ANZAC Research Institute
discovery
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Remembering Professor Derek Hart

25 May 1952 – 13 December 2017

Professor Derek Hart was a passionate, driven and inspired clinician scientist who had a consuming motivation to improve medical care through a life committed to medical research.

Professor Derek Hart

During a career full of achievements he made many important discoveries that together built his grand vision for immune therapies based on dendritic cells as novel therapeutics for solid and liquid cancers as well as immunosuppression and controlling graft vs host disease.

At the ANZAC Research Institute he established the Dendritic Cell Research group which flourished under his inspiring and energetic leadership, propelling it to become the focal point of a wide network of collaborating scientists at Concord, Westmead and RPA Hospitals supporting more than 25 senior basic and clinical scientists, postdoctoral Fellows and students.

In July last year he outlined his vision to the Cancer Institute NSW.

"My ultimate ambition is that between the University of Sydney, the Cancer Institute NSW and Sydney Catalyst, what I would like to see here is a really substantial immune therapies program," he said.

"The potential is to establish something pretty significant. We're quietly building an immense capacity around immune therapy for cancer in Sydney. My ambition is in five years' time, we would have a 100 to 300 million dollar immune therapy centre – a translational cancer research centre for immune therapy."

Derek Hart was born and educated in New Zealand, graduating with distinction and numerous awards from the Faculty of Medicine, University of Otago. He started surgical training before winning a Rhodes Scholarship and, in 1981, submitting his DPhil on transplantation antigens while working at the Nuffield Department of Surgery, Oxford University. There he met his wife, Dr Georgina Clark, an Australian post-doctoral fellow co-worker, forging a formidable career-long scientific team.

Derek was particularly proud to have been the first to identify human dendritic cells, critical effectors in immune rejection, soon after Ralph Steinman's 2011 Nobel Prize-winning discovery of dendritic cells in the mouse. In 1981 Derek returned to Christchurch to gain specialist medicine and pathology qualifications as a haematologist, setting up a research-focussed Bone Marrow Transplantation Unit. In 1998 he was appointed the inaugural Professor/ Director of the Mater Medical Research Institute in Brisbane where he served for a decade before being recruited to the ANZAC Research Institute and the University of Sydney as Professor of Transplantation and Immunotherapy and NHMRC Senior Principal Research Fellow.

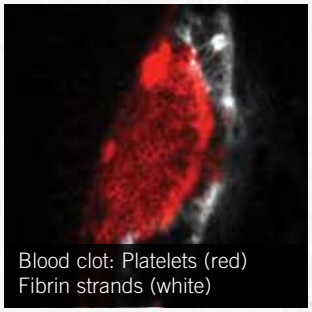
Over his career Derek made many important discoveries as well as winning awards and honours in the course of training numerous clinician scientists as well as basic scientists. Like all contemporary medical researchers he suffered regular mixed success in the peer-review grant system but the thought of giving up or changing direction never crossed his mind. Derek was also very active in commercialising his discoveries taking out key patents and establishing a spin-off company Dendrocyte BioTech which works towards developing new dendritic cell-based immune therapies.

Derek Hart lived and worked by his own high standards with a seemingly inexhaustible drive for scientific achievement and excellence. With characteristic courage and tenacity, Derek faced his final illness for over a year without flinching or self-pity. Instead, he redoubled his efforts, including the careful installation of succession plans to secure his legacy of novel immune therapies. The world of medical research is a better place for Derek's unequivocally committed life. He and his indomitable drive will be missed beyond measure.

Amazing advances in microscope facility

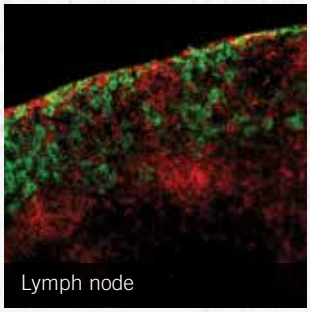
A research equipment grant of $365,000 from the Cancer Institute of NSW has enabled the ANZAC Research Institute to purchase an incredibly powerful microscope which allows scientists to examine cells within living animals.

Vivien Chen (left) and post-doctoral researcher Helena Liang working with the new microscope.*



Blood clot: Platelets (red)
Fibrin strands (white)

Tumour spheroid (cyan)
Drug: Doxorubicin
chemotherapy (green)



Lymph node

Already the high speed, multichannel fluorescence microscope is providing state of the art images and assisting researchers in many fields to advance their projects.

The application for the equipment grant was co-ordinated across ten research groups within the ANZAC Research Institute, the Asbestos Diseases Research Institute and the Centenary Institute, all of which are now seeing significant benefits.

Dr Vivien Chen, Staff Specialist Haematologist at Concord Hospital and Leader of the Platelet and Thrombosis Research Laboratory at ARI, says recent developments in microscopy have contributed to astonishing advances in scientists' ability to produce images of biological processes.

"We can put a live mouse onto the platform, then, by fluorescent tagging the cells, activation markers, or proteins of interest, we can directly visualise events occurring in real time within our animal models.

"My group is interested in the process of blood clot formation in the context of heart attack, stroke or cancer associated deep venous thrombosis. Using this microscope, we can image the blood flow within a vessel and watch the blood clot. We can measure the rate of individual platelets as they come in to form the clot and monitor the stabilising proteins as they form around the blood clot.

"Thus, when we develop drugs for inhibiting blood clot formation, in our search for therapies for improving outcomes after a heart attack or stroke, or for prevention of deep vein thrombosis or pulmonary embolism, we don't just have to test it in a test tube. We can evaluate them in a live model where all the components of the clotting system are together: the blood vessel, the blood components and the forces of blood flow. This becomes a very powerful experiment bringing us much closer to translation to the clinic."

Dr Chen explains that the microscope also allows researchers to look at the underlying mechanism of biological processes.

"So if you're interested in a particular protein and a particular pathway you can modify that pathway either genetically or pharmacologically, and by comparing that mouse with a wild-type mouse with the pathway intact, you can get some powerful information about how that pathway is working in that biological system."

The new equipment is proving to be invaluable in cancer research. Being able to view a live animal means, for example, that researchers can watch to see how a drug is able to get within a tumour. The team at the Asbestos Diseases Research Institute is using fluorescence to see how deeply a steroid penetrates a tumour and which cells it is getting into. The biogenerentology group can directly image drugs as they are delivered to the liver cells.

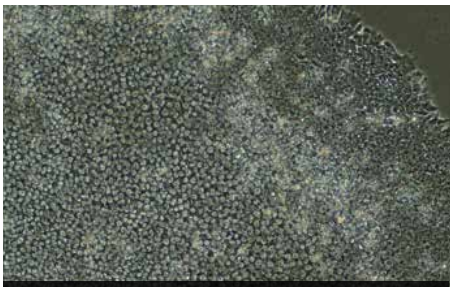
The Neurological Group, investigating inherited neuropathies, uses fluorescent worms where they have knocked out pathways which are important in inherited neuropathies. The worm can be viewed under the microscope, and researchers can see where the proteins are within the worm and see what happens to the worm's movements when the abnormal protein or gene is put in.

As Dr Chen says, the new equipment has been a welcome addition to the facilities available at the ANZAC Research Institute, enabling researchers in various fields to continue to contribute at the highest level internationally. In particular, it provides a valuable step in the process of translating the findings in fundamental research made at the Institute into the development of new treatments for disease.

*Photo: Edison Chiu @ Image Episode Photography Service

Advances welcomed in stem cell technology

Anthony Cutrupi, a researcher completing his PhD at the ANZAC Research Institute, has returned from six months at the University of Miami, bringing back to the Concord campus specialised skills in growing and maintaining live nerve cells. The technique will be especially valuable for the Neurobiology team investigating Charcot-Marie-Tooth and associated diseases.



Induced Pluripotent Stem Cells (iPSCs)

During his stay in Miami, Anthony studied under Assistant Professor Mario Saporta and Dr Stephan Züchner, a research collaborator with the ANZAC Institute's Associate Professor Marina Kennerson.

"The purpose was to learn how to maintain and use the cell lines called induced pluripotent stem cell lines – that is, they are stem cells from which nerves can develop - so we can use them in researching neurological disease," says Anthony.

Anthony at tissue culture hood.

"You can't get spinal cord tissue from living humans so the only way to do that is to have some form of stem cell technology. We can take skin cells from affected individuals and using exciting new discoveries (awarded the 2012 Nobel Prize in Medicine) we can now turn those skin cells into stem cells, then turn the stem cells into neuronal cell type of interest – in our case motor neurons."

"It's a really exciting prospect for us here because we have families without mutations in known genes. These families are good candidates in which we can now use these stem cell-derived motor neurons to help us better understand the genetic changes occurring in the nerves of patients with CMT and similar diseases."

Work is under way to establish the stem cell lines at the ANZAC laboratory and to train other staff to grow and maintain them, giving researchers a powerful new tool as they seek therapies for neurological diseases.

Prevention of age-related disease

The Biogerontology Group, led by Professors David Le Couteur and Victoria Cogger, has received an NHMRC grant of $560,241 over three years to conduct further research into the role played by blood vessels in the liver as we develop diseases later in life.

The group's ultimate goal is to find a new therapy to prevent and treat age-related cardiovascular disease and diabetes.

The research is centred on the liver sinusoidal endothelial cells (LSEC), which line the liver blood vessels and are essential for the filtration and scavenging of metabolic and waste materials from the blood, the development of immune tolerance, and iron sensing. However, as we age, LSEC undergo predictable and distinct changes that impair function, significantly reducing filtration of substances such as lipoproteins and insulin from the blood. In turn this can lead to the development of cardiovascular disease and diabetes.

Studies at the ANZAC Research Institute have already found ways of targeting the changes in the liver cells with nanomedicines to prevent and treat these changes. Nanomedicine covers a wide variety of technologies and applications, but it is usually broken down into two broad areas: diagnostics and therapies. Diagnostics looks at using nanotechnology to aid in the diagnosis of diseases using sensors, analytical assays, or imaging technology. Therapy is usually focussed on drug delivery and interactions in the body that will allow specific targeting, as in this case, of the structure of the LSEC.

The role of bones in preventing diabetes and obesity

The Endocrine Society has honoured the ANZAC Research Institute's Sarah Kim by presenting her with the Outstanding Abstract Presentation Award at its 99th annual meeting, in Orlando, Florida.

Sarah, who is a researcher in the Bone Laboratory and now in her final year of PhD study, presented the findings from her study of the role played by bone and diet in regulating diabetes and obesity.

"The skeleton used to be something which we regarded as giving structure or mechanical properties, but now it's increasingly seen as something that can regulate energy metabolism," explains Sarah.

"So something that's secreted from the bone can actually regulate whether you get diabetes or obesity or something similar. With my project what I do is look at high fat diet induced obesity and diabetes but I also look at it in the context of examining the role that glucocorticoid signalling in the bones have in this whole process."

Sarah's PhD project was based on feeding mice with special diets, one a high fat, high calorie diet, and the other a high calorie diet but with standard amounts of fat, to establish whether it is fat specifically or a high energy diet with excess calories causing these disorders.

"Both of them were able to induce obesity and were insulin resistant and glucose intolerant to the same extent. Both diets were able to cause bone loss. But the genetically modified mice were completely protected from getting fat, they had a good response to glucose and their bones were protected from the diet induced bone loss."

Sarah's presentation to the Endocrine Society argued that the genetically modified mice had been protected from diet-induced disturbances by switching off glucocorticoid signalling in the bone forming cells.

"Regardless of dietary fat levels, energy-dense diets are a major driver of metabolic disturbances and importantly, these negative effects are mediated by increased glucocorticoid signalling in the skeleton. This highlights that the skeleton has more than just a mechanical function in the body – it is intimately involved in the control of energy metabolism."

Sarah says her research now is focused on finding exactly what is secreted by the bone, or what is being suppressed, in the genetically modified mice. Her work is significant in discovering how diet can be tailored to prevent diabetes and obesity, both of which are increasingly prevalent in Australia.

Outstanding medical leadership

Two of the ANZAC Research Institute's most prominent scientists have been inducted as Fellows of the Australian Academy of Health and Medical Sciences (AAHMS). Election to the Academy is based on their career achievements in Medicine and Science and is voted on by the existing Fellows. Election to this highly prestigious Fellowship represents the top distinction available for Australian clinician scientists.

Professor David Le Couteur and Professor Markus Seibel were part of the 2017 intake at the AAHMS Annual Scientific Meeting, bringing the Academy's total national Fellowship to 321 of which the Institute now has three.

Professor David Le Couteur is an expert on ageing and geriatric pharmacology, Professor of Geriatric Medicine at Sydney Medical School and leader of the Biogerentology Group at the ANZAC Research Institute. He also specialises in nutrition, pharmacology And hepatology research with a focus on the elderly and for improving long-term health. Professor Le Couteur has served on many key Australian federal medicines committees.

Professor Markus Seibel is the inaugural Director of the Bone Research Program at the ANZAC Research Institute. He is also the Chair in Endocrinology at Sydney Medical School and has undertaken extensive research into musculoskeletal health and biology. Professor Seibel broke new ground with the development of new biochemical markers of bone metabolism, discoveries in the biology of cancer metastases to bone and the effects of steroid hormones on bone and general health.

Targetting genes with the potential to cause breast cancer

Dr Andrew Burgess, an experienced cell biologist who is the Institute's new Microscopy and Cytometry Manager, has been awarded a grant of $398,049 over three years by the National Breast Cancer Foundation to further his research into the genetic background of breast cancers.

A primary driving force behind the initiation and ongoing development of breast cancer is the activation of oncogenes, genes with the potential to cause cancer. Dr Burgess explains that oncogenes act like a car accelerator, driving excessive growth and spreading of the cancer cells throughout the body. Consequently, identifying new oncogenes and determining their functions is essential for understanding how breast cancers grow and spread.

"We recently identified a novel oncogene called MASTL that is amplified and over-expressing up to 45% triple-negative breast cancers (TNBC). Importantly, increased MASTL correlates with higher grade, unstable tumours and poor patient survival. Our preliminary data shows that MASTL is able to drive normal breast cells to grow and spread abnormally.

"Conversely, removal of MASTL from TNBC cells reverses the abnormal growth and spreading. Initial analysis of the underlying mechanisms suggests that MASTL rewires key signalling pathways in breast cells and is essential for regulating how cells duplicate their DNA. We hypothesise that MASTL is an ideal candidate to develop inhibitors, as blocking MASTL would prevent breast cancer growth and spreading, and enhance response to current chemotherapies, leading to improved patient survival.

"The purpose of this project is to better understand the mechanisms by which MASTL drives breast cancer, confirm that targeting MASTL can successfully block breast cancer in mice models, and to establish the tools necessary to develop specific inhibitors of MASTL that could be used to treat breast cancer."

Dr Burgess expects this project will primarily benefit patients with TNBC, especially metastatic disease. These patients are normally unable to undergo curative surgery, are unresponsive

to hormone therapy, and therefore chemotherapy is the only treatment option. Unfortunately, the majority (~80%) of patient tumours do not respond to current chemotherapy treatments, and very few new treatments have been developed. Consequently, metastatic TNBC has some of the lowest overall survival rates for breast cancer and these have not improved in the past 20 years.

"There is a significant need to identify new targets for TNBC in order to improve these worst-case patients. We believe that MASTL represents a promising new target that could be used to improve the outcomes for TNBC patients."

In 2017 it was estimated that almost 18,000 Australians (including about 150 men) would have been diagnosed with breast cancer, and at least 3000 deaths would be recorded.

Dr Burgess joined the ANZAC Research Institute in 2017, after five years at the Kinghorn Cancer Centre within the Garvan Institute of Medical Research. His career began in 1998 as an honours student at the Queensland Institute if Medical Research, and after graduating with 1st class honours, he studied for a PhD at the University of Queensland. In 2004 he was awarded a prestigious NHMRC C J Martin fellowship, which took him to the French National Research Centre in Montpellier. Two additional French fellowships allowed him to remain in France for seven years, continuing to explore the basic mechanism of how cells control the division process. In 2012 Dr Burgess received a five-year Fellowship from the Cancer Institute NSW which led to his return to Sydney.

World leading research to assist organ transplants

CANCER INSTITUTE GRANT AIDS CLINICAL TRIALS

Professor Derek Hart (centre) with the Dendritic Cell research team

A NSW Cancer Institute grant of $3.4 million over five years has paved the way for a revolutionary new treatment to treat certain cancers, and to stop the body rejecting bone marrow and other organ transplants. A partnership, led by the Dendritic Cell research team at the ANZAC Research Institute, is now fielding inquiries from international pharmaceutical companies keen to manufacture and market immune therapy drugs which could improve transplants and help cure several cancers.

Shortly before his death in December, Professor Derek Hart welcomed the Cancer Institute translational program grant as providing the "backbone of the project," enabling the team to move to clinical trials after proving already in pre-clinical research that the drug has strong potential to be both safe and effective in humans.

"Our focus now is on how we get our initial novel specific immune suppressive drug into patients and see if it prevents the unwanted transplant response but provides protection against infection and cancer," said Professor Hart.

"We would start with bone marrow transplants and if it works, move pretty swiftly to other transplants.

"We will be looking for at least $15 million dollars in commercial partnerships and philanthropic grants to develop that first drug. It will take $6 million to make the drug, about $5 million to run the first trials, and then $5 million to run a second trial. It would be something like five to ten years before it became an established pharmaceutical benefit, but the potential rewards, world-wide, are simply enormous."

Under Professor Hart and his wife and scientific colleague Associate Professor Georgina Clark, the ANZAC Research Institute team has been leading a collaboration with the Haematology Departments at Concord, Royal Prince Alfred and Westmead Hospitals, Sydney Catalyst (Chris O'Brien Lifehouse), the Burnet Institute and the University of Sydney. Their work is focused on the rare type of white blood cell known as a Dendritic Cell, which has the ability to direct all other immune cells in mounting defence against cancers and other diseases.

The work has been built on more than 25 years of research, which Professor Hart began when he was a Rhodes Scholar at Oxford University.

Speaking just weeks before his death, he explained it as follows:

"My argument has been that if we had an antibody and we removed the dendritic cells when we do an organ transplant you would stop the rejection of the transplant because you've removed the cell that starts the rejection response. The key thing was that you left all the other immune cells intact, and it's all the other immune cells that carry your established protective responses against viruses, fungi and everything else. No-one before us addressed the beginning of the immune response.

"All the treatments so far for suppressing the immune response against the transplant are focused on the late stage or the effector cells that carry out the rejection. The trouble is that with existing treatments you wipe out all of the protective immune response at the same time."

The team at the ANZAC Research Institute has proved that Dendritic Cells initiate, direct and maintain the immune response, so by targeting the activated cells, but not the un-activated cells, the human body itself can suppress adverse reactions leading to transplant rejection. In the case of a leukaemia patient receiving a bone marrow transplant, the treatment is designed to put in a new donor immune system to kill off the leukaemia. However, this can result in graft versus host disease, in which the new, transplanted cells attack the patient's body because they regard it as foreign, leading in many cases to the patient's death.

The potential of this research is enormous, not only in advancing transplant and cancer operations, but also in commercial windfalls. To protect the intellectual property and to advance the clinical trials, the collaborating scientists have set up a spin-off company, DendroCyte Biotech Pty Ltd, with international connections. This has been done with the blessing of the ANZAC Research Institute.

The discovery could have a wider application in some other immunological diseases, such as rheumatoid arthritis. At the moment, by non-specific suppression of the immune system, flare-ups of the arthritis can be prevented but patients develop other problems.

One of the advantages, and one of the attractions for a pharmaceutical production

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agreement, is that all the elements needed are in place through the collaborating Institutes in Sydney. The scientists at the ANZAC Research Institute have gone beyond simply proposing a theory but have actually developed and proved that the new drug could have widespread application, by working with medical teams at the hospitals, which are partners in the research.

ON THE VERGE OF FINDING A CANCER VACCINE

The research by the Dendritic Cell Research (DCR) unit described in this issue of Discovery has also led to major new developments in the treatment of acute myeloid leukaemia, a cancer which affects the blood and bone marrow.

In a research paper submitted to Blood, the medical journal published by the American Society of Haematology, Professor Hart explained that the ANZAC Research Institute team has developed a new antibody, which targets acute myeloid leukaemia. The antibody targets a specific molecule identified by the fundamental DCR research program.

In a second submitted paper, DCR has described an antibody that identifies the Blood Dendritic Cells and attaches to them. This overcomes the problem of finding these comparatively rare white blood cells, which are the key to fighting infection and disease. The paper describes the use of this antibody for a "second generation" cancer vaccine and the "window of opportunity" to vaccinate patients with acute myeloid leukaemia to prevent their disease coming back.

These exciting new treatment option for acute myeloid leukaemia, a cancer which has not had any new drug developed for its treatment in at least 20 years, are ready to go into clinical trial.

Each year in Australia upwards of 1000 patients are diagnosed with acute myeloid leukaemia, most aged 60 or older. Intensive chemotherapy can induce complete remission but it comes at a heavy cost to the patient's health and the majority of patients eventually relapse.

"Most people who get this disease get minimal treatment because it's mainly a disease that affects older people," Professor Hart told Discovery just weeks before his death.

"We'll carry out transplants for those aged 50-plus, maybe up to 60, but since most of the patients are 60-plus, most miss out on treatment. At the moment that treatment is conventional chemotherapy which has been used for 20 years, with lots of toxicity, which is why the older patients can't receive it.

"Antibodies are not toxic, so they're great therapeutics. We have proved our antibody works because we have used this technique to kill human leukaemia in mice.

"Our vaccination strategy also enables us to treat elderly patients. We can pull out the dendritic cells, after they've had some initial chemotherapy to control their disease, and we've found that we can get some anti-leukaemia response generated in a test tube.

"Our second generation blood dendritic cell vaccine can be loaded with any cancer target, making it an exciting prospect for developing therapeutic vaccines for a wide variety of cancers."

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