TP53), PBT-24FH (*PMS2*), and PBT-27FH (*HIST1H3B, TP53, NTRK2*). Models demonstrated radiation-resistance similar to the patient from whom the culture was generated, supporting the models' relevance (e.g. cell viability after 8 Gy was 36%, 81%, 71%, and 61% in PBT-09FH, -22FH, -24FH, and -27FH, respectively, compared to 7% in the medulloblastoma model MED-411FH). We evaluated cell viability and apoptosis following treatment with a panel of HDAC inhibitors, identifying the low nanomolar IC_{50} of quisinostat (~50 nM) and romidepsin (~5 nM). While RNA expression changes induced by 100 nM panobinostat and quisinostat included shared overexpression of the top 20/25 genes (e.g. *FSTL5*, *ITIH5*) and shared downregulation of the top 22/25 (e.g. *GPR37L1*, *HEPACAM*), only 9/25 were downregulated by panobinostat, quisinostat, and romidepsin (e.g. *C21orf62, IFIT2*), identifying these as potential vulnerabilities or biomarkers of lethal HDAC inhibition. Mass-spectrometry (LC-MS) demonstrated panobinostat as the greatest acetylator of cortactin, potentially related to thrombocytopenia. While PBT-09 flank models demonstrated quisinostat's on-target acetylation and efficacy, orthotopic xenograft models did not, supporting our model's intact blood-brain barrier and emphasizing the need for CNS penetrant versions of potentially efficacious agents.

DIPG-11. A PHASE I DOSE ESCALATION STUDY OF BXQ-350 IN CHILDREN AND YOUNG ADULTS WITH RELAPSED SOLID TUMORS

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BXQ-350 is a novel agent composed of the multifunctional, lysosomal activator protein Saposin C (SapC) and dioleoyl- phosphatidylserine (DOPS). BXQ-350 demonstrated antitumor effects *in vitro and in vivo*. Many tumors, including diffuse intrinsic pontine glioma (DIPG), and cells of tumor vasculature have aberrantly-exposed PS-rich domains on the cell surface. BXQ-350 is an anti-tumor agent in development from Bexion Pharmaceuticals, Inc. that selectively targets tumor cell PS, particularly those translocated to the outer leaflet of the plasma membrane in tumor cells. BXQ-350 activates and participates in various cellular processes, including apoptosis and necrosis, and may also exhibit novel mechanisms leading to cell death that require further investigation. An adult Phase I trial with BXQ-350 completed enrollment in 2019 having dosed 86 recurrent solid tumor patients, including glioblastoma, with only one serious infusion-related reaction. The highest planned dose of 2.4 mg/kg was achieved and seven patients remain on study with multiple cases demonstrating an objective response. A Phase I pediatric dose escalation trial in recurrent solid tumors, including central nervous system (CNS) tumors, also completed enrollment in 2019. The highest planned dose of 3.2 mg/kg was achieved and there have been no BXQ-350 related serious adverse events. Eight patients (7 CNS and 1 non-CNS) completed at least one cycle with one DIPG patient completing cycle five. A pediatric Phase I trial in newly diagnosed DIPG and diffuse midline glioma (DMG) is planned for 2nd quarter 2020.

DIPG-12. TARGETING EPIGENETIC MODIFIERS TO INDUCE IMMUNE SIGNALING IN DIPG

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DIPG is a universally fatal pediatric brainstem tumor with no effective therapy. Recent work has shown that over 80% of DIPG cases harbor the H3K27M mutation leading to global loss of the repressive H3K27 trimethylation mark, global DNA hypomethylation, and a distinct gene expression signature. We sought to exploit epigenetic vulnerabilities in DIPG through the use of DNA methyltransferase inhibitors and histone deacetylase (HDAC) inhibitors. We find that treatment with low-dose 5-aza-2'-deoxycytidine (decitabine), alone and in combination with HDAC inhibitors, elicits profound genome-wide demethylation in DIPG patient-derived neurosphere cell lines, impairs proliferation, and induces apoptosis. We show that this treatment induces immune activation, with induction of type I interferon signaling, increased expression of major histocompatibility complexes, and expression of tumor antigens. These results suggest that the immunogenicity of DIPG may be modulated by epigenetic therapies, suggesting the possibility of novel combination approaches to immunotherapy of DIPG in the future.

DIPG-13. TARGETING HYPOXIA AND MITOCHONDRIA WITH REPURPOSED METABOLIC DRUGS AS AN APPROACH TO RADIOSENSITIZATION FOR DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPG)

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DIPG is the leading cause of brain tumor-related death in children. Currently, radiation is the only treatment that offers transient benefit. Compared to normal brain tissue, DIPGs are hypoperfused with tumors being exposed to hypoxia, a potent barrier to effective radiotherapy. Biguanides are hypoglycemic agents that can reduce the oxygen consumption rate (OCR) in mitochondria, thereby reducing hypoxia. Our previous study has shown that metformin significantly improves the radiosensitivity of DIPG and extends survival in a patient-derived xenograft (PDX) model. In the present study, phenformin, a second biguanide derivative, demonstrated even greater anti-DIPG activity and radiosensitising effect *in vitro*. As a single agent, phenformin dose-dependently inhibited OCR and increased extracellular acidification rate (ECAR). Low-dose phenformin reduced mitoATP/glycoATP ratio, whereas high doses significantly suppressed net ATP production. To attenuate the phenformin-induced ECAR, phenformin was combined with dichloroacetate (DCA), a clinically relevant pyruvate dehydrogenase kinase inhibitor that can suppress the elevated glycolytic rate of cancers. This combination significantly blocked the phenformin-induced ECAR and killed DIPG cells synergistically by inducing apoptosis, DNA damage and metabolic catastrophe. Moreover, protein expression of HIF-1α and c-Myc, two master regulators that collaboratively enhance the metabolic capacity of tumor cells through increased glycolysis thereby contributing to radioresistance, were also suppressed by phenformin-DCA treatment *in vitro*. This combination therapy upregulated genes inhibiting cell proliferation while downregulating genes for DNA repair. The triple combination of phenformin, DCA and irradiation demonstrated the most potent efficacy *in vitro* and is currently being tested in our PDX cohort *in vivo*.

DIPG-14. TARGETING POLO-LIKE KINASE 1 IN COMBINATION WITH KEY ONCOGENIC DRIVERS IN DIPG: FROM SINGLE AGENT TO COMBINATION STRATEGIES

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Diffuse Intrinsic Pontine Glioma (DIPG) are devastating paediatric brainstem tumours. Loss of function mutations in DIPG decrease genetic stability and impair DNA damage response pathways promoting tumourigenesis. Polo-like Kinase 1 (PLK1) is a pivotal controller of cell growth, regulating key intermediaries of DNA replication, homologous repair, the cell cycle and cell division. We have found DIPG cultures consistently overexpress PLK1 with inhibition resulting in decreased tumour cell growth, heightened cell cycle arrest and apoptosis. Single agent treatment using PLK1 inhibitors unprecedentedly doubled the median survival of animals harbouring DIPG tumours. Through gene expression analysis, we've showed PLK1 inhibition affected multiple pathways which control the cell cycle, cell death regulation, microtubule organization and regulation of cell migration. We found these pathways of differentially expressed genes were significantly enriched for known targets of both E2F1 and E2F4. Analysis of gene expression and proteomic studies also revealed PLK1 inhibition decreased the activation and expression of key tumour promoting mediators within multiple phases of the cell cycle, decreased expression of tumour promoters including MYC and the PI3K/mTOR pathway and reactivated tumour suppressors p53 and PTEN. Assessing these changes in the treated transcriptome and proteome, we aim to develop multiple potentially translatable combination treatment strategies for DIPG. We have performed mechanistic studies and identified synergism with PLK1 inhibitors and the epigenetic regulator panobinostat, bet/bromodomain inhibitor JQ1, dual PI3K/mTOR inhibitor bimiralisib and PI3K inhibitor BKM120. Finally, we found PLK1 inhibitors act as potent radiosensitizers, enhancing the therapeutic effects of radiotherapy *in vitro* and *in vivo*.

DIPG-15. POLYAMINE PATHWAY INHIBITION IS A POTENT NOVEL THERAPEUTIC STRATEGY AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA

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