Double discovery boosts global quest for leukaemia cures

Researchers at Peter MacCallum Cancer Centre have discovered how a form of leukaemia fights back against a ground-breaking treatment, providing vital new leads on how to outwit the deadly disease.

Acute Myeloid Leukaemia (AML) stem cells are particularly aggressive, insidious and nimble. Knowing how they respond when under attack enables researchers to devise interventions that can neutralise the source of resistance before it develops.

As part of the research - and for the first time - Peter Mac’s Cancer Epigenetics Laboratory team has been able to grow and maintain leukaemia stem cells in a laboratory dish, making it easier and faster to test new treatments with the potential to eradicate the disease.

Published overnight in the premier scientific journal *Nature*, the research shows how leukaemia stem cells react to BET-inhibitors – a novel treatment which is the subject of a current international clinical trial active at Peter Mac. This promising treatment targets epigenetic mechanisms of disease to effectively “turn-off” cancerous genes in AML.

The research found that resistance develops when the cells adapt, increasing expression of proteins in the WNT/β-catenin pathway to circumvent the drug and reactivate key cancer driving genes through a previously under-recognised mechanism.

The double discovery will boost understanding of AML, which affects more than 900 Australians each year, and 300,000 globally, with five-year survival rates of just 25% according to lead investigator, Associate Professor Mark Dawson

“Our clinical trial of BET-inhibitors is giving new hope to selected patients with aggressive forms of AML. However, the risk of resistance developing is common in any cancer treatment. Knowing precisely how that happens in advance puts us one step ahead in outmanoeuvring the disease.

“Being able to grow and maintain leukaemia stem cells in vitro, also gives us unprecedented access and insight into how they work, so we can find new and better ways to target and destroy them.

Victorian Minister for Health Jill Hennessy said this is just one example of the world-leading research being undertaken at Peter Mac.
“We have some of the world’s best researchers and clinicians here in Victoria and at Peter Mac, who are making advances in cancer research which could change the lives and outcomes of cancer patients.”

The Leukaemia Foundation is a major supporter of the lab’s work at Peter Mac. Head of Research & Advocacy, Dr Anna Williamson says it is exciting to see the Foundation’s support for talented researchers with great ideas delivering important new knowledge.

“This advance in our understanding of leukaemia stems cells is opening the doors to new treatment approaches.

“AML is a leukaemia that has long needed a major breakthrough to improve the future for all AML patients.”

The findings build on over ten years of research and clinical work, commenced at the University of Cambridge by Associate Professor Dawson, who is now a consultant haematologist and head of the Cancer Epigenetics Laboratory at Peter Mac.

In 2011, Associate Professor Dawson and the team in Cambridge were instrumental in the initial development of this class of epigenetic drugs called BET bromodomain inhibitors. These drugs alter the way DNA is packaged and deciphered ultimately resulting in the “switching off” of cancer causing genes.

This therapeutic strategy is very effective in pre-clinical models of aggressive leukaemias and now Associate Professor Dawson is leading a first-in-class international clinical trial of these drugs in Australia, with the goal of increasing survival rates and advancing cures for aggressive blood cancers over the longer term.

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For further information or to organise an interview with Associate Professor Mark Dawson, please contact the Peter Mac media and communications team on 0417 123 048.

Peter Mac Website

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Collaborators on this research included:

- Peter MacCallum Cancer Centre
- The University of Melbourne
- The Walter & Eliza Hall Institute of Medical Research
- Cambridge Institute for Medical Research, Cambridge, UK
- Wellcome Trust /MRC Stem Cell Institute, Cambridge, UK
- GlaxoSmithKline
- Memorial Sloan Kettering Cancer Center, New York, USA
- Berghofer Medical Research Institute, University of Queensland
- Gurdon Institute, University of Cambridge, UK

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- The Peter MacCallum Cancer Foundation
- The Leukaemia Foundation
- National Health and Medical Research Council
- Veski
- Leukaemia and Lymphoma Society
- Cancer Council Victoria
- Snowdome Foundation
- The Wellcome Trust
Background

Lead Investigator - Associate Professor Mark Dawson

Associate Professor (University of Melbourne) Mark Dawson is a consultant haematologist in the Department of Haematology and Head of the Cancer Epigenetics Laboratory at the Peter MacCallum Cancer Centre.

Associate Professor Dawson’s research interests lie in understanding the epigenetic regulation of normal and malignant haematopoiesis. He is a fellow of the Royal Australasian College of Physicians and Royal College of Pathologists of Australasia. After completing his clinical training in Melbourne, Associate Professor Dawson was awarded the prestigious General Sir John Monash Fellowship and Cambridge Commonwealth Trust Fellowship, which he used to complete his PhD at the University of Cambridge in the United Kingdom. Following his PhD, Associate Professor Dawson was awarded the inaugural Wellcome Trust Beit Prize Fellowship to pursue his research into epigenetic regulation of leukaemia stem cells. This research identified a novel therapeutic strategy for acute myeloid leukaemia by targeting the BET bromodomain proteins that function as epigenetic readers. The Cancer Epigenetics Laboratory aims to understand the role of epigenetic regulators in normal and malignant haematopoiesis and to use these insights to identify novel therapies for the treatment of blood cancers.

Associate Professor Dawson’s research is currently supported by a Senior Fellowship from the Leukaemia Foundation, the VESKI Innovation Fellowship and a Herman Clinical Fellowship through the University of Melbourne and the Victorian Comprehensive Cancer Centre. His laboratory is currently supported by funding from the NHMRC, Cancer Council Victoria, Peter Mac Foundation, Leukaemia and Lymphoma Society and Snowdome Foundation.

First Author – Dr Chun Yew Fong

Dr Chun Yew Fong is a consultant haematologist in the Department of Haematology at Peter MacCallum Cancer Centre. He completed his dual medical specialty training as a physician and pathologist in 2013 and is a fellow of the Royal Australasian College of Physicians and Royal College of Pathologists of Australasia. He is currently undertaking a PhD in molecular and cell biology having spent the first 12 months of his PhD at the University of Cambridge prior to relocating to the newly established Cancer Epigenetics Laboratory at Peter MacCallum Cancer Centre with Associate Professor Dawson. His key interests are understanding the underlying epigenetic mechanisms which drive malignant haematopoiesis and the development of new therapies to aid in the eradication of aggressive haematological malignancies.

His current work focuses on resistance mechanisms to emerging epigenetic therapies with the novel identification and indefinite maintenance of leukaemia stem cells as key findings of his PhD thus far. This work has been published as a first author in Nature, and has also been recognised through the awarding of the prestigious Victorian Comprehensive Cancer Centre Picci Award for Excellence in Cancer Research in 2014. He has also been awarded the Leukaemia Foundation PhD Clinical Scholarship, Cancer Therapeutics CRC PhD Scholarship, Royal Australasian College of Physicians Arnott Research Entry Scholarship in Cancer Research and Haematology Society of Australia and New Zealand New Investigator Scholarship.
Acute myeloid leukaemia (AML)

Acute myeloid leukaemia (AML) is a type of cancer that affects the blood and bone marrow. AML is characterised by an overproduction of immature white blood cells, called myeloblasts or leukaemic blasts. These cells crowd the bone marrow, preventing it from making normal blood cells. They can also spill out into the bloodstream and circulate around the body. Due to their immaturity, they are unable to function properly to prevent or fight infection. Inadequate numbers of red cells and platelets being made by the marrow cause anaemia, and easy bleeding and/or bruising. Acute myeloid leukaemia is sometimes called acute myelocytic, myelogenous or granulocytic leukaemia.

AML is a devastating disease that affects 900 Australians each year, and 300,000 globally. Five-year survival rates are just 25%.

Source: Leukaemia Foundation Australia