recurrence-associated changes in genetics and the microenvironment that can be targeted to shape disease progression following initial diagnosis.

OMRT-5. THERAPY-INDUCED REPROGRAMMING DRIVES GLIOMA VASCULAR TRANSDIFFERENTIATION AND RECURRENCE

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Therapy-resistant glioma cells elicit remarkable phenotypic plasticity leading to aggressive tumor recurrence. Here, we used single-cell and whole transcriptomic sequencing to uncover that radiation treatment induces a dynamic shift in functional states of glioma cells allowing for acquisition of either stem-like, mesenchymal-like or vascular-like phenotypes. The predominant phenotype switch induced by radiation in surviving tumor cells is the vascular-like cell state, resulting in transdifferentiation to endothelial-like and pericyte-like cells in distinct cell clusters. The transdifferentiated endothelial-like and pericyte-like cells secrete trophic factors to support proliferation of tumor cells, and their selective ablation results in reduced tumor growth and recurrence post-treatment. Mechanistically, the acquisition of vascular-like phenotype is driven by increased acetylation and chromatin accessibility in vascular genes and in regions for binding of vascular specification transcription factors. Blocking histone acetylation using a small molecule inhibitor targeting P300 histone acetyltransferase activity prior to radiation treatment inhibits the vascular-like transdifferentiation of glioma cells and tumor growth. Our findings indicate that radiation therapy-induces rewiring of glioma cells that promotes vascular cell-like transdifferentiation, tumor growth and recurrence.

OMRT-6. OPTIMIZING MDM2 INHIBITION FOR THE TREATMENT OF HIGH-GRADE GLIOMA

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Over 80% of high-grade gliomas have alterations in members of the p53 pathway, a central regulator of cell cycle progression and apoptosis that becomes activated in response to cellular stress and DNA damage. For tumors that retain wild-type p53, pathway deregulation frequently occurs through the amplification of negative regulators of p53, including the E3 ubiquitin ligase MDM2. The p53/MDM2 interaction axis has served as basis for the development of several classes of MDM2 inhibitors, with AMG232 being the most potent molecule currently undergoing clinical evaluation. As the effects of MDM2 inhibition (MDM2i) remain poorly understood in high-grade glioma, we performed genomic and transcriptomic analyses in patient-derived models to better characterize sensitive tumors and identify putative biomarkers of drug response. Treatment with AMG232 impaired the growth of cell lines with wild-type p53 status, particularly in tumors with additional amplification of MDM4 or PPM1D activating mutations. Treatment with AMG232 upregulated both cell cycle arrest and apoptotic cellular responses, as measured by annexin V/PI staining and immunoblotting. Interestingly, the dynamics of these two downstream p53 signaling axis were dependent on treatment duration across models. In addition to p53 pathway activation and apoptotic induction, RNA-sequencing revealed MDM2i to be associated with the activation of oncogenic MAPK and KRAS signaling as well as epithelial to mesenchymal transition markers. In most solid tumors, resistance to MDM2i is mainly mediated by acquisition of p53 inactivating mutations. We hypothesized that resistance mechanisms in glioma may be partially driven by transcriptional changes, as these tumors consist of subpopulations with diverse cell differentiation states. By chronic AMG232 treatment, we have developed in vitro and in vivo models of acquired MDM2i resistance that are not mediated by p53 inactivation. Ongoing work is focused on characterizing the transcriptional profile of these cells to identify transcriptional changes leading to decreased drug response.

OMRT-7. ANGIOGENESIS INHIBITORS STRONGLY SYNERGIZE WITH THERAPEUTICS TARGETING TUMOR METABOLISM

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Angiogenesis inhibition has become a mainstay of oncology despite having fallen short of its early promise. As originally envisioned, angiogenesis inhibition would cut off the blood supply, deprive tumor cells of key nutrients, leading to their death. In practice, while there is evidence that tumors under angiogenesis treatment do in fact exhibit some degree of metabolic stress, this is stress is not sufficient to induce significant cancer cell death. We posit that the full potential of angiogenesis inhibition can be realized by the combination of angiogenesis inhibition with emerging tumor metabolism targeting therapies. Because tumors under angiogenesis inhibition are already in a state of nutrient stress, the effects of metabolically targeted therapies such as amino acid depletion (e.g. asparginase, methionine restriction), inhibitors of stress adaption (AMPK and GCN2 inhibitors) or energy metabolism (e.g. IACS-010759, Metformin, POMHEX) stand to dramatically increase in potency whilst remaining selective for (angiogenic) tumor versus (non-angiogenic) normal tissue. Here, we provide proof-of-principal for this thesis. First, we performed metabolomic profiling of angiogenesis-inhibited tumors, which corroborates a state of nutrient stress in angiogenesis-inhibited tumors. Second, we demonstrate dramatic anti-neoplastic synergy (effectively curing of xenografted tumor-bearing mice, irrespective of initial tumor size), without enhanced adverse toxicities, between the OxPhos inhibitor IACS-010759 and the angiogenesis tyrosine kinase inhibitor, Tivozanib. The same results were recapitulated with the anti-VEGFA antibody, Avastin, and the OxPhos inhibitor could be substituted with the Enolase inhibitor HEX, with similar effects. The synergy was observed in a broad range of tumor types, even those without clear genetic susceptibilities. Together, these results suggest that angiogenesis inhibitors synergize broadly with cancer therapies targeting metabolism, allowing the realization of the full potential of these previously disappointing drugs. Our results warrant systematic combination clinical trials between angiogenesis inhibitors and established, as well as emerging anti-metabolic cancer therapies.

OMRT-8. PRECISION TARGETING OF CELLULAR PATHWAYS WITH COMPLEMENTARY DIAGNOSTICS

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Precision medicine tailors treatment for each patient by identifying the molecular drivers of their disease. This can allow more effective tumour targeting, avoid harmful standard chemotherapeutic side-effects, and offer savings to the healthcare system through not treating patients who are unlikely to respond to a specific agent. Treatment regimes are usually designed by identifying DNA-level alterations and selecting drugs tailored to that mutation. However, cancer is not a one-pathway disease and not all patients with particular mutations will respond to treatment, while patients without canonical pathway-activating mutations are excluded from potentially life-saving treatment. To address this, we have developed a NanoString assay combining proteomic and transcriptomic profiles of 4 key actionable, cancer-related pathways (MAPK, PI3K, NFκB and JAK/STAT). We used RNA-Seq data from gold standard cell lines with defined pathway changes to identify minimal gene sets indicative of pathway activation, and integrated them with phospho protein measurements to generate a pathway activation score. The combined panel was run on isogenic cell lines as well as glioma samples with both known and unknown driving alterations. We found pathway activation to be more variable than expected based on DNA alterations alone, implying that consideration of proteomic and/or transcriptomic-level information is important for future therapeutic decision-making.

OMRT-9. EFFECT OF PRE-OPERATIVE STEREOTACTIC RADIOSURGERY ON BRAIN METASTASIS: ANALYSIS OF DNA AND RNA GENOMIC PROFILES FROM PHASE-II CLINICAL TRIAL NCT03398694

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BACKGROUND: With improved systemic therapy that has limited impact on the intracranial compartment, the incidence of brain metastasis (BM) from solid cancers is rising and negatively impacting patient's overall survival (OS). Treatment varies based on presentation, however, for patients with <4 symptomatic BMs current clinical practice involves surgical resection followed by stereotactic radiosurgery (SRS) to the resection cavity. Post-operative SRS is associated with increased risk of leptomeningeal disease (LMD) and local recurrence in the follow-up period. We hypothesize that pre-operative SRS will decrease the incidence of LMD as well as local recurrence and increase patient's OS by delivering a lethal dose of radiation to tumor cells before they are disturbed by surgical resection. In a Phase II clinical trial (NCT03398694) we are treating patients with 1–4 symptomatic BMs with pre-operative SRS while collecting DNA and RNA sequencing data from core and peripheral edges of the resected tumor to examine the genomic effects of SRS on tumor. METHODS: Post-SRS resected tumor specimens were divided into two groups: 'center' and