Priming the blood-brain barrier to improve drug delivery and treatment outcomes in diffuse midline glioma (DMG)

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Diffuse midline glioma (DMG) is an aggressive and incurable paediatric cancer with less than 10% of children with this cancer surviving beyond two years from diagnosis. The treatment of DMG is a challenging clinical problem due to the location of the tumour in the brainstem, which makes surgical resection impossible. To date, radiation remains the only effective therapy for DMG, but this is largely palliative. New therapies are, therefore, urgently required to improve survival outcomes for children with this cancer. Unfortunately, the development of novel treatments for DMG is severely hampered by the inability to deliver drugs across the blood brain barrier (BBB) to reach cancer cells, with the BBB being impermeable to an estimated 98% of anti-cancer drugs. The lack of effective pharmaceutical treatments that can cross the BBB significantly limits the availability of chemotherapies for the treatment of this cancer.

Our research will address this need by investigating an innovative pharmaceutical strategy to enhance drug delivery to DMG tumours, with the goal of unlocking new avenues for pharmaceutical-based therapies to treat this devastating disease. Here, we have developed a game-changing pharmaceutical approach using a new type of molecule, termed a transient vasculature modifying agent, or TVMA, that can increase drug delivery to tumours in vitro and in vivo. Our research will examine whether TVMAs can be used to prime the BBB vasculature to enhance the delivery of chemotherapy to the brain and enable effective treatment of DMG in pre-clinical, orthotopic patient-derived xenograft models of DMG. This approach has the potential to improve treatment outcomes for children with DMG and represents an important step towards improving the prognosis for this vulnerable patient population.

Hypothesis: We hypothesise that transient vasculature modifying agents (TVMAs) will increase delivery of anti-cancer drugs to the brain, enabling effective treatment of DMG.
Aim 1: To determine the optimal dosing schedule of anti-cancer agents when used in combination with TVMAs, in order to maximise the concentrations achievable in the brain while minimising side effects in vivo
Aim 2: To determine whether TVMAs increase tumour sensitivity to cancer drugs in mouse models of DMG

Our study will generate essential pre-clinical data demonstrating the efficacy of TVMAs in increasing CNS drug delivery to enable effective treatment of DMG in mouse models, while limiting side effects. We anticipate the results from this study will form the basis for a clinical trial assessing TVMA-chemotherapy combination therapies in the treatment of DMG

tumours. Critically, this work has the capacity to revolutionise DMG treatment, thereby improving outcomes for affected children who would otherwise do very poorly.