OP33. GLYCOGEN SYNTHASE KINASE INHIBITORS REDUCE 3D MIGRATION OF PATIENT DERIVED GliOBLASTOMA MULTIFORME STEM CELLS
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INTRODUCTION: Glioblastoma multiforme (GBM) is a fast growing, highly invasive malignant brain tumour. Inhibition of tumour cell migration into normal brain tissue represents a major target for treatment. Glycogen synthase kinase (GSK-3) inhibition has been associated with reduced GBM invasion in vitro and in vivo models. Targeting this pathway with established and/or novel drugs may elucidate more effective treatment combinations.

METHOD: The effect of GSK-3 inhibitors BIO, AZD2858, AZ1293 and AZ1080 on GBM migration was assessed in patient derived GBM stem cells (GBM-1) and two established cell lines (U251 and U87) using a 3D collagen based assay. Multiple drug concentrations were investigated with up to 72 hours exposure. A migration index was determined using aggregate core size and cell migration area. Immunohistochemistry and immunocytochemistry were used to assess cell morphology and cytoskeletal changes. RESULTS: All compounds inhibit migration in this model. AZD2858 was the most potent, causing significant effects at 1 micro molar. All compounds were cytotoxic at between 10 and 20 micro molar. Cytoskeletal and nuclear abnormalities were noted following drug exposure in all cell lines. These data suggest that possible mechanisms for the anti-migratory effect of these compounds include effects on F-actin localization and microtubule polarity. Inhibition of migration and cell architecture changes occurred at non-toxic doses. CONCLUSION: Inhibition of GSK3 significantly reduced migration of this highly invasive tumour. It is evident from these data that inhibiting the complex biological mechanisms driven by GSK3 may aid treatment of GBM through a number of different mechanisms.