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ANTIBODY COMPANY CHANNEL BIOLOGICS JOINS ANZAC RESEARCH COMMUNITY

The Channel Bio team, pictured from left: Doris Shim, Rachael West, Charlotte Haslam, Anna Bracken, Mona Lei, Jonathan Nambiar, Adam Clarke, Tanya Estephan, Joshua Wingerd

The burgeoning field of developing antibody therapies has been given fresh impetus at the ANZAC Research Institute by the advent of a recently formed entity, Channel Biologics.

"It's a very specialised field," says Dr. Adam Clarke, who heads the team. "There are probably only two or three companies in Australia that actively work in this area."

Channel Biologics was formed in September 2019, and its first challenge was to find a home for scientific research and development. The ANZAC Research Institute offered space in its ANZAC2 laboratories, located within the Bernie Banton Centre, and the team, currently numbering ten researchers, has been based there since January.

"Channel Biologics was founded on the idea of developing new technologies for discovering novel biologics to help patients," Dr. Clarke explains.

"Most people would understand the word antibody, the way in which the immune system protects itself from attack. You can make antibodies artificially using different systems. Such antibodies form a class of drugs known as biologics. A lot of the most effective and biggest selling drugs on the market right now are biologics or antibodies. We specialise in making these types of antibodies against certain disease targets in the body, named GPCRs (G protein-coupled receptors) and ion channels."

Dr. Clarke completed his Ph.D. at Sydney University and his career, along with others in the team, has been with major pharmaceutical companies. He previously led a team that discovered several biologics that have entered clinical trials.

"Our expertise is in discovering these antibodies from scratch using molecular biology tools; taking the DNA that codes the antibodies and putting it into cells; making the cells that produce antibodies; and testing them. The challenge is that making


Dr Adam Clarke

antibodies against GPCRs and ion channels is difficult. These are hard targets. With the technologies we develop we're unlocking these targets and opening up new classes of therapies."

When starting Channel Biologics, Dr. Clarke struggled to find laboratory space in the Sydney area for a start-up biotechnology company. Dr. Clarke has nothing but praise for the welcome and cooperation Channel Biologics has received from everyone at the ANZAC Research Institute.

TWO NHMRC INVESTIGATOR GRANTS AT THE MOST SENIOR AND PRESTIGIOUS LEADERSHIP LEVEL 3 HAVE BEEN AWARDED TO THE ANZAC RESEARCH INSTITUTE.


Prof. David Handelsman

Professor David Handelsman, Director at the ANZAC Research Institute, was awarded $3.164m over five years for his project "Overcoming Androgen Misuse and Abuse."

With the aim of exploring an effective prevention and management of recovery, this program marks a new initiative to tackle prescription testosterone misuse when it is prescribed for invalid medical reasons in middle-aged and older men in whom it creates iatrogenic and androgen dependence, making it hard to stop the pointless treatment.

The other side of that coin is image-driven, community-based androgen abuse ("gym junkies"). Androgen abuse is a neglected public health concern of young men using non-prescribed androgens ("anabolic steroids") for image enhancement.

On stopping, suppressed male reproductive function causes withdrawal symptoms during a slow recovery period, creating a cycle of dependency with addictive, drug-seeking/craving behaviours and relapse into resuming androgen intake to alleviate symptoms. High dose androgens can induce hypomania, aggression and violence within characteristic patterns of addictive and criminal behaviours.

This program will be a world's first in conducting well-controlled clinical trials to formally evaluate for the first time drug treatments aimed at accelerating recovery.


Prof. Markus Seibel

Professor Markus Seibel, Head of the Bone Research Program at the ANZAC Research Institute, was awarded $1.5m over five years for his project "Making the first osteoporotic fracture the last – Implementation and analysis of an evidence-based, integrated model of care for secondary fracture prevention".

Osteoporosis is a common chronic condition characterised by fragility fractures. It is estimated that 160,000 osteoporotic fractures occurred in Australia in 2016, and this number is likely to increase to 180,000 in 2022. Any fragility fracture signals a greatly increased risk of a further fracture, with 60 – 80% of these "secondary" breaks occurring within two years of the initial fracture.

However four out of five Australians are not being investigated or treated for osteoporosis following a fragility fracture, which means that up to 75% of these people will sustain further ("secondary") fractures, resulting in lengthy hospital stays, excess morbidity and mortality, and great cost to the taxpayer. This widespread failure to manage a common disease and its often catastrophic complications exists despite the wide availability of effective, safe and subsidised diagnostics and treatments.

Professor Seibel's vision is to *make the first osteoporotic fracture the last* by creating irrefutable evidence that secondary fracture prevention programs, if fully integrated across primary, secondary and tertiary health care, will prevent fractures, and thus unnecessary hospital admissions, fracture-related morbidity and mortality, and significant cost to the Australian health care system.

Professor Seibel says Australia's few hospital-based Fracture Liaison Services are insufficient to address the need for secondary fracture prevention.

"While improvements could be made to their operational efficiency, they do not close the secondary fracture prevention gap under the present model of predominantly specialist care at most stages of care," he argues.

"To close this gap, full engagement with, and integration of primary health care into the fraction prevention model is required."

FROM GENE DISCOVERY TO THERAPY FOR PATIENTS

The below diagram shows the program which has been implemented at the Northcott Neuroscience Laboratory, showing the translation of our research as we work to develop therapies for patients with inherited neuropathies.

''I am very excited that the laboratory has the capacity to go from gene discovery to the development of pre-clinical disease models which are the necessary step for moving discoveries into treatment for patients tested in clinical trials'' said Professor Marina Kennerson who heads the Gene Discovery and Translational Genomics Program at the ANZAC Research Institute.

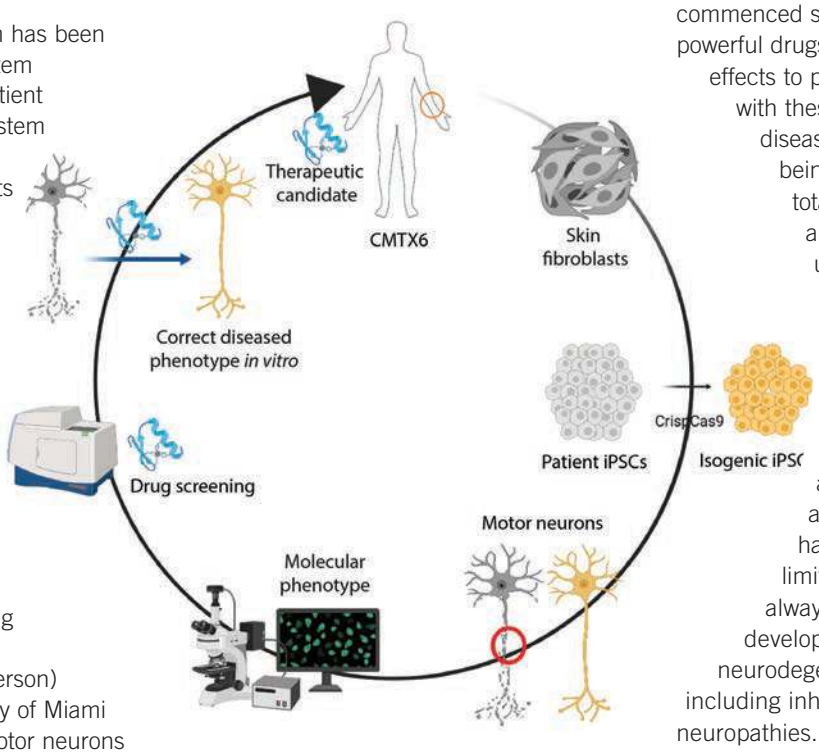
Key to this program has been the introduction of stem cell technologies (patient induced pluripotent stem cells) to make motor neurons from patients with inherited neuropathies, a chronic debilitating group of diseases affecting the nerves that allow us to move (motor neurons) and have sensation (sensory neurons).

The program began in 2016 when Dr Anthony Cutrupi (who was undertaking his PhD candidature with Professor Kennerson) went to the University of Miami to train in making motor neurons from patient iPSC cells with Assistant Professor Mario Saporta. Since 2017 the Northcott Neuroscience Lab team has been developing projects using iPSC motor neurons under the guidance of Dr Gonzalo Perez-Siles, a talented postdoctoral neuroscientist who has been developing cell models for inherited neuropathies since joining Professor Kennerson in 2012.

Dr Perez-Siles' most recent publication reports a motor neuron model for CMTX6, a form of X-linked Charcot-Marie-Tooth neuropathy in which our laboratory discovered the *PDK3* gene mutation. This is the second stem cell paper published by Dr Perez-Siles after reporting the development of iPSC derived motor neurons for X-linked distal motor neuropathy (dHMNX), which models another disease mutation the laboratory discovered in the copper transporter (ATP7A) as the cause of dHMNX.

"This technology is allowing us to study live patient motor neurons in the laboratory that have been re-programmed from a patient's skin cells" Professor Kennerson explains.

"Importantly, as we are working in the neurons, the cell type that is affected in the patients, all information



gained on how the mutations cause the disease is based on the most suitable genetic background. This is the key to developing therapies that may be able to improve the function or reverse the damage to genetically affected motor neurons."

"For the CMTX6 model, we have shown that damage to the motor neurons is caused by the disruption in a pathway of metabolism that provides energy to the nerves."

Using the patient motor neurons, Dr Perez-Siles invented a robust cellular model of disease (molecular


Anthony Cutrupi and Gonzalo Perez-Siles

phenotype) so that the lab is now able to screen thousands of chemicals as potential drugs to improve or protect nerve function. Through his work to understand how the disease causes its damage, Dr Perez-Siles has now commenced screening for effective, powerful drugs with minimal side effects to potentially treat patients with these motor neuron diseases. The drugs currently being screened (1800 in total) have already been approved for patient use which provides the opportunity for the re-purposing of existing drugs to treat CMTX6 disease.

Diseases of neurodegeneration is an area in which the availability of therapies has so far been sadly limited. Historically, it has always been challenging to develop effective therapies for neurodegenerative conditions including inherited peripheral neuropathies. This impasse has always been hindered by the big obstacle of having appropriate models to mimic disease in a "human" nerve setting.

"Our stem cell program is showing the advantages of reproducing pathogenic conditions in a dish in human nerve tissue which can then facilitate acceleration of a drug screening process, said Professor Kennerson.

"This arm of our research program will continue to grow and as we move forward our continuing goal will be to make therapies a reality for these patients.''

FURTHER STUDIES HAVE POTENTIAL TO CHANGE PATIENTS' LIVES

One of the most satisfying aspects of supervising PhD students is seeing their work progress towards scientific papers and then finally culminate in a PhD. In the case of clinicians who pursue a laboratory-based research project for studies as part of their professional training as medical specialists, watching them become hooked on designing the next best experiment is a pleasure.

Dr Edward Abadir is one such student who, under the supervision of Associate Professor Georgina Clark, recently submitted his PhD thesis, focused on developing one of the Dendritic Cell Research (DCR) group's monoclonal antibodies towards an effective treatment for acute myeloid leukemia (AML).

DCR has long had an interest in monoclonal antibodies to dendritic cell and myeloid cell surface molecules and strategies to use them as immune therapies for cancer and immunological diseases. Of the numerous monoclonal antibodies that DCR has produced there have been a few standouts including our DCR-2 antibody, which was developed as part of the studies performed by our previous student Dr Robin Gasiorowski, now working as a fully qualified hematologist.

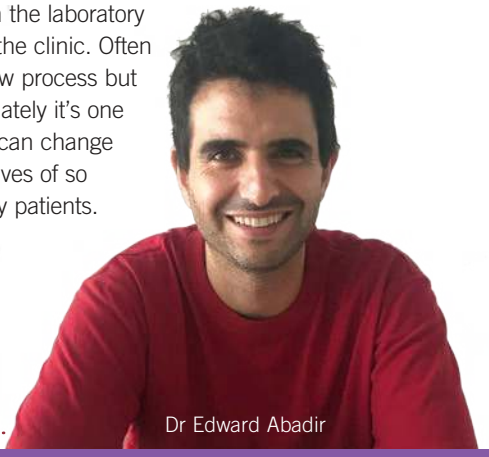
Edward continued this work after Robin returned to clinical practice and saw the potential of DCR-2 to target AML cells. This led to an initial paper published in 2018. This paper reported our findings that the DCR-2 antibody targeted AML cells, and identified DCR-2 as a unique antibody with excellent potential to be developed into a therapeutic for immunosuppression of blood cancers.

However, there was, as often in research, a downside. The antibody also targeted healthy stem cells - the cells that keep replacing your blood cells. Targeting healthy stem cells is quite undesirable and would prevent this DCR-2 antibody developing as part of an immune therapy to treat AML without a follow up haematopoietic stem cell transplant.

Thinking about this, Edward quickly took a new approach and wrote a review arguing the case for using antibody drug conjugates that target AML and healthy haematopoietic stem cells at the same time – making a virtue of this necessity - as a part of the pre-transplant conditioning treatment. The benefits would be in eradicating the leukemia but also, novel antibody drug conjugates may be less toxic allowing elderly patients, who are otherwise too frail, to benefit from bone marrow transplants.

Proving that DCR-2 as an antibody drug conjugate targets AML and prevents its growth in preclinical models led to another paper and the preliminary work towards a successful 2020 Anthony Rothe Memorial Trust grant. This grant will support the continuation of Edward's studies to improve the characteristics of the DCR-2 antibody for antibody drug conjugate treatments.

This work has led to papers, patents, and progress towards the goal that we as scientists have – that is seeing ways of moving what we work on in the laboratory into the clinic. Often a slow process but ultimately it's one that can change the lives of so many patients.



Dr Edward Abadir

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