# **Abstract:**

This project explores the use of an anti-sense oligonucleotide (ASO) against the *htt* mRNA to downregulate the huntingtin (HTT) protein in proneural glioblastoma brain tumours, with the aim of sensitizing the tumours to treatment with temozolomide (TMZ). N13-1520 glioblastoma stem cells were injected into mice, who were then co-treated with TMZ and either the anti-*htt* ASO or a control ASO. The results demonstrated a significant reduction in tumour growth rate in mice with downregulated *htt*. Additional analysis revealed a decrease in the rate of tumour growth, the number of proneural stem cells as well as proliferating cells. *In* *vitro* experiments also showed a decrease in stem cell self-renewal capacity. These results suggests that HTT depletion enhances the effects of TMZ by increasing apoptosis and reducing proliferation. The paper discusses potential mechanisms through which HTT depletion may sensitize glioma stem cells to TMZ, such as its involvement in DNA damage repair, transcriptional regulation of pro-survival factors, and base excision repair processes. This project suggests that this could be a promising therapy for glioblastoma patients undergoing TMZ treatment, but further research is required to elucidate the exact mechanisms involved as well as safety in human patients. To summarise, this research project presents a novel and innovative approach to glioblastoma therapy.

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