'periphery' with respect to the center of SRS treatment with periphery within 50% isodose line. Previously resected untreated BMs were used as control. DNA and RNA were isolated from all samples for sequencing. CONCLUSIONS: Our initial analyses show that pre-treatment with SRS, results in significant genomic changes at DNA and RNA levels throughout the tumor, in both center as well as periphery. Furthermore, significant transcriptomic differences were noted among matched samples between the central and peripheral SRS locations implicating differential effect of SRS dosing within a tumor. Initial gene ontological analysis on non-small cell lung cancer samples demonstrated an overexpression of WNT and BMP signaling pathways ($p < .001$, $p < .01$). These pathways are typically involved in neuronal development, hinting that adaptation to the brain microenvironment was occurring post SRS treatment.

OMRT-11. THE EFFECT OF MICROENVIRONMENT ON GLIOBLASTOMA STEM CELLS THERAPEUTIC RESISTANCE

Tamara Lah Turnsek[1,2], Barbara Breznik[1], Bernarda Majc[2,3], Metka Novak[1], Andrej Porčnik[3], Anamarija Habič[1,2], Mateja Mlinar[1], Roman Bošnjak[4]; [1]National Institute of Biology, Ljubljana, Slovenia. [2]The Jožef Stefan International Postgraduate School, Ljubljana, Slovenia. [3]Department of Neurosurgery, University Medical Centre, Ljubljana, Slovenia. [4]Department of Neurosurgery, University Medical Centre Ljubljana, Ljubljana, Slovenia

Epithelial-to-mesenchymal transition (EMT) is an essential molecular and cellular process in physiologic processes and invasion of various types of carcinoma and glioblastoma (GBM) cells. EMT is activated and regulated by specific endogenous triggers in complex network of intercellular interactions and signaling pathways. The hallmark of cancer-linked EMT are intermediate states that show notable cell plasticity, characteristic of cancer stem cells (CSCs), including glioblastoma stem cells – GSCs. GSCs resistance to irradiation (IR) and temozolomide (TMZ) chemotherapy is responsible for early relapses, even at distant brain sites. As GSCs are mostly homing to their "niches" as slowly-dividing GSC-subtype, mimicking a proneural-like non- invasive phenotype PN-genotype, we assume that this, by undergoing an EMT-like transition, GSCs are-reprogrammed to an invasive mesenchymal (MES) GBs/GSCs phenotype in a processes, called PMT (1). However, it is not known, if and by which environmental cues within the niche, this transition of GSCs is induced in vivo. In this work, we are presenting the transriptome data obtained when we exposed GSC spheroids to irradiation alone, TMZ alone and to the combined treatment *in vitro* and compared their differential genetic fingerprints related to EMT/PMT transition to the GSCs PMT transition, when embedded in their natural microenvironment in the GBM organoid model. The differential gene expression upon GSCs therapeutic perturbation (when alone and *vs* in the tumoroid microenvironment) will reveal the effects of the major candidate genes, associated with micronevironmendt stromal cells and matrix are contributing their observed EMT/PMT transition of GSCs in vivo.

•1. Majc, B., Sever, T., Zarić, M, Breznik, B., Turk, B, Lah Turnšek, T. Epithelial- to-mesenchymal transition as the driver of changing carcinoma and glioblastoma microenvironment. DOI: 10.1016/j.bbamcr.2020.118782

OMRT-12. NANOPARTICLE-BASED CRISPR-CAS9 DELIVERY FOR ANTI-GLIOBLASTOMA IMMUNOTHERAPY

Rocio Aguilar, Javier Fierro, Joshua Perez, Huanyu Dou; Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

Anti-glioblastoma GBM) immunotherapy poses a great challenge due to immunosuppressive brain tumor environments and the blood brain barrier (BBB). Programmed death ligand 1 (PD-L1) is an immune checkpoint that mediated the immune resistance. Inhibition of PD-L1 by antibodies was widely studied to treat many type of cancers. However, the inefficient therapeutic immune response became a significant barrier for treatment of GBM. CRISPR/Cas9 gene editing can be used to knockout both membrane and cytoplasmic PD-L1, leading to an enhanced immunotherapeutic strategy. It is extremely difficulty to deliver CRISPR/Cas9 containing plasmid for translational and clinic applications. We have been developed a core-shell nanoparticle (NP) to carry CRISPR/Cas9 plasmid for PD-L1 knockout. The different NP formulations were made and optimized to deliver CRISPR/Cas9 plasmid. NPs were prepared by modifying the water temperature, sonication power and time and formulation time. The obtained NPs had a size of 115-160nm and a charge of 40-50mV. The size and charge were significantly altered after CRISPR/Cas9 plasmids were loaded into NPs (Cas9-NPs). Agarose gel electrophoresis showed that CRISPR/Cas9 plasmids were fully encapsulated by NPs with 1 and 2 ug. The positive DNA bands occurred with 4ng, indicating the overloaded CRISPR/Cas9 plasmid. Fluorescence microscopy determined Cas9-NPs uptake by U87 cells under a time-dependent manner. GFP tagged Cas9-NPs were treated to U87 cells for transfection evaluation. The obtained different NPs delivery of CRISPR/Cas9 exhibited various transfection efficiencies in U87 cells. Visualization of intracellular Cas9-NPs showed increases in uptake by U87 cells from 0.5, 1, 2, and 4 hours. The greater nuclear accumulation of Cas9-NPs was seen at 24 hours. A western blot assay determined the success of PD-L1 deletion by Cas9-NPs in human GBM U87 cells. NPs-based CRISPR/Cas9 gene-editing system has great potential as an immunotherapeutic platform to treat GBM.

OMRT-13. DELIVERY OF UBIDECARENONE (BPM 31510) TO MITOCHONDRIA EFFECTUATES METABOLIC REPROGRAMMING AND REDOX ACTIVATED APOPTOSIS IN GLIOBLASTOMA

Rangaprasad Sarangarajan[1], Seema Nagpal[2], Jiaxin Sun[2], Anne Diers[1], Punit Shah[1], Vladimir Tolstikov[1], Gregory Miller[1], Vivek Vishnudas[1], Stephane Gesta[1], Michael Kiebish[1], Elder Granger[1], Niven Narain[1], Lawrence Recht[2]; [1]BERG, Framingham, MA, USA. [2]Department of Neurology and Clinical Neurosciences, Stanford University, Palo Alto, CA, USA

GBM is a highly metabolic cancer phenotype that confers sustained growth and evasion of cell death mechanism via mitochondrial dysregulation. Efforts to re-engage mitochondrial metabolism via anti-cancer therapeutics has not been successful. BPM 31510 is a CoQ10-lipid conjugate nanodispersion for delivery of CoQ10 preferentially to mitochondria of human cells. BPM has demonstrated anti-cancer effects across multiple cancers, without adversely affecting normal tissue. The anti-cancer mechanism of CoQ10 was elucidated by Interrogative Biology, a data-driven approach to understand disease biology, identify targets and biomarkers of disease. Specifically, oncogenic and corresponding non-disease normal cell-based models (e.g. breast, liver, prostate, kidney) were subjected to cancer specific perturbations (e.g. hypoxia, metabolic stress). Comprehensive multi-omic (genome, proteome, lipidome, metabolome) and functional endpoints data were profiled. A Bayesian artificial intelligence analytics was used to generate network models in a data driven manner to identify BPM 31510 mechanism (i.e. shift in oxygen and glucose utilization, increase in oxidative stress and apoptosis in cancer cells). BPM 31510 re-capitulated its anti-cancer effect in GBM models, including LN-229 xenograft and C6 glioma allograft, both as monotherapy and in combination with temozolomide (TMZ)/radiation. The platform generated network maps from longitudinal pharmacodynamic samples (20 samples/28 days) collected from GBM patient refractory to TMZ/radiation/bevacizumab (Phase 1, NCT03020602, Stanford) identified alterations in intermediary metabolism as drivers of Progression Free Survival (PFS) and Overall Survival (OS) in response to BPM 31510 treatment. The platform supports the ongoing Phase 2 trial of adjuvant BPM 31510 plus TMZ/radiation in newly diagnosed GBM patients and potential accelerated approval.

OMRT-14. SMALL MOLECULE CIRCADIAN CLOCK COMPOUNDS EXHIBIT POTENTIAL AS A NOVEL THERAPY PARADIGM FOR GLIOBLASTOMA

Priscilla Chan[1], Tsuyoshi Hirota[2], Meng Qu[1], Guoxin Zhang[3], Khalid Shah[4], Hiroaki Wakimoto[5], Theodore Kamenecka[6], Laura Solt[6], Jeremy Rich[3,7], Steve Kay[1]; [1]University of Southern California, Los Angeles, CA, USA. [2]Nagoya University, Furocho, Chikusa Ward, Nagoya, Japan. [3]University of California, San Diego, La Jolla, CA, USA. [4]Harvard Medical School, Boston, MA, USA. [5]Massachusetts General Hospital Cancer Center, Boston, MA, USA. [6]Scripps Florida, The Scripps Research Institute, Jupiter, FL, USA. [7]University of Pittsburgh, Pittsburgh, PA, USA

Glioblastoma multiforme (GBM) is the most prevalent and aggressive primary brain tumor type, claiming the lives of patients within 2 years of diagnosis. The major challenges in treating GBM are largely due to the biological characteristics of the tumor and the brain and pharmacokinetics of many drugs approved for other cancers. These tumors are located in areas that make it difficult to surgically resect without posing major issues and exposure to many drugs and therapies are limited due to the blood-brain barrier (BBB). GBMs also contain cancer stem cells, called GSCs, that have self-renewal and tumor initiating abilities, can secrete angiogenic factors, invade into the normal brain, and are chemoresistant and radioresistant. We found that GSCs have an exclusive dependence on core circadian clock transcription factors, Brain and Muscle ARNT-Like 1 (BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK). These results suggest the potential for small molecule modulators of the circadian clock as a novel therapy paradigm for GBM treatment following surgical resection to prevent GSC infiltration and reoccurrence of the primary tumor. Here we found that multiple classes of clock compounds (Cryptochrome (CRY) stabilizers, REV-ERB agonists, Casein Kinase 1 (CK1) inhibitors, and Casein Kinase 2 (CK2) inhibitors) have the ability to elongate circadian periods in a clock reporter cell line. They also selectively and potently target patient-derived GSCs that range in sensitivity to temozolomide (TMZ) chemotherapy treatment while having limited effects on control cells both as single agents and in combination with each other. This data provides a platform for further exploration of synergistic effects of combining clock compounds with each other or with current GBM therapies, such as chemotherapy and radiation, with the ultimate goal of developing a clinical model of treatment.