Using a novel approach to modulate levels of MGMT protein in brain tumour cells

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Glioblastoma multiforme (GBM) is the most common and most aggressive type of primary brain tumour. It is currently treated by a mixture of ionising radiation and Temozolomide (TMZ) chemotherapy, however virtually all patients experience disease recurrence and 75% die within two years of diagnosis. Tumours which express elevated levels of the DNA repair protein methylguanine methyltransferase (MGMT) have a particularly poor prognosis, suggesting that the levels of MGMT and the inefficacy of treatment are linked.

MGMT is a “suicide” repair protein that binds irreversibly to a DNA adduct (such as those caused by TMZ) and is destroyed by the proteasome once repair has taken place. Therefore the ability of the cell to repair DNA damage relies on the rate at which it can resynthesise MGMT. Previous research has shown that reducing MGMT levels via RNA silencing increases the effectiveness of treatment, however this causes toxicity in bone marrow stem cells and is therefore unable to be used as a possible treatment option. Our preliminary data suggests that inhibition of mTOR signalling reduces the steady state levels of MGMT without affecting mRNA levels, potentially making them more sensitive to TMZ treatment. We are therefore using inhibitors of the mTOR pathway to determine how these affect MGMT levels and determining whether a mixture of these inhibitors with DNA damaging agents could be used to increase the efficacy of TMZ treatment.