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 propose the use of Magnetic Resonance Image-guided Focused Ultrasound (MRgFUS) 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.

Through an ongoing collaboration with Dr Meaghan O'Reilly of the focused ultrasound laboratory at the Sunnybrook Research Institute, we have successfully demonstrated both the safety of MRgFUS in the rodent brainstem and the ability to concentrate an intravenously administered chemotherapy agent (Doxorubicin) into the region (**Fig. C-H & J**). We now wish to conduct the next steps required for the clinical translation of MRgFUS as a method of drug delivery in DIPG. As such, our aims are as follows:

Aim 1: To identify clinically available drugs that target DIPG cell lines. This will include identifying agents that show efficacy as monotherapies as well as combination agents that act in synergy.
Aim 2: To demonstrate the efficacy of intravenously administered chemotherapeutics when combined with MRgFUS in the treatment of pre-clinical models of DIPG.

Working in conjunction with the Ontario Institute of Cancer Research, we will have access to several hundred clinically available drugs which we will use to conduct a high throughput drug screen on multiple DIPG cell lines. From this screen, we will select effective single agent therapies as well as drug combinations that demonstrate synergy. Having identified the most effective agents, we will test these in a genetically engineered mouse model (RCAS-Tva PDGFRA-driven DIPG model) as well as an orthotopic xenotransplantation model (stereotactically injecting SU-DIPG VI cells into the pons of immunocompromised mice). We will then quantitatively measure (using mass spectrometry) the delivery of drug(s) to the tumour in addition to parameters of *in vivo* therapeutic efficacy.

By re-evaluating exisiting chemotherapeutics and demonstrating their efficacy in combination with MRgFUS delivery, we could open the gateway of potential therapeutic options to children afflicted with the disease. With this information and our ready access to a clinical focused ultrasound delivery device we would be poised to offer the first ever Phase I/II safety and efficacy trial of an MRgFUS delivered treatment in DIPG.

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