Final Report to Australian Lions Childhood Cancer Research Foundation (ALCCRF)

Project Name:
An innovative approach to tackling treatment resistance in medulloblastoma by using bioinformatics and machine learning.

Chief Investigator:
Associate Professor Melissa Davis, Joint Division Head, Bioinformatics.

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Medulloblastoma is a devastating brain cancer that largely affects children and young adults. It is the most common childhood brain cancer yet sadly there are few treatment options. Existing treatments have serious and ongoing side effects and for patients that relapse following treatment, there are currently no effective therapies.

A/Prof Melissa Davis

In December 2021, WEHI was grateful to receive a grant of $220,000 from The ALCCRF towards a two-year research project in WEHI's Bioinformatics division. Support from ALCCRF has enabled a postdoctoral researcher at WEHI, under the supervision of Professor Melissa Davis, to carry out sophisticated machine learning, data analysis and modelling of drug sensitivity and resistance in childhood brain cancer, giving hope to the families of children diagnosed with medulloblastoma.

The project used machine learning to expand the genetic map of medulloblastoma to discover the genes and pathways that control tumour dormancy, drug resistance and relapse. By discovering how cells that are tolerant to existing therapies survive treatment and lead to drug resistance, the team identified weak points in the process that can be targeted by drugs and used in combination with existing effective therapies to prevent relapse and resistance.

The project aimed to help improve survival rates for children with medulloblastoma by developing evidence that new drug combinations are more effective at killing cancer than standard-of-care drugs. By taking a computational approach, the route from fundamental biological discovery to clinical trials can be drastically shortened.

Accelerating understanding of drug resistance in medulloblastoma

In the first six months of this project, we undertook a study to map the gene activity in a patient-derived laboratory model of aggressive medulloblastoma. This data provided important insight into the interactions between the brain and the tumour by demonstrating how the tumour responds to treatment, a critical first step towards identifying drug combinations that may work alongside existing therapeutics.

The project's focus on developing bioinformatics approaches to improve understanding of drug resistance and relapse in medulloblastoma patients has since produced exciting new computational methods and analysis pipelines. Applying the new methods to WEHI's medulloblastoma dataset, we identified processes that explained resistance following treatment. We then used a new method, known as vissE, to study medulloblastoma tissue, by identifying regions of cancers that had

different biological processes active. The vissE analyses of medulloblastoma data led to new biological insights that have piqued the interest of WEHI's collaborators, including Dr. Laura Genovesi, a leading paediatric brain cancer researcher at the University of Queensland. These processes are observed at the interface of the tumour and normal tissue, but not at the core of the cancer. In order to better understand post-treatment resistance mechanisms, researchers then performed a bioinformatics analysis of medulloblastoma tissue post-treatment data and found that specialised cell types in the brain, known as microglia and astrocytes, were assisting cancer cells in evading treatment in a region-specific manner.

These findings and insights will be further explored using next-generation high-resolution childhood brain cancer tissue datasets that allow studies to be conducted at the sub-cellular level. Real-world patient datasets are being acquired with the assistance of WEHI's clinician collaborator and leading Australian childhood cancer researcher, Professor Jordan Hansford, and hold the promise of improving our understanding of the complex mechanisms of resistance in childhood brain cancers.

To prepare for the analysis of these highly complex datasets, and with ALCCRF's support, WEHI's bioinformaticians have developed new bioinformatics methods and pipelines specific for these data. Our biggest contribution to the field of computational cancer biology to date has been a correction to a standard analysis pipeline that will improve data analysis and enhance insights gained from spatially-resolved tissue data. Our current efforts are directed towards developing methods that are able to automatically identify differences in the tissues that make up a patient's tumour, which will help to identify potential combination therapies that may be able to eradicate cancerous tissue.

A brand-new method benefitting childhood cancer research worldwide

The potential of the methods developed for this project goes beyond this specific study and can be used to better understand different subtypes of childhood brain cancers. These computational methods will form the backbone of future computational analysis in the study of childhood brain cancers, ensuring maximal insights from valuable brain cancer datasets.

The first new approach was the vissE method that enables researchers to identify common biological processes that are found in the experimental data and map these results onto networks of interacting genes and drugs. This method was well received by researchers and bioinformaticians and led to the implementation of vissE into a web application, vissE cloud. To ensure widespread usage, vissE and all computational methods developed have been implemented as open-source software that can be readily used by the scientific community and we have designed and delivered multiple workshops to train researchers around the world to use these new tools. The application has since been widely adopted by the research community as evidenced by over 600 analyses completed to date. Since February 2023, it has been accessed by scientists over 16,000 times from more than 40 countries.

The generous support from the ALCCRF has helped WEHI to develop essential computational approaches to study high-resolution tissue datasets, critical for studying childhood brain cancers in unprecedented depth. The state-of-the-art computational and machine learning methods developed will help derive insights from complex datasets generated by next generation technologies. With this grant, we have demonstrated the ability of these methods to study therapeutic mechanisms and treatment resistance in medulloblastoma. We thank ALCCRF for granting us the opportunity to develop these essential methodologies that fill a critical gap in global childhood brain cancer research.