**Targeting refractory Acute Lymphoblastic Leukaemia – Drug repurposing with combinatorial bispecific antibodies**

*Ernest MolesA,B,C, Christopher B. HowardD,E,F, Kris ThurechtD,E,F, Maria KavallarisA,B,C*

AChildren’s Cancer Institute, UNSW Sydney, NSW, Australia; BARC Centre of Excellence in Convergent Bio-Nano Science and Technology and Australian Centre for Nanomedicine, UNSW Sydney, NSW, Australia; CSchool of Women’s and Children’s Health, UNSW Sydney, NSW, Australia; DAustralian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, QLD, Australia; ECentre for Advanced Imaging, The University of Queensland, St Lucia, QLD, Australia; FARC Centre of Excellence in Convergent BioNano Science and Technology, The University of Queensland, St Lucia, QLD, Australia.

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer. Advances in treatment has led to the majority of patients surviving their disease. However, children with drug-refractory or resistant ALL are difficult to cure, and survivors frequently experience life-long health issues as a result of high dose chemotherapy. Effective and less toxic therapies for this subgroup of ALL patients is urgently needed.

Here in, we developed an approach to repurpose a clinically approved anti-cancer liposomal drug, Doxil® by attaching bispecific antibodies that recognise the ALL cells. Acute Lymphoblastic Leukaemia is caused by an overproduction of defective B or T cell precursors (pre-B or pre T ALL cells), which accumulate in the circulation and the major haematopoietic organs. ALL is the second leading cause of death from disease during childhood4. In this study, pre-B cell-specific CD19/mPEG and CD22/mPEG BsAbs were engineered using humanized Ab sequences retrieved from clinically-approved pharmaceuticals and individually conjugated to Doxil® as a mPEG-nanotherapeutic. Data will be presented on the preclinical evaluation and optimisation of BsAb-Doxil® conjugation in terms of maximising Doxil® recognition, intracellular delivery and cytotoxicity towards pre-B cell lines isolated from children with high-risk ALL5. To maximize pre-B cell targeting and drug delivered payloads, a combinatorial strategy based on the simultaneous administration of CD19- and CD22-Doxil® has been performed.

This study shows that repurposing a clinically approved liposomal nanoformulation using BsAbs may be a promising strategy for the treatment of drug resistant/refractory ALL.

Presenting author: m.kavallaris@ccia.unsw.edu.au