Short Communication

# Radiosensitizer Development Plan for Glioblastoma

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## Introduction

Glioblastoma is the most prevalent type of primary brain cancer and has a bad prognosis. New agents are desperately needed, yet nearly every Phase III study of GBM patients conducted in the last 25 years has failed to show a significant improvement in outcomes. The Glioblastoma Working Group (GBM WG) of the National Cancer Institute's Clinical Trials and Translational Research Advisory Committee (CTAC) highlighted five main areas of research in 2019 that are anticipated to be significant in the development of new GBM therapeutics. Optimizing radioresponse for GBM in situ was one of them. The inclusion of a radiosensitizer to improve the therapeutic ratio by increasing tumour sensitivity while having low to no effect on normal tissue is one such technique for increasing radiation efficacy. Although the bulk of studies involving radiosensitizers have failed in the past, they do provide valuable insight into what is needed to produce agents more quickly. Improved target selection is required for a medicine to deliver maximum benefit, and after that target has been discovered, it must be verified in preclinical research. To prove that a medicine justifies advancement to clinical inquiry, careful selection of acceptable *in vitro* and *in vivo* models is required to demonstrate improved radiosensitivity and proper bioavailability. Patient trials, once experimental drugs have been validated pre-clinically, require consistency in terms of study design as well as reporting efficacy and toxicity in order to assess the drug's potential value. Using the examples of XPO1 inhibitors and HDAC inhibitors developed in our own lab as models, we seek to detail methodologies for generating efficient radiosensitizers against GBM in this study. The most prevalent primary brain tumour in adults is Glioblastoma (GBM).

Despite the fact that the Stupp study established maximal safe resection followed by Radiotherapy (RT) with contemporaneous and adjuvant Temozolomide (TMZ) as the gold standard in treating these patients, results are still poor, with a median survival of 15 months. The Glioblastoma Working Group (GBM-WG) of the National Cancer Institute's Clinical Trials and Translational Research Advisory Committee (CTAC) highlighted five main areas of research in 2019 that are anticipated to be significant in the development of new GBM therapeutics. Improvements in the radioresponse of GBM tumours *in situ* were one of these areas. The most prevalent location of recurrence is inside the high-dose RT field, hence improving local control by boosting radioresponse is an important area of research. Attempts to improve RT efficacy by altering fractionation or employing local boost methods to increase the radiation dose have not only failed to improve survival rates, but have also resulted in increased toxicity manifested as higher rates of reoperation and radionecrosis. The inclusion of radio sensitizers to improve the therapeutic ratio of radiation treatment by increasing tumour sensitivity to radiation without increasing the harm to normal tissues is an alternative technique for boosting responsiveness to RT. Despite the fact that using radiosensitizers is a promising method, the development of these new agents has been slow. According to a review of phase III trials on systemic medicines in GBM, only the addition of TMZ resulted in a statistically significant improvement in survival

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in seven trials conducted on newly diagnosed patients from 1991 to 2016. However, because TMZ was used in both the concurrent and adjuvant phases of the Stupp experiment, it is unclear whether the contemporaneous TMZ worked as a radiation modifier. The lack of tumor molecular data leading to unknown target availability, the lack of pharmacodynamic testing leading to unknown degree of inhibition, the use of imaging criteria as a surrogate endpoint, and the suboptimal design of the preceding phase II studies are all proposed as reasons for radiosensitizers' failure. Another possibility that will be investigated in this article is whether the failures were caused by poor drug selection in phase III trials. Many of these trials have little pre-clinical evidence, no successful Phase II study prior to the Phase III investigations, or no Phase II study at all. Using examples from our own lab, we will discuss development techniques and the minimal reporting data required to proceed from bench discovery to a successful Phase III study of a radiation sensitizer in GBM.

Due to a lack of treatment efficacy and/or excessive drug toxicity, most clinical trials have failed to improve GBM patient outcomes. Pre-clinical optimization of the treatment is crucial for improving the success of GBM clinical trials and avoiding the exposure of patients to potentially harmful medication. By collecting data on the feasibility, safety, and efficacy of a medication before starting a Phase I trial, laboratory research can help guide the choice of whether it can progress from the bench to the bedside. In the drug discovery process, target identification and validation are two critical processes. Furthermore, in vitro and in vivo models that are the most accurate representations of the patient's tumor are required.