TELETHON KIDS INSTITUTE

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DEVELOPMENT OF A NEW AND EFFECTIVE THERAPY AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA

Translational
DIPG, Childhood (Brain Cancer)
Affiliation: Cure Fund
Requested Funding: $49,512

EXECUTIVE SUMMARY

Background- Cancer currently stands as one of the leading causes of death worldwide, killing nearly 10 million people in 2018. Among the different forms of cancer, those affecting the brain and Central Nervous Systems are among the deadliest and most difficult to treat. According to figures from the World Health Organization, in 2018 over 70% of all patients diagnosed with brain cancer died in the United Stated, and over 80% in Australia. Despite these troubling figures, no significant improvement in high grade brain cancer treatment has been made over the past 30 years. This situation is worsened by a notable lack of funding for brain cancer research, particular in children. In Australia, for example, the 2017-2018 federal funding from the National Health and Medical Research Council (NHMRC) for children brain cancer represented only 0.36% of the total NHMRC research budget for that time period. Among childhood brain cancers, Diffuse intrinsic pontine glioma (DIPG) is the most difficult to treat: more than 99% of all DIPG patients will die, due to a lack of effective treatments. However, in recent years a highly effective anti-cancer treatment called targeted therapy has been developed. These drugs are used to specifically target the cellular pathways involved in carcinogenesis and tumour growth. This approach has worked well against several types of cancers but has not been successful against any form of brain cancer. A key reason behind this failure may be the innate ability of DIPG cells to adapt to changes in their environment by rewiring their inner cellular machinery. This property is called plasticity and is a trait found in all neural cells. DIPG are, in essence, neural cells, and may be using their inherent plasticity to evade the effects of targeted drugs, by finding new ways to grow and spread. To break this deadlock, we need to stop DIPG cells from evading targeted drugs.

Hypothesis- Previous studies have shown that a crucial cellular component driving cell plasticity are ion channels: proteins found in the cell membrane, where they regulate the flow of ions in and out of the cell. Our central hypothesis is that DIPG plasticity is mediated by ion channels and that their inhibition, using drugs known to cross the blood–brain barrier, will prevent DIPG plasticity, thereby increasing the efficacy of targeted therapies.Thus, we propose a new approach to treat DIPG, using drugs that prevent the biochemical rewiring associated with cellular plasticity, in combination with targeted therapies already available in the clinic.

Goals– We aim to identify the ion channels present in DIPG that drive plasticity and validate these channels as effective therapeutic targets. Then, we will determine if blocking ion channels associated with DIPG plasticity enhances the efficacy of targeted therapies. Also, given that many of the drugs we plan to use are already approved for clinical use, once we identify a treatment that can overcome DIPG's resistance to targeted therapy and increase its anti-tumour activity, our approach could rapidly reach clinical trials.

Design and methods– This project will identify the types of ion channels present in DIPG cells, characterise their role in mediating resistance to targeted therapies and establish effective combinations of targeted therapies with drugs that target ion channel function. The proposed work utilizes patient-derived DIPG cells, sophisticated orthotopic xenograft mouse models of DIPG and state-of-the-art equipment (e.g. patch-clamp technology) that will help us obtain clinically relevant data.

Clinical significance- We will identify which drug combinations should be taken forward to clinical trials, and how the treatment should be given to patients. In the short term, our findings will form the basis of an application for a phase I/II clinical trial in paediatric brain cancer. In the medium term, approval for clinical trials will lead to the assessment of the most promising drug in paediatric DIPG patients. Ultimately our long-term goal is to improve current therapies and increase survival rates of DIPG patients.

Feasibilityand Expertise- The research proposed here has a solid scientific base, backed by strong preliminary data obtained from our studies in adult high-grade glioma. Our laboratory, led by Professor Terrance Johns, is placed in a privileged position to attain the proposed goals. Professor Terrance Johns is a world expert with over 20 years of experiencein brain cancer research. He is also a prolific author, with 8 brain cancer papers published last year alone, including 3 as senior author. Prof Johns is also highly experienced in the application of targeted therapeutics in brain cancer, with a track record advancing both new and repurposed drugs into the clinic. Indeed, his discoveries are already in large Phase 3 clinical trials. Furthermore, Prof Johns is the inventor of an unique guide screw technique, used to grow patient-derived cancer cells in the brains of mouse models. The cell-based assays and orthotopic xenograft models required for this study are routinely conducted in our laboratory. Prof Johns

recently recruited Dr Emily Fletcher to his laboratory; Emily is a world-class researcher in ion channel function and biophysics. Overall, this background demonstrates that Prof Johns has the experience and technical capability needed to lead and successfully complete the proposed project.

The rarity of paediatric cancer requires that clinical trials be performed collaboratively within cooperative groups. **Our results will be shared with international colleagues and we aim to design and apply for approval of a new clinical trial for DIPG within 3-5 years.**