Final Report

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Title of Project: **Better drugs for brain cancer**

Summary:
Each year, over 1,600 Australia are diagnosed with a brain tumour, with over half of these being aggressive malignant high-grade tumours. Even with the advances in genetics, surgery and radiotherapy, the outcome for patients has not improved for decades and the complications associated with the toxicity of standard treatments severely reduce quality of life for patients.

The current drug used is temozolomide (TMZ) which has broad non-specific cytotoxic effects on both tumour and healthy cells. Such drugs can cause severe negative side-effects due to the toxicity on normal cells. New drug development is slow, expensive process. One way of bypassing the enormous cost of drug development with diseases that attract less attention from major pharmaceutical companies is to repurpose existing drugs. Many drugs have a wide range of actions that benefit many diseases, particularly in combination with existing therapies. The first step in this approach is to identify a molecular target important for promoting a disease state. We discovered an important mechanism involved in killing brain cancer cells, which opened the potential use of existing FDA-approved drugs in brain cancer patients; drugs not previously considered for brain cancer therapy. Our discovery was that cAMP cell signalling activity could trigger brain tumour cell killing (Daniel et al., 2016).

<u>cAMP-mediated killing of brain tumour cells</u>
The most aggressive brain cancer in adults, glioblastoma (GBM) and other high tumours exhibit low cAMP activity. While mutations in cAMP pathway proteins are not common in cancers, there is evidence that altered expression of factors regulating the cAMP signals in cells may be responsible for decreased levels of cAMP in cancer. The inverse relationship between cAMP levels and tumour malignancy has raised the possibility of using this pathway as a potential therapeutic target in GBM patients.

Other studies have likewise shown that cAMP activation occurs by inhibition of enzymes called phospho-diesterases (PDEs) which can inhibit growth, increase differentiation and increase cells death via apoptosis in the GBM cells.

A family of pharmaceuticals called phospho-diesterase inhibitors (PDEi), activate cAMP. Many PDEi drugs are used for neurological conditions, thereby fulfilling two important criteria – they are approved for human use and they cross the blood-brain barrier, which is a critical issue in delivering drugs to the brain, since many drugs useful for systemic cancers cannot cross the blood brain barrier. The Brain Foundation research gift was used to better understand the mechanism by which PDEi drugs can kill brain tumour cells and to test the efficacy of several existing PDEi drugs in killing brain tumour cells.

Hypothesis vs Findings
The hypothesis is that PDEi drugs can kill brain tumour cells, alone or in combination with other drugs.

We tested the efficacy of 3 PDEi drugs: rolipram, apremilast and folumilast, alone or in combination with new drugs which activate a tumour cell death program, called apoptosis. We have identified a combination of PDEi and a BH3 mimetic drug which appears to be more effective at killing brain tumour cells than each drug alone and more than simply an additive effect: the drugs synergise by working on different components of the apoptosis cell death pathway.

Unanswered Questions
We have tested 3 PDEi drugs and 4 BH3 mimetic drugs and have short-listed a further 7 PDEi drugs to test in cells. Once this is done, we then need to test the best drug combinations identified in cell-based experiments in mice, which we have not yet completed.

What these research outcomes mean
Our results from experiments conducted as part of the Brain Foundation Research Gift project have led to the better understanding of a novel tumour cell death mechanism driven by PDE inhibition and the possibility that existing safe brain-available PDE inhibitor-based medicines, could be used for brain cancer patients.

Other outcomes directly attributable to this project and the support of the Brain Foundation, were the training of two young scientists, Ms Corrina Grima and Ms Christina Pelosi-Thorpe. The project has also enabled the development of a new collaboration with A/Prof Grant Dewson, Walter & Eliza Hall Institute, who is an expert in cell death biology and BH3 mimetic drug development. We also published a review article on hypothesis and evidence on which we based this project and acknowledged the support of the Brain Foundation.
Article link: https://doi.org/10.1016/j.cellsig.2019.01.011.
We are now preparing a research publication on the research discoveries of this project, in which the support of the Brain Foundation will be acknowledged.