DEVELOPMENT OF METTL5 INHIBITORS FOR THE TREATMENT OF SOLID TUMOURS IN CHILDREN AND ADULTS

SMALL MOLECULE THERAPEUTICS

At the Children's Cancer Institute, the THerapeutic INnovations for Kids (THINK) program, led by **Prof Ian Street**, Director, and **A/Prof Greg Arndt**, Head of Drug Discovery Biology, is an end-to-end drug discovery capability dedicated to generating new therapeutics for clinical application to transform the lives of children suffering from rare genetic diseases, cancer, and neurodevelopmental disorders.

The team has received multiple Pipeline Accelerator awards across multiple projects, one of which focuses on developing inhibitors of Methyltransferase-like protein 5 (METTL5), an RNA methyltransferase linked to neuroblastoma progression and poor survival outcomes. The goal is to create a novel, patentable METTL5 inhibitor and demonstrate its potential in preclinical cancer models to attract investment for further development.

The Pipeline Accelerator award was instrumental in accelerating METTL5 inhibitor development. The Australian Translational Medicinal Chemistry Facility (ATMCF) supported medicinal chemistry work, while the Centre for Drug Candidate Optimisation (CDCO) provided assays to assess pharmacokinetics.

With limited funds, sourced from different providers, the Pipeline Accelerator boosted the initial seed funding to enable a rapid start and provide early proof of concept data. This data was then leveraged by the team to raise an additional $3,184,000 from successful grant application and philanthropic donations. The team is now continuing medicinal chemistry optimisation, aiming to develop a first-in-class METTL5 inhibitor that offers a targeted, less toxic treatment option for children with neuroblastoma and potentially also adults with some solid tumours. The Pipeline Accelerator scheme has been critical in bridging the funding gap between early research and major grants, enabling the generation of preliminary data necessary to support long-term development. This initiative highlights how strategic early investment can drive drug discovery and the development of potentially life-saving therapies.

> "The TIA Voucher program enabled early access to medicinal chemistry and physicochemical expertise through ATMCF and CDCO, to initiate the early development of small molecule inhibitors of METTL5, and generate key proof-of-concept data to support applications for further funding."
> **Prof Ian Street**

Impact:

TRL 1 | TRL 2 | **TRL 3** | **TRL 4** | TRL 5 | TRL 6 | TRL 7 | TRL 8 | TRL 9