Identification of Genomic Factors Controlling Therapy Outcomes and Survivorship in Paediatric Brain Cancer Patients

Paediatric brain cancer is the most common solid tumour of childhood and remains the largest cause of death in Australian children by disease. Current multi-modal treatment often results in adverse late effects in paediatric brain cancer survivors. Patients must undergo the full extent of treatment at a cost, with survivors experiencing many **late effects** which are conditions that appear after their cancer treatment is complete. These late effects include reduced capacity in their physical, academic, vocational, and social aspects of life. Including but is not limited to neurocognitive dysfunction (e.g. IQ, education, motor impairments), fertility and reproduction, organ issues (hearing loss, visual impairments), and secondary malignancies. Even with advances in brain cancer treatment, we still have not eliminated the significant late effects in survivors. As such, **improving outcomes and quality of life for all patients diagnosed with brain cancer is urgently needed, requiring novel treatment options complemented by advanced survivorship research.**

With the generous support of the Australian Lions Childhood Cancer Research Foundation, the Paediatric Neuro-Oncology team lead by Professor Jordan Hansford will use advances in molecular biology to further investigate brain cancers, revealing the underlying causation of the disease and begin to better risk stratify to perhaps prevent late effects. South Australia's first Paediatric Brain Tumour Biobank was established by the team and provides a snapshot of brain cancer patients diagnosed and treated in South Australia. Advances in diagnostic technology has meant that these samples are now amenable to meaningful deeper-level genomic and epigenomic analyses. Access to biobanked samples, matched clinical data and modern techniques to analyse these samples means that we're in a strategic position to apply these research tools and link the molecular data to real-world patient data using established state-based databases such as SA-NT DataLink, Birth, Deaths and Marriages, Pharmaceutical Benefits Scheme, and Medicare to track late effects of treatment. **Understanding the mechanisms of late effects will lead to new approaches to designing clinical trials and treatments for all types of brain cancer to improve survivorship through a reduction in these late effects and toxicities associated with existing treatments.**

We will achieve this goal through the following aims:

1) Undertaking advanced testing of the tumour samples within the biobank using tools such as: a. DNA methylation profiling - DNA methylation analysis allows us to gain

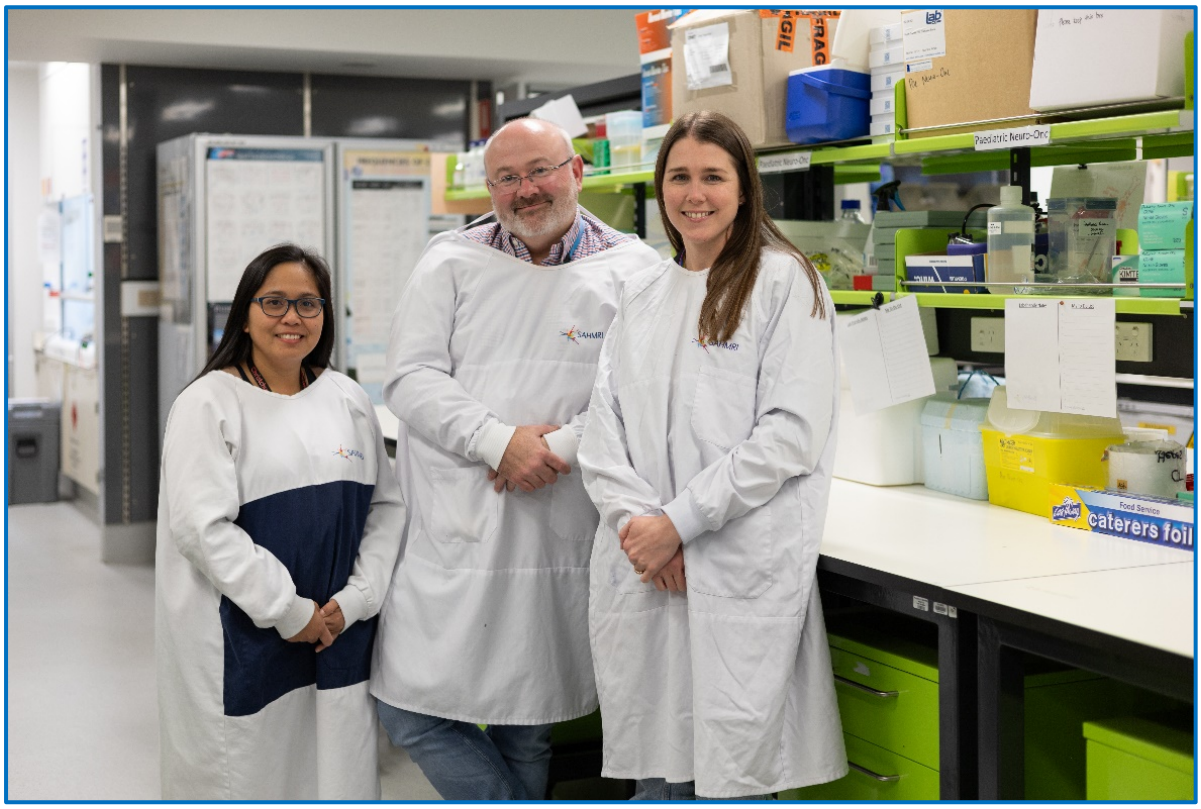
valuable insight into gene regulation and identify potential biomarkers for brain cancer. Aberrant DNA methylation has been implicated in many disease processes, including cancer.

b. **Whole genome sequencing** - allows us to determine the entirety of the DNA sequence of an organism's genome at a single time. This process allows us to determine cancer-causing mutations within a patient's tumour which may influence response to therapies.

c. and **Spatial transcriptomics profiling** – a cutting-edge technique in molecular biology that allows mapping of the gene expression profiles of individual cells within patient samples.

2) Linking these molecular data sets from the above analysis with the patient records (MRI images, clinical records, SA-NT DataLink, Birth, Deaths and Marriages, Pharmaceutical Benefits Scheme, and Medicare) to help identify patient survivorship outcomes and factors associated with late effects. We plan to map whether certain factors found on a molecular level correlate with poorer outcomes in the patients.

3) Identifying biomarkers of late effects using artificial intelligence analysis. Biomarkers of late effects will allow us to identify patients who are likely to develop adverse effects and intervene early to mitigate them.



Dr Noralyn Manucat-Tan, Professor Jordan Hansford and Amanda Luck in the Paediatric Neuro-Oncology laboratory.