resorptive agent such as a bisphosphonate. All of that costs money but when you balance that against the cost of further fractures, in particular hip fractures, the service we deliver is peanuts compared with the follow on cost of further fractures. Just one example, a re-fracture has an average stay in hospital of 22 days. The direct costs are so large we don't even have to take into account the indirect costs."

The team put together a business case and the Sydney Local Health District agreed to establish and support a part-time position for a doctor to run the Fracture Liaison Service at Concord Hospital.

"If I'm not mistaken we're the first hospital in NSW if not in Australia to have an institutionalised, integrated Fracture Liaison Service funded by the Local Health District," says Prof Seibel.

Atherosclerosis laboratory moves to ANZAC Research Institute

The ANZAC Research Institute has achieved a significant expansion with the establishment at Concord of the Atherosclerosis Research Laboratory, previously at the Centre for Vascular Research at the University of NSW.



Prof Len Kritharides

“Having the laboratory here will greatly enhance the opportunities to collaborate with our colleagues at the ANZAC Research Institute,” said Professor Len Kritharides, who is the Director of Cardiology at Concord Hospital, and heads the Atherosclerosis and Vascular Biology Groups at the ANZAC.

“I am delighted that my colleague of many years, Professor Wendy Jessup, will be joining us to continue our laboratory research, funded by an NHMRC program grant which has just been renewed.”

The Vascular Biology team has been working closely with Concord Hospital’s Cardiology Department for several years, researching disorders of the heart and blood vessels, including platelet abnormalities and thrombosis. The addition of the atherosclerosis laboratory will provide fresh impetus and valuable resources to this research.

Atherosclerosis is a disease of the artery wall caused by a combination of cholesterol accumulation, inflammation, degeneration, and thrombosis. It is a major cause of illness and premature death worldwide, underlying almost all heart attacks, most strokes and the narrowing of

arteries causing gangrene of the legs. It is promoted by conditions such as high levels of low-density lipoprotein cholesterol (LDL), low levels of protective high-density lipoprotein (HDL), diabetes, and smoking. Cardiovascular disease causes 30% of deaths worldwide according to the World Health Organisation, and 34% of deaths here in Australia.

“Our laboratory has a long standing interest in understanding the cellular biology of atherosclerosis, particularly the investigation of cholesterol metabolism and protein secretion by macrophages,” says Prof Kritharides.

“Our laboratory research so far has been cell-based. Now that we are established at the ANZAC Research Institute we can work even more closely with colleagues within the ANZAC and Concord Hospital to develop translational research to unravel the complexities of atherosclerosis and heart disease in people.”

NHMRC grant recognises groundbreaking research on genetic mutations



Associate Prof Marina Kennerson

The grant will enable Associate Professor Marina Kennerson and her colleagues to use the latest technologies to map the defective genes that cause

Charcot-Marie-Tooth disease in particular.

“We’ve already looked at 114 families with CMT and have solved about 30 per cent, by finding mutations in known genes, so now we need to do more work on the other families to identify new causative genes,” says Dr Kennerson.

“The challenge is no longer what gene will we screen, but to ask what DNA changes identified are actually causing the disease. It’s a big job but we can make very good headway in the next few years.”

Dr Kennerson says CMT is a disorder

The National Health and Medical Research Council has acknowledged the outstanding results achieved by the ANZAC Research Institute’s neuroscience team by awarding a grant of \$585,000 over three years to allow further investigation of genetic mutations that lead to diseases of the nervous system.

that is very amenable to these new technologies because it’s a disorder caused not just by one gene but by many, many genes.

“It’s exciting to get this grant and to know that we will push the boundaries of finding more genes. There are a lot more out there that need to be found.”

Dr Kennerson paid tribute to the foundation work by Professor Garth Nicholson, who spent decades collecting DNA material from patients and whole families affected by CMT, so these samples are now available to researchers using the most modern technology.

“To get this national support to do this is rewarding,” she adds. “We can change things not only for families in Australia with CMT, but internationally as well.”

Solving the mysteries of the bowel

One Australian in every 5 who consults a GP does so because of a bowel condition such as Irritable Bowel Syndrome, constipation or faecal incontinence. Yet the intricate workings of the gastro-intestinal system remain a mystery.



Prof. Marc Gladman

Solving that puzzle is the challenge facing the ANZAC Research Institute's newest team, the Colorectal Group, headed by Professor Marc Gladman, who now divides his time between performing surgery at Concord Hospital and conducting research at the Institute's laboratories.

Colorectal cancer is the second most common cancer and will affect about 8% of the Australasian population.

"Most of our surgery for colorectal cancer involves cutting out sections of the bowel containing the cancer," says Prof Gladman.

"Then we rejoin the bowel back together, and miraculously and fortunately it usually works, but we don't understand that at all. It's an incredibly complex situation. So most of my research is focused not on the direct mechanisms of the cancer, but more on the consequences of it."

Prof Gladman explains that the human gut has its own intrinsic nervous system, known as the enteric nervous system.

"Some people call it the brain of the gut because it has a lot of nerve cells within it," he says.

"It has an extrinsic nerve supply, part of which is not under voluntary control, and another part under our voluntary control - that's how we control the evacuation of faeces.

"So there are three nervous systems interacting. You've got the brain and the spinal cord sending signals to the guts, and within the gut there are muscle and other cells involved in the squeezing and the churning and mixing of material, and then lower down again is another set of muscle for the removal of waste product.

"So we're trying to understand how all those very diverse processes interact in normality and then surgeons like me come along and disrupt that."

Initially the Colorectal group also includes two research scientists, two PhD students and three research nurses. By combining basic laboratory experiments with clinical measurements in patients, the team is looking at ways to study all three areas simultaneously - the brain, the nerves and the gut.

"It's about improving life for patients who've had the operation," says Prof Gladman.

"The first step is to understand in patients who've undergone surgery for bowel cancer why things are not working well, and once we know that, we can better target our remedies, to the nerves or the bowel wall or whatever it might need to be.

"We don't have the sophisticated level of understanding as we do in the way the heart works, for instance, so that's what is exciting and attractive to me, as an opportunity to go back to basics to understand how it works, and then, with that knowledge, find ways to improve it."

Annual symposium

The ANZAC Research Institute's 11th Annual Symposium was hosted in September by the Andrology Research group, with the theme "Frontiers in Steroid Assay and Action."

The meeting brought together many specialists, national and Institute scientists, and three international speakers, to share information on state of the art technologies in steroid measurement and anti-doping

science, as well as updates on how those steroids work in the body.

The Institute also hosted an all-day technical workshop for small groups of scientists to study the novel world-leading methods operating the Institute's Andrology laboratory which serves as the Australian reference centre for mass spectrometry steroid assays in clinical research.

Early career research prizes

Three young scientists at the ANZAC Research Institute have each been awarded \$1000 for their outstanding research achievements under the Concord Repatriation General Hospital "Early Career Research Prize" scheme which is jointly sponsored by the Institute and Concord Hospital's Research Committee.

Winner of the Postgraduate Student prize was Kelly Williams, for Identification of a Novel ALS Gene Using Genetic Linkage Analysis and Exome Sequencing. Kelly is a PhD student of Dr Ian Blair in Prof Garth Nicholson's Northcott Neuroscience laboratory and described a novel, world's first discovery of a new gene causing familial ALS. Other finalists were Cassandra Chong, Yan Ru Gao and Regina Leung.

The Undergraduate Student prize was awarded to Sarah Kim, for The Role of RANK in Breast Cancer Growth in a Murine Model of Bone Metastasis. Sarah is a student whose work was performed in Professor Markus Seibel's bone research laboratory and described important new discoveries of why breast cancer spreads so often to bone where it causes severe pain, disability and death. Other finalists were James Doherty, Paul Lunney and Tegan Ryan.

Michaela Kirschner won the Non-student category for Circulating miR-625-3p: A Potential Blood-based Biomarker for Malignant Pleural Mesothelioma. Michaela works in the Bernie Banton Centre laboratories where, in another world's first, she has identified a new type of biomarker for mesothelioma which may become valuable in the future for screening exposed people as well as monitoring progress with treatment. Other finalists were Jerret Lau, Kifah Shahin and Shu Yang.

NHMRC grant for Andrology group



Prof David Handelsman

An NHMRC grant of \$234,200 over the next two years will allow a team from the ANZAC Research Institute's Andrology group to develop a new ultrasensitive method of measuring extremely low levels of estradiol (E2) circulating in the bloodstream, using liquid chromatography-mass spectrometry.

The Andrology lab facility serves as the national reference centre for steroid mass spectrometry assays, the gold standard for clinical and experimental laboratory research.

Prof David Handelsman and Drs Tim Harwood (from New Zealand) and Pekka Keski-Rahkonen (from Finland) aim to find a way of measuring levels of serum estradiol (E2), the only biologically active estrogen in animals (including humans), responsible for the development of the all female reproductive organs and function as well as some aspects of male health. Accurate measurement of serum E2 is crucial to understanding reproductive development, physiology, health and disease, including

the origins and treatment of estrogen-dependent diseases such as breast cancer, endometriosis, and endometrial cancer.

Commercial immunoassays currently used to measure high blood E2 levels are reasonably accurate only in women before menopause but are too inaccurate for use in postmenopausal women, men or children as well as in any sub-primate animals including mice and domestic, agricultural and endangered species. This limitation has restricted medical scientists from uncovering crucial new insights from genetic mice models as well as understanding reproduction in larger sub-primate species.

Accurate measurement of serum E2 levels in mice will assist research into sex

steroid regulation of reproductive functions (notably ovulation), endogenous estrogen effects on breast, uterus, prostate, brain, bone, vascular, liver, metabolic and adipose tissues, and disease pathophysiology where estrogens have impact (especially breast, uterine, ovarian, prostate and testis cancers as well as cardiovascular and neurodegenerative diseases.)

An ultrasensitive E2 assay will also allow a significant re-evaluation of present knowledge of the neuroendocrine regulation of female reproductive function and estrogen effects, given that most current textbook knowledge is based only on inaccurate immunoassays.

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