Project Title: Development of broad spectrum, non-genotoxic cancer treatments for acute myeloid leukaemias and multiple myeloma.
Grant Awarded: $340,000 over 3 years: $113,333 in 2016-17
Principal Investigators: Prof Ross Hannan and A/Prof Anneke Blackburn, John Curtin School of Medical Research, The Australian National University.

New therapeutic approaches for cancer are urgently needed. This project is investigating combining two novel approaches that have been developed by our team, that target processes fundamental to cancer cell growth – the making of proteins and controlling metabolism. We are studying the impact of these treatments in models of two different blood cancers, multiple myeloma (MM) and acute myeloid leukaemia (AML), which are both considered incurable with current standard therapies.

In the lab, PhD student Laura Ferguson has been focusing on treatment of AML with CX-5461 combined with metabolism-modifying drugs. CX-5461 is a novel drug that inhibits the making of proteins and is currently in clinical trials against cancer. She has combined CX-5461with drugs already in use for metabolic problems such as high cholesterol, diabetes, or which can inhibit the uptake of glucose by cancer cells. This in vitro screening has identified several promising agents that act synergistically with CX-5461. Two agents have also been tested in vivo in a mouse model of AML, with one of those showing significant improvement in the effectiveness of CX-5461 against this aggressive disease. In vitro investigations to verify the mechanism of action are under way, while further in vitro combination testing is being done on additional agents. Choosing agents already in use in patients will allow successful combinations to be rapidly translated into patients.

In a second part of this project, PhD student Dan Dan Tian has focused on treating MM with the novel metabolism-modifying agent dichloroacetate (DCA), verifying its ability to inhibit cancer cell growth under clinically relevant conditions. This work is complementary to the clinical trial underway at The Canberra Hospital (TCH). This current CCACT grant has been supporting A/Prof Blackburn (ANU) to work with Dr D'Rozario (TCH) and the DiCAM team in the Department of Haematology. DiCAM (DiChloroAcetate in Myeloma) is a world-first early phase clinical trial evaluating the ability of DCA to improve the remission of MM patients who have made a partial response to other therapies. The side effect of most concern with DCA is peripheral neuropathy. We have treated 6 patients, closely monitoring blood drug levels, and have demonstrated the safety of using DCA in MM patients with some existing neuropathy from previous treatments. We are now moving into patients with a greater disease burden to examine the impact of DCA on cancer cells, using doses adjusted according to the ability of each patient to break down DCA (GSTZ1 genotypes) so as to avoid side effects.

We expect these new approaches will lead to more effective cancer therapies with minimal additional toxicity to normal cells, relevant to many cancer types.

Conference Abstracts:
GSTZ1 genotypes correlate with dichloroacetate levels and chronic side effects in multiple myeloma patients. Dan Dan Tian, Samuel K Bennett, Lucy A Coupland, Kathryn Forwood, Yadanar Lwin, Teresa Neeman, Philip Crispin, James D'Rozario and Anneke C Blackburn.
At the 14th European Meeting of the International Society for the Study of Xenobiotics (ISSX), Cologne, Germany, June 2017.

Dichloroacetate at clinically achievable concentrations can reduce pPDH and reverse the glycolytic phenotype in multiple myeloma cells. Dan Dan Tian, Anneke C Blackburn.
At the 2nd Australian Cancer and Metabolism Meeting, Melbourne, May 2017.