ACT001 – a promising therapeutic for diffuse intrinsic pontine gliomas

Supervised by Dr Dannielle Upton and Dr Benjamin Rayner

Hons/PhD project for 2022

Background and Preliminary data

This project will develop novel combination therapies for the most aggressive childhood cancer, diffuse intrinsic pontine glioma (DIPG). Our team performed a comprehensive high-throughput drug screen, testing 3,570 drugs for their ability to prevent DIPG cell growth and found ACT001 to be one of the most effective drugs tested. ACT001 is known to have both antioxidant and anti-inflammatory properties and readily crosses the blood brain barrier.

We have initiated a world first Phase 1 paediatric clinical trial of ACT001 for children with relapsed/refractory solid or CNS tumours, including patients with DIPG/DMG. Currently, fifteen patients, seven of which are DIPG/DMG patients, are enrolled and no dose-limiting toxicities have been observed. Excitingly, clinical activity has been demonstrated in three DIPG/DMG patients including improvement in the appearance of the tumour on MRI imaging, as well as improvement in patient symptoms (Fig 1.).

Using our preclinical models, we now seek to evaluate potential ACT001 combination therapies, to enhance the effectiveness of ACT001. As such, this project will provide valuable information for developing new combination treatments that may lead to ACT001 as the first active treatment for children suffering from DIPG.

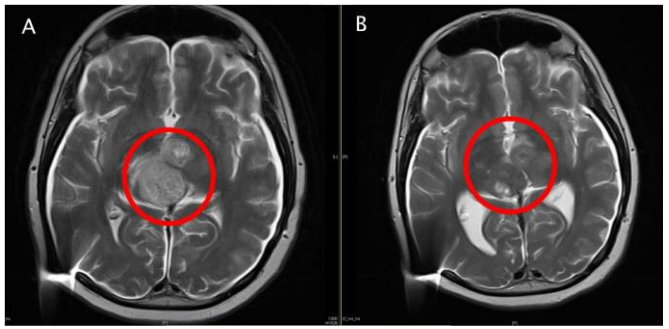

Fig. 1 MRI of clinical response observed in a patient with DMG with H3K27M mutation treated with ACT001. (A) shows T2 weighted MRI pre study enrolment, (B) shows T2 weighted MRI after 6 months of treatment with ACT001.

Hypothesis and Aims

We have both preclinical and clinical evidence that ACT001 is active as a single-agent against DIPG/DMG and hypothesize that the development of rational combination therapies will significantly increase its clinical efficacy.

Aim 1: To evaluate the cytotoxic efficacy of ACT001 combinations in a panel of DIPG and glioma cells and determine the mechanism of synergistic interaction of candidate combinations. (Hons & PhD)

Aim 2: To evaluate the therapeutic efficacy of lead ACT001 combination treatments in a DIPG orthotopic animal model. (PhD)

Methods

Honours project: This project involves a variety of in vitro techniques including cell culture and cell based assays, real time quantitative PCR, flow cytometry and western blotting.

PhD Project: In addition to above, the project will also involve in vivo animal work including treatment and monitoring of DIPG injected animals.

Candidate

The successful candidate will join the Brain Tumour Research Group, with in the Molecular Targets and Therapeutics Theme at the Children's Cancer Institute. We are seeking a highly engaged, honest and motivated student who has a flexible attitude to work and excellent communication skills.

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