

Targeting NAD Metabolism to Overcome Therapeutic Resistance in Adult and Paediatric Acute Myeloid Leukaemia



Dr Klaartje Somers: Children's Cancer Institute

Acute myeloid leukaemia (AML) is a highly fatal blood cancer in adults and children. On average, less than 30% of adults with AML survive 5 years after diagnosis and in children, one-third of patients relapse on current treatment, with only 30% of relapsed children surviving. Resistance of AML patients to current treatment is thus a major challenge. In addition, current treatment protocols often cause detrimental long-term health effects, negatively impacting quality of life, especially in children, where two thirds will suffer long-term side effects as a result of their treatment.

There is thus an urgent need to develop ways to overcome resistance to treatment in AML. In addition, a more personalised approach - the identification of those patients who are more likely to respond to a particular therapy - would be a tremendous step forward in current AML treatment.

Based on their complimentary expertise within the field of therapeutics for childhood leukaemia and adult leukaemia, Dr Klaartje Somers (Children's Cancer Institute) and Dr Donia Moujalled (WEHI) joined forces to develop clinically relevant strategies to mitigate AML treatment resistance. Together, they showed that AML cells are addicted to the metabolic enzyme nicotinamide phosphoribosyltransferase (NAMPT). They have demonstrated that inhibition of NAMPT can kill AML cells, block AML progression in their living models and re-sensitise treatment-resistant paediatric and adult AML cells to chemotherapeutics and molecular targeted



Dr Donia Moujalled Assisting Colleague WEHI

agents. Based on their exciting new data, they hypothesise that addiction of AML cells to NAMPT contributes to resistance to AML therapy. NAMPT inhibition therefore constitutes an exciting new therapeutic strategy for AML that could substantially improve treatment outcome in children and adults and lead to a new standard of care.

With the generous support of the Australian Lions Childhood Cancer Research Foundation, Dr Klaartje Somers and Dr Donia Moujalled will determine effective combination therapies combining a novel, targeted inhibitor drug of NAMPT, OT-82, with standard of care therapies by utilising their internationally unique panel of patient-derived living models of adult and paediatric AML. Moreover, they will identify biomarkers that predict which leukaemias are likely to respond to these combination therapies. This project will provide the preclinical evidence needed to rapidly advance NAMPT inhibition-based combination therapies into the clinic for adult and paediatric AML, and if successful, will lead to the development of an exciting new treatment approach for treatment-resistant AML with the potential to substantially improve patient outcomes.