### DDRE-21. THE FUNCTION OF MITOCHONDRIAL OSMR IN GLIOMA STEM CELL RESPIRATION AND GLIOBLASTOMA PATHOGENESIS

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Glioblastoma contains a rare population of self-renewing brain tumor stem cells (BTSCs) which are endowed with properties to proliferate, spur the growth of new tumors, and at the same time, evade ionizing radiation (IR) and chemotherapy. However, the drivers of BTSC resistance to therapy remain unknown. The cytokine receptor for oncostatin M (OSMR) regulates BTSC proliferation and glioblastoma tumorigenesis. We have discovered that OSMR translocates to the mitochondria and regulates oxidative phosphorylation, independent of its role in cell proliferation. Mechanistically, OSMR is targeted to the mitochondrial matrix via the presequence translocase-associated motor complex components, mtHSP70 and TIM44. OSMR interacts with NADH ubiquinone oxidoreductase 1/2 (NDUFS1/2) of complex I and promotes mitochondrial respiration. Deletion of OSMR impairs spare respiratory capacity, increases reactive oxygen species, and sensitizes BTSCs to IR-induced cell death. Importantly, suppression of OSMR improves glioblastoma response to IR and prolongs lifespan.

### DDRE-22. TARGETING SERINE SYNTHESIS IN BRAIN METASTASIS

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The brain environment is low in amino acids, including serine and glycine, both of which are important for tumor growth as they are precursors of proteins and nucleotide bases. How tumor cells overcome these conditions to proliferate and survive in the brain is incompletely understood. Here, we show that 3-phosphoglycerate dehydrogenase (PHGDH), which catalyzes the first and rate-limiting step of glucose-derived serine synthesis, enables brain metastasis in multiple human types and in preclinical models. Genetic suppression and small molecule inhibition of PHGDH attenuated brain metastasis, but not extra cranial tumors, and improved the overall survival of mice bearing brain metastasis. These results demonstrate that the tumor nutrient microenvironment determines tumor cell sensitivity to loss of serine synthesis pathway activity and raise the possibility that serine synthesis inhibitors may be useful in the treatment of brain metastases.

### DDRE-23. A COMPREHENSIVE CHARACTERIZATION OF THE GBM LIPIDOME REVEALS A MOLECULARLY-DEFINED SUB-GROUP WITH HEIGHTENED SENSITIVITY TO LIPID PEROXIDATION INDUCED CELL DEATH

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Cancers, including the universally lethal glioblastoma (GBM), have reprogrammed lipid metabolism to fuel tumor growth and promote survival. However, the full extent to which lipid content is altered across molecularly heterogeneous patient tumors has yet to be fully elucidated. Additionally, the molecular alterations responsible for aberrant lipid metabolism, and the potential for identifying new therapeutic opportunities are not fully understood. To systematically investigate the GBM lipidome, we performed integrated transcriptomic, genomic and shotgun lipidomic analysis of an extensive library of molecularly diverse patient-derived GBM tumors across tumor microenvironments both *in vivo* (*n=23*) and *in vitro* (n=30). Using this comprehensive approach, we discovered two GBM sub-groups defined by their combined molecular and lipidomic profile. Triacylglycerides (TAGs) enriched in polyunsaturated fatty acids (PUFAs) were among the most significantly altered lipids between the two groups of GBM tumors. TAGs are the main components of lipid droplets, which have been shown to sequester PUFAs away from membrane phospholipids where their sensitivity to peroxidation leads to cell death. The GBM subgroup with a depletion of PUFA TAGs showed heightened sensitivity to lipid peroxidation both under basal conditions and in response to pro-oxidant compounds *in vitro*. Our findings suggest a novel association between specific molecular signatures of GBM, lipid metabolism and lipid peroxidation-induced cell death. This relationship may present a new therapeutic opportunity to target reprogrammed lipid metabolism in a molecularly-defined subset of GBMs.

### DDRE-24. TARGETING PURINE METABOLISM TO OVERCOME GLIOBLASTOMA THERAPY RESISTANCE

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Intratumoral genomic heterogeneity in glioblastoma (GBM) is a barrier to overcoming radiation (RT) resistance. To discover genotype-independent mediators of RT resistance, we correlated RT resistance with the concentration of approximately 700 metabolites across 23 GBM cell lines. Purine metabolites, especially those containing the base guanine, were most correlated with RT resistance. Similarly, increased abundance of tumor purines was associated with decreased survival in GBM patients treated with RT. This relationship is causal. Purine supplementation protected RT-sensitive GBMs from RT and promoted the repair of RT-induced double strand DNA breaks (DSBs). In vitro and in vivo stable isotope tracing confirmed that GBM cell lines and orthotopic patient-derived xenografts primarily generated purines through the *de novo* synthetic pathway. RT treatment further increased *de novo* purine synthesis in GBM through signaling via the DNA damage response. Inhibition of *de novo* GTP synthesis with mycophenolic acid (MPA) sensitized multiple GBM cell lines and neurospheres to RT by slowing the repair of RT-induced DSBs. MPA-induced radiosensitization was GTP-dependent as it was rescued by nucleoside supplementation. Modulating pyrimidine metabolism affected neither RT resistance nor DSB repair, suggesting these GTP-specific effects are due to active signaling rather than its ability to act as a physical substrate for DNA repair and candidate signaling molecules have been identified. These results were recapitulated *in vivo* with mycophenolate mofetil (MMF), the orally bioavailable FDA-approved prodrug of MPA. MMF potentiated RT efficacy, reduced tumor guanylates and slowed the repair of RT-induced DSBs across multiple models. Because *de novo* purine synthesis is activated by many of the oncogenic alterations that drive GBM, its inhibition is a promising genotype-independent strategy to overcome GBM RT resistance. We have now begun a clinical trial to determine whether combining MMF and RT is safe and potentially efficacious in patients with GBM.

### DDRE-25. INVESTIGATING MITOCHONDRIAL SLC25A TRANSPORTERS INVOLVED IN SUPPORTING BRAIN TUMOUR METABOLISM AND SURVIVAL UNDER HYPOXIC CONDITIONS

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Advancements in prevention, detection and treatment over the last 40 years have significantly transformed cancer healthcare however there are a few cancers, such as brain tumours, which are consistently lagging behind. The most common adult brain tumour is glioma; a highly aggressive cancer that invades deep into the surrounding brain consequently making treatment challenging. The severe hypoxic nature of glioma adds further complications to therapeutic efficacy as hypoxia limits efficient drug delivery as well as increasing treatment resistance. Therapies that therefore target both the hypoxic tumour microenvironment and metabolic pathways that sustain growth have significant potential to improve patient prognosis. It is well known that cancer cells demonstrate an abnormal metabolism, resulting in an altered requirement for amino acids to aid uncontrolled proliferation. Furthermore, tumour metabolism can also be influenced by this hostile hypoxic microenvironment, leading to a more malignant phenotype. We are therefore interested in a family of mitochondrial transporters, SLC25A, which translocate numerous solutes across the mitochondrial membrane and are crucial for many metabolic reactions. TCGA analysis has shown that many of these amino acid carriers are upregulated in glioma. Remarkably however, around 23 of the 53 mammalian SLC25A members lack defined substrate