

discovery

DISCOVERING WHY SOME AUSTRALIANS ARE MORE LIKELY TO HAVE CARDIOVASCULAR DISEASE

Aboriginal Australians, patients with schizophrenia, women who have developed preeclampsia during pregnancy – three very diverse groups with one shared characteristic being their higher risk of heart disease and stroke.

These three groups are the subject of new research which aims to discover new ways of predicting heart disease, funded over the next three years by a \$750,000 grant from the NSW Government.

Professor Len Kritharides, head of cardiology at Concord Hospital and leader of the Atherosclerosis Laboratory at the ANZAC Research Institute, will work closely with other researchers and clinicians who have established cohorts of patients in each of the three groups.

“Our hypothesis is that an inability to clear cholesterol from the body is one of the causes of premature heart disease and stroke,” he explains.

“We are looking at the function of good cholesterol by taking a small sample of people’s blood and looking at how it removes cholesterol from cells and how it delivers that cholesterol to other cells. Imagine you are clearing cholesterol from your body like you take garbage to the tip. The garbage truck has to pick up rubbish from your house and then deliver it to the tip and offload it. We’re interested in both steps of the process – the pickup and the delivery to the tip. Each of those involves two separate assays, one of which is well established in the world literature, and one of which we’re developing ourselves.

“The novel thing about what we’re doing is that we’re applying these two measurements to Australian populations who we think are at risk of heart disease and for whom we don’t have a good way of predicting that risk.”

Prof. Kritharides says very little has been done to study the quality and function of HDL, the so-called “good” cholesterol, in these groups.

“We will be measuring HDL function in these people by testing the capacity of HDL in blood to remove cholesterol from cells in a culture dish, and to deliver the cholesterol to the liver. We plan to analyse these results in relation to other risk

factors, to see if we can find associations, and predictors of future heart disease risk.”

There is a large difference in life expectancy for Aboriginal and non-Aboriginal Australians. Young indigenous men will often suffer heart attacks and strokes 20 years earlier than non-Aboriginal men. The researchers at Concord will work closely with Professor Alex Brown, from the South Australian Health and Medical Research Institute.

Schizophrenia patients have an even wider gap in life expectancy of up to 25 years, substantially due to chronic diseases such as premature cardiovascular disease.

“They have very high rates of diabetes, obesity sometimes caused by medication, high smoking rates, but their cardiovascular risk remains incompletely explained,” says Prof. Kritharides.

“We’ll be working closely with Professor Tim Lambert, Professor of Psychiatry at Concord Clinical School and Dr Vincent Chow, staff specialist cardiologist at Concord Hospital, who have ongoing experience in managing the metabolic health of men and women with schizophrenia.”

The third group consists of young women who have had preeclampsia, a disease of high blood pressure during pregnancy. These women are predisposed to developing heart disease many years later, with twice the risk of women who’ve never had preeclampsia. The reasons for this are unclear.

“We are very fortunate to have the chance to work with Professor Mark Brown at St George Hospital. He has been following a cohort of women who have had preeclampsia and women who haven’t had preeclampsia, so we can do comparative studies of the behaviour of their HDL early and longer term after successful pregnancy.”

Prof. Kritharides suggests that if the investigation confirms that these groups are at higher risk of cardiovascular disease because they have an inability to clear cholesterol, not only will it assist in predicting heart attacks and strokes but could also identify future therapies.

A MESSAGE FROM OUR PATRON



His Excellency General the Honourable David John Hurley AC DSC (Retd) and wife Linda.

The ANZAC Research Institute is proud to announce that His Excellency General the Honourable David John Hurley AC DSC (Retd) Governor-General of the Commonwealth of Australia, has agreed to be the Institute’s Patron. This continues a tradition of Vice-Regal Patronage since the opening of the Institute in 2000.

“The ANZAC Research Institute is making an immense contribution to health and medical care in Australia,” said His Excellency.

“Through their work across so many research disciplines, and their leadership, they are creating a lasting legacy to the veterans and their families who have contributed to the society we enjoy today.

“I am delighted to serve as Patron and, with Linda, look forward to actively promoting and supporting the work of the Institute over the next five years.”

SYDNEY HOSTS INTERNATIONAL ASIAN OCEANIC CMT CONFERENCE



Professor Marina Kennerson

The ANZAC Research Institute's Marina Kennerson is the key organiser for an

international conference on Charcot-Marie-Tooth disease taking place in Sydney in early September. Presentations will be made by representatives of the ten nations which are members of the Asian Oceanic Inherited Neuropathy Consortium (AOINC), which was formed in 2016 to share research on this disease, thereby leading to the discovery of effective therapies and improving patient care.

"CMT is present in our region and we represent almost half the world's population," says Associate Professor Kennerson.

"We're working to build up a network of researchers who work on CMT so we can understand the genetics and natural history of the disease based on Asian and Oceanic ethnicities. A lot of work has been done on

the European and Western genomics but we need to do that in other parts of the world and other populations."

By bringing CMT researchers and clinicians together, the Consortium aims to increase awareness of the disease and to overcome barriers that can be encountered in helping patients recognise and understand the disease. CMT is an inherited disease causing the degeneration of the peripheral nerves to the feet, legs, arms and hands.

"The most common form of CMT is CMT1A, which is caused by a mutation of the PMP22 gene and is seen in all ethnicities," Prof. Kennerson explains.

"We have over 90 genes that have been identified for CMT but there are still 40 percent of families that remain genetically unsolved. We are now getting down to private rare gene mutations (genetic changes that occur exclusively in one family) and DNA re-arrangements (structural variation) that may have caused the disease, and we want to get a picture of what types of gene mutations exist in the Asia-Oceania populations. There could be

unique mutations which would be important discoveries.

"I've been involved with identifying a gene variation which we found only in a particular Malaysian family of Indian ethnicity, and with my colleagues in Malaysia we have mapped and reported that genetic change. Are there other families in the region who might have this mutation? Having the AOINC provides a network to help validate new gene findings."

The idea is to bring researchers together to be able to pool clinical resources, knowing that eventually there will be the chance for clinical trials.

"This has happened in Europe and North America and I feel we ought to be working towards doing this in our region so we can benefit from our combined patient and genetic resources and from the advances in the CMT field."

The ten countries forming AOINC are Australia, China, India, Japan, Korea, Malaysia, Singapore, New Zealand, Taiwan and Thailand. To learn about AOINC and become a member see the website (www.asianoceanicinc.org).

YOUNG INVESTIGATOR AWARD FOR ANDROLOGY RESEARCH INTO MALE FERTILITY



Dr Nandini Shankara Narayana

Dr Nandini Shankara Narayana is an endocrinologist with special interest in Andrology.

She has recently submitted her PhD thesis, with research work in a range of topics in Andrology at the ANZAC Research Institute and Concord Hospital's Andrology Department, the only department of its kind in Australia.

Her main project was on investigating the reversibility and time course for recovery of testicular function after abuse of androgens (sometimes misnamed "anabolic steroids") for body building. Her other areas of work include sperm cryostorage for men about to undergo gonadotoxic treatment for cancer or other serious diseases, and the genetics of disorders of sexual differentiation and development.

Her paper *'Sperm Cryopreservation Prior To Gonadotoxic Treatment: Experience of a Single Academic Centre Over 4 Decades'* published as an editor's highlight article in the leading international journal *'Human Reproduction'*, has been chosen for *'ESA Young Investigator Scientific Article Award'* for 2019 from the Endocrine Society of Australia.

This paper describes an effective sperm cryostorage program at Concord Hospital (and previously at Royal Prince Alfred Hospital), operating within the same department and laboratory from the late 1970s in men scheduled to undergo gonadotoxic treatment, usually for cancer, which would cause often irreversible loss of gametes, the cells that grow into mature sperm. Loss of fertility is virtually a universal consequence of gonadotoxic (chemo- and/or radiotherapy) regimens or surgery when it causes severe damage or destruction of gametes in the testes or their complete removal by excision of one or both of the testicles. All these medical or surgical

treatments cause severe spermatogenic damage resulting from temporary or permanent gamete loss that cause male infertility.

Sperm cryopreservation is an established technique to preserve male fertility prior to gonadotoxic treatment. This paper reported detailed analysis from over 2000 cases of pre-freeze sperm/seminal parameters in various disease categories, impact of the disease on sperm output, feasibility of sperm cryostorage especially at young age, and regional access to the urban cryostorage facility. It concluded that sperm cryostorage is feasible virtually in all men, including sufficiently mature adolescents, who can collect semen to ensure future paternity, but regional areas were likely underserved by urban-based sperm banking programs.

Sperm cryopreservation should be an integral part of comprehensive treatment in men receiving gonadotoxic treatment but remains under-utilised.

A REWARDING PARTNERSHIP

A NSW Ministry of Health grant of \$750,000 over the next three years acknowledges not only the achievements of the ANZAC Research Institute's Platelet and Thrombosis Laboratory, but also the successful way in which it works closely with the thrombosis management clinic at Concord Hospital.

The grant, awarded under the NSW Cardiovascular Disease Research Capacity Building Program, will support further research into the role of blood platelets in affecting the incidence of heart attacks and strokes and also partly fund the employment of a trainee to expand the capacity of the clinic.

Dr Vivien Chen, the laboratory leader and Staff Specialist Haematologist at the hospital, says it is "fantastic" that the Ministry recognises that clinician scientists can add enormous value to health outcomes and this type of funding can encourage more trainees to enter a dual pathway, combining both clinical activity and biological research.

"By leading clinical care as well as biological research programs, clinician scientists can identify key knowledge gaps in clinical outcomes to direct relevant biological research questions".

Cardiovascular disease on a global basis is responsible for 40% of deaths.

"Our research has shown that not all platelets act in the same way, that there are different populations within our platelets that have different roles. There's one particular population that is very active and has a lot of different coagulation activities that seem to be in excess in patients who have a heart attack or stroke, and they're not as important in stopping bleeding.

"Our hypothesis was that if you can interfere with the function of this sub-population of platelets, that drives the bad clots, you could decrease the incidence or frequency of heart attacks and strokes, without affecting the good function, which is to stop bleeding."



Morgane Bourcy, Helena Liang, Ibrahim Tohidi, Vivien Chen & Heather Campbell

Dr Chen's research has a three-pronged focus:

"The first is to develop our new patented technology that measures "hyperactive platelets" into a routine diagnostic test that can be used to identify which heart disease patient may need increased to prevent further events."

Dr Chen's research includes patients with coronary artery disease who are traditionally studied in terms of cardiovascular risk, but also focuses on blood clotting in cancer. She studies cohorts of patients who have an increased risk of heart attack or stroke, deep vein thrombosis (DVT) and pulmonary embolism (PE) thrombosis. These include patients with lung cancer and a type of blood cancer called essential thrombocythaemia.

"We're looking at whether our novel tests can better risk stratified management in these patients."

The second focus is in developing drugs which will reduce the tendency that cardiovascular patients have in producing excessive quantities of procoagulant platelets, tiny blood cells that form clots to stop bleeding from cuts and wounds, but which can in different circumstances produce clots that lead to heart attack or stroke.

"Our third focus is what we call a discovery approach, where the data from

the experimental results tell us how to ask the next research question. This has the opportunity to open up new means of investigation. We are taking platelets from healthy individuals and comparing them with platelets from patients with coronary disease and to see how their platelets differ in both RNA (ribonucleic acid in the chromosomes of living cells) and the proteins in the platelets.

"By understanding the differences we can actually see the platelet biochemistry pathways that have been altered in the diseased patients that are not altered in the healthy patients. That will give us new avenues of investigation and discovery."

An additional benefit of the grant will be the ability to employ a clinical fellow, to free Dr Chen's time to focus more on progressing research outcomes while allowing the clinical service at Concord Hospital to expand to provide a thrombosis service five days a week.

"Currently there's a six to twelve week waiting list to get into my thrombosis clinic," she says.

"This will increase our capacity to see urgent patients and enrol patients into clinical trials, and directly feed into our research program so we're continually linking what we do from a research perspective into the clinical needs of our local community."



SACRIFICE WAS NOT IN VAIN

This is an edited version of an address given by ANZAC Research Institute chairman, Prof. Bob Lusby, on 16 August, Sandakan Day.

Professor Robert Lusby AM

With only six Australian prisoners-of-war surviving out of 1787 men in the three years on the Sandakan-Ranau camps it represents one of the darkest moments in Australian history. Little is known about the events that took place due to the lack of survivors.

In late 1944 at Sandakan in Borneo, 2600 Australian and British POWs were being held as labourers building an airstrip. They were starved of food, scourged, and worked excessively till they dropped. Even the water was rationed.

With the approach of allied forces Japanese commander Lt General Baba Masao ordered the POWs to be marched some 260 km through dense jungle with minimal rations to Ranau. Clearly this was an attempt to kill all the prisoners. The only survivors were six men who escaped and were sheltered by local villagers.

Prisoners across Asia faced quite different conditions depending on local situations and the attitudes of camp commanders. At Sandakan, in the first year the situation

was not so bad but got far worse with the change of commanders and even worse later on. Starved, scourged, infected with malaria, suffering dysentery, beriberi and stinking tropical ulcers, the POWs hung on in desperation. When death reached out it was welcome as a blessed relief.

Of course the suffering and loss among Australians extended far beyond the battlefield or POW camp. It engulfed those at home, the families of all those men who died and possibly even more so those who had to care for the mentally and physically injured survivors.

The war crimes commission dealt with the worst individual offenders and there was a recognition that there had been much suffering among the Japanese people also. With time, understanding and acceptance by Australians led to an accommodation of the Japanese people. Looking forward is the solution that many who have suffered have adopted.

This freedom enables us to understand aspects of our enemies and deal with

them with clear heads, not side-tracked by hatred or seeking revenge. We can see there is much to admire in the post-war recovery of Japan. In many ways, our prosperity has been built on the industry, ability, and fervour of a people who rebuilt their shattered country and our ability to put the war behind us.

The insight of the USA in not seeking reparation but encouraging prosperity in both Germany and Japan has been a formula for reducing the risk of war and building prosperity for all.

Out of the tragedy that was Sandakan, Burma, and Changi a new kind of freedom was won by individual sacrifice. The Australian character was strengthened and we worked through the many issues to emerge as strong trading partners and friends of a people who were once our enemies.

It is fitting that today we remember the many who died fighting for our freedom and the lessons learned as a result by us as a nation.

GIVING OPPORTUNITIES

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