SECTION 2: EXECUTIVE SUMMARY

Diffuse Intrinsic Pontine Glioma (DIPG) is a devastating tumour that occurs predominantly in young children and results in a near 100% fatality rate within 2 years of diagnosis. Its diffuse growth pattern and eloquent location precludes surgical resection. Numerous clinical trials of chemotherapeutic agents have failed to demonstrate an improvement in prognosis or survival. Our current best standard of care is radiation therapy which provides temporary relief of symptoms and minimal gains in life expectancy.

In recent years, greater understanding of the molecular landscape of DIPG has resulted in the development of exciting new molecular therapies and sophisticated pre-clinical models. Drug delivery however, remains a major challenge due to the blood brain barrier (BBB). To circumvent this obstacle, we have previously used Magnetic Resonance Image-guided Focused Ultrasound (MRIgFUS) to transiently open the BBB without tissue injury. Intravenously administered microbubbles prior to focused ultrasound (FUS) treatment results in a mechanical interaction between ultrasonic waves, injected microbubbles and the capillary bed resulting in enhanced permeability and a window of opportunity for drug delivery.

Whilst this technique has very recently been used in patients with cerebral tumours in Toronto, disruption of the BBB using MRIgFUS has never before been performed in the brainstem, home to crucial regulatory centres for wakefulness and cardiovascular control. **We have recently completed proof of principle experiments that demonstrate successful disruption of the BBB in the rat brainstem (Fig 1 & 2).** Excitingly, our studies demonstrate that MRIgFUS disruption of the BBB in the pons is technically feasible & we are now poised, in collaboration with Dr Kullervo Hynynen and his 25 years of experience in the field of focused ultrasound, to conduct safety and efficacy studies to evaluate drug delivery in preclinical DIPG models. Accordingly, we have 2 specific aims:

Aim 1: To determine the safety of transient disruption of the BBB of the murine brainstem by MRIgFUS
Aim 2: To develop and optimize preclinical models of DIPG for delivery of known and novel chemotherapeutics using MRIgFUS.

Using a genetically engineered mouse model (RCAS-Tva PDGFRA-driven DIPG model) as well as an orthotopic xenotransplantation model (stereotactically injecting GS2 human glioma sells into the pons of mice) we will test both conventional CNS tumour chemotherapeutics (cisplatin) and novel agents (panobinostat) delivered following MRIgFUS. We will quantitatively measure the presence of these drugs in the brainstem using mass spectroscopy and thereby determine enhanced delivery as well as *in vivo* therapeutic efficacy.

By overcoming the limitation of the BBB by MRIgFUS not only will we be able to re-evaluate existing chemotherapeutics which were previously discontinued due to insufficient delivery but we could open the gateway for enhanced delivery of other anti-cancer therapies such as immune cells, antibodies and nanoparticles. Most importantly, MRIgFUS has been used in patients – thereby offering the potential for rapid translation into clinical practice.