Research Grants 2024

Brain tumour | A ddPCR-based ctDNA Liquid Biopsy for Glioma

Associate Professor Andrew Morokoff

Gliomas, the most common brain cancer remain a devastating diagnosis, disproportionately affecting young people and despite best treatment with surgery, chemotherapy and radiotherapy, they have a universally dismal prognosis.

A circulating molecular biomarker (known as a "liquid biopsy") does not currently exist for brain tumours but is desperately needed. Liquid biopsies for other cancers are now available in the clinic and provide the huge advantage of being able to diagnose and guide treatment for patients via a simple blood test rather than invasive surgery or tissue biopsies. This problem is particularly important for brain tumours, because they require a high-risk neurosurgical procedure to access biopsy tissue. Furthermore, tissue biopsies can be subject to sampling error, whereas a blood test is more able to give a complete picture of the tumour gene mutation profile, which can then be used to predict outcome.

Our research group has been working on glioma circulating biomarkers for more than 10 years and has a large world-leading biobank of matched tissue and blood samples. This test could also distinguish between true tumour progression and 'pseudoprogression', which is enlargement of the tumour on the MRI due to inflammation rather than tumour growth.

Since 2018 we have been focusing on developing a liquid biopsy for glioma based on circulating tumour DNA (ctDNA) in plasma (from blood tests). ctDNA has the advantage of extremely high specificity for gliomas, because the known mutations in the tumour can also be detected in the blood and therefore used for diagnosis or monitoring.

This grant funding in 2024 is to focus on one specific part of the research program which is validating a ddPCR test (digital droplet PCR) for a set of specific glioma gene mutations, including IDH1, IDH2, TERTp and EGFRvIII as well as novel mismatch repair mutations in glioma (MSH2/6) that we have identified with deep sequencing (results submitted to Neuro-oncology Advances pending review).

In 2024, we are pleased to welcome back Dr Jordan Jones who has successfully completed his PhD in 2021 in glioma liquid biopsy, and who has just finished neurosurgery training to be the RMH brain tumour research fellow. Dr Jones will be conducting the majority part of this research project which will run in combination with the liquid biopsy gene profiling project run by the PMCC group, which will test our custom ctDNA panel in plasma. This grant covers the sequencing and consumables part of the budget for this project.

Grant $92,000

THE ROYAL MELBOURNE HOSPITAL NEUROSCIENCE FOUNDATION

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Progress Report

A very exciting update is that our work over the last 2 years, with the assistance of the RMH Neuroscience Foundation grant funding, has culminated in two published papers in 2024 in Neuro-oncology Advances.

Firstly, we found that using ddPCR we can detect key DNA mutations in the blood of glioma patients including IDH mutations in low grade glioma.

Second, using Next Generation Sequencing (NGS) techniques on blood (AVENIO) from high grade gliomas, we reported the early detection of DNA mismatch repair mutations caused by chemotherapy leading to resistance.

This is a first in the world discovery that is garnering a lot of international attention and offers of collaboration. For instance, we have recently been invited to collaborate to provide our expertise on glioma ctDNA to a prospective trial in the UK and also to research with the University of Toronto.

We now plan to extend our work significantly and validate our ctDNA tests clinically. We have a large successful program with Parkville Precinct partners to integrate ctDNA liquid biopsy into our glioma research, which includes the funded BrainPOP trial that started in 2023 and research programs ("GLIMMER" which has $4.5M MRFF funding until 2028). The liquid biopsy project is also part of the Parkville Brain Cancer Centre based at WEHI.

Over the last 6 months we have been prioritising ddPCR for IDH1 mutation for the ANHEART Phase 0 trial running at RMH (PI – Jim Whittle) and this has allowed us to optimise our ddPCR methods and techniques which are working well. In 2025, we will focus on expanding the ddPCR work including IDH1, IDH2, TERTp and EGFRvIII as well as novel mismatch repair mutations in glioma (MSH2/6) mentioned above to the whole of our stored biobank samples.

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