Precision Immunotherapeutic Strategy for Paediatric Brain Tumours

SUMMARY

Diffuse midline glioma (DMG) is a universally fatal paediatric and adolescent cancer responsible for 1/5th of all cancer-related deaths in children. DMGs are localised to the midline of the central nervous system, most commonly diagnosed in the pons (called diffuse intrinsic pontine glioma), thalamus, midbrain and spine. The tumours are characterised by an immunodeficient/cold tumour microenvironment, meaning the patient's immune system cannot/ doesn't recognise the tumour as "foreign", and so does not automatically mount a defensive response against the malignancy. Novel therapies previously developed by our group are currently being assessed in a clinical trial, and excitingly, further studies have shown that these therapies promote increased visibility of the tumour to the immune system. In this project we will test whether these therapeutics (plus newly identified, more potent drugs), can further illuminate DMGs to the immune microenvironment, aiming to develop combination strategies that enhance tumour recognition and destruction.

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INTRODUCTION

Diffuse midline glioma (DMG) is an aggressive paediatric high-grade glioma most frequently diagnosed in the brainstem (especially the brain's control centre known as the 'pons'; tumours here are called diffuse intrinsic pontine glioma - DIPG). Located within critical structures of the brain, surgical resection is extremely challenging, leaving radiotherapy as the only standard treatment option available. However, benefit following radiotherapy is temporary, and despite decades of research, <10% of DMG patients survive two years post-diagnosis. Immunotherapies, including checkpoint inhibitors (ICIs), have shown promising results in other types of cancer, however, are yet to increase survival in DMG. This failure is due to the "cold" tumour microenvironment of DMG; the immediate surrounds of the tumour lacks both tumour-infiltrating immune cells and pro-inflammatory cytokines (necessary for activation/initiation of an immune response to destroy cancer cells). Previous studies conducted by our group identified novel therapies that provided survival benefit in lab-based models of DMG, seeing the therapies move to clinical trial assessment in DMG patients (PNOC022 – NCT0500992). Excitingly, our additional research has identified that these therapies can enhance tumour recognition – treatment promotes the presentation of cancer specific proteins ('antigens'), to immune

cells, effectively "warming" the cold tumour environment. Given the drastic improvement in survival immune-based therapies have delivered to patients with other types of cancer (e.g. melanoma and some blood cancers) we will exploit this finding to develop immunotherapies that harness the patient's own immune system to fight DMG/DIPG tumours.

HYPOTHESIS AND AIMS

We hypothesis that a precision-immuno-therapeutic treatment strategy will improve the survival of DMG patients. To test this hypothesis, we aim to:

1. Increase DIPG antigen presentation in *in vivo* clinical models using exciting combination therapies used in the clinic, with novel therapeutic drug, TR-107.
2. Identify cancer specific 'neoantigen complexes' expressed across different subtypes of DIPG following treatment with these exciting novel therapies,
3. Generate a subtype and/or DIPG specific immunotherapy, and validate the specificity of novel immunotherapeutics.
4. Test efficacy, specificity and toxicity of precision immunotherapeutic strategy using our preclinical models of DIPG.
5. Progress findings to an international precision immunotherapeutic clinical trial in collaboration with Pacific Neuro-Oncology Consortium (PNOC) and Australian and New Zealand Children's Haematology and Oncology Group (ANZCHOG).

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