Targeting the YAP pathway in glioblastoma stem cells

Dr Andrew Gogos
Co-Investigators: Dr Andrew Morokoff, Professor Tony Burgess, A/Prof Kate Drummond

Glioblastoma multiforme (GBM) is the most common and most deadly form of primary brain cancer. Most patients survive only 12 months from diagnosis, often with significant disability. Despite a huge volume of research into the disease, there are few proven treatments and their benefit can be measured in months at best. A possible reason for this translational gulf is that most therapies focus on the mature group of cells composing the tumour. In contrast, we study glioma stem cells: a subpopulation of the tumour that may be responsible for initiating the tumour, and for regrowth after existing treatments fail.

Specifically, we investigated the role of the Hippo pathway, and the protein YAP. This is an intracellular signalling system promotes growth, proliferation, migration and differentiation. In the normal brain this pathway is active during development but not in mature neurons or supporting cells. We and other research groups have noted that the pathway is highly active in GBM cells, specifically in the glioma stem cells. It appears the tumour has co-opted a normal developmental system for its own abnormal growth. The YAP pathways high activity within the tumour, but not normal brain, makes it an ideal potential therapeutic target. Using the TCGA glioma data set we demonstrated that YAP expression is higher in glioblastoma than in normal brain. We also demonstrated that, for grade 2 and 3 tumours, higher YAP expression was associated with significantly worse survival for patients.

We developed a model in glioma stem cells where we could experimentally inhibit YAP signalling. We demonstrated that lowering YAP expression resulted in significantly reduced cellular proliferation, migration and survival. We then developed a mouse model and demonstrated that lowering YAP expression resulted in 100-fold decrease in tumour size. After two weeks of YAP suppression, 72% of the tumours were no longer visible.

With the help of the Brain Foundation we demonstrated that YAP has great potential as a therapeutic target in glioblastoma. We aim to continue this work and develop novel therapies to improve that lives of patients with brain cancer.