metastatic tissue samples as well as a lack of clinically relevant models. As such, it is possible that the inability to properly study this disease may result in metastasis driver-genes remaining undiscovered. Typical models of BM utilize direct implantation of tumor cells into the mouse brain, or inoculation into the blood *via* intracardiac/intracarotid injections; these routes are invasive and cannot fully recapitulate the entirety of the metastatic cascade. Here we present a novel, non-invasive method to develop primary lung tumors and brain metastases. A 10μL tumor cell suspension in phosphate-buffered saline was applied to the nostrils of lightly anesthetized mice, allowing direct deposit of cells into the lungs. Mice were monitored with bioluminescence imaging bi-weekly and culled at 2.5–3 months post-inoculation. Lungs and brains were also removed and imaged, where tumors in both organs were observed. Further research is necessary to elucidate either the linear or parallel progression of tumor formation within this model. Nonetheless, our technique presents a novel preclinical tool to interrogate the metastatic process, allowing validation of genetic drivers as well as therapeutic screening.

TMOD-25. GLIOBLASTOMA ORGANOIDS: A MODEL SYSTEM FOR PATIENT-SPECIFIC THERAPEUTIC TESTING

Ryan Salinas[1], Daniel Zhang[2], Fadi Jacob[2], Phuong Nguyen[2], Saad Sheikh[1], Stefan Prokop[1], Jay Dorsey[1], MacLean Nasrallah[1], Steven Brem[1], Donald O'Rourke[1], Guo-li Ming[2], and Hongjun Song[2]; [1]University of Pennsylvania, Philadelphia, PA, USA, [2]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Glioblastoma treatment options remain limited due to its aggressive and invasive nature. It is increasingly appreciated that molecular heterogeneity between tumors and within tumors likely contributes to the lack of therapeutic advances. To maintain the inherent heterogeneity of glioblastoma, we employed a novel method to rapidly culture glioblastoma organoids (GBOs) directly from neurosurgical resection. GBOs are routinely generated around two weeks following initial resection. Comprehensive histologic and sequencing analyses demonstrated similarity to primary tumors. Leveraging clinical molecular and sequencing data, selected GBOs were treated with radiation/temozolamide and targeted inhibitor therapies. The effect on proliferation was measured by the percentage of KI67+ cells and gene set enrichment (GSEA) analysis was performed to compare the pre-treated expression signature amongst responsive and non-responsive tumors. Treatment of organoids with radiation/temozolamide led to a decrease in the percentage of KI67+ cells in four of eight patient-derived organoid lines with some evidence of correlative radiographic response Gene sets associated with radiation response and TNF signaling were enriched in radiation/temozolamide sensitive GBOs. GBO response to EGFR inhibition via gefitinib treatment was specific to EGFR altered tumors, whose expression also enriched for EGF signaling pathway expression. Two GBOs had downstream NF1 mutations that responded to the MEK inhibitor trametinib. On GSEA, gene expression of NF1 mutated GBOs enriched for RAS signaling. One GBO line was found to have a PI3K mutation and responded dramatically to mTOR inhibition via everolimus. Dichotomous efficacy of MEK and mTOR inhibition was also noted by tumor-specific changes in GBO diameter following treatment. This novel culturing method of GBOs maintains intertumoral and intratumoral heterogeneity and allows for therapeutic testing within two weeks of neurosurgical resection. As clinical sequencing because increasingly prevalent, GBOs may become a valuable tool to functionally test mutation-specific treatment strategies in a patient-specific manner within a clinically relevant time frame.

TMOD-26. MODELING GLIOBLASTOMA BY IMPLANTATION OF INTACT PATIENT-DERIVED ORGANOIDS INTO RODENT BRAINS

Phuong Nguyen, Fadi Jacob, Ryan Salinas, Daniel Zhang, Hongjun Song, and Guo-li Ming; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Glioblastoma multiforme (GBM) is the most common primary and aggressive brain tumors in adults with extremely poor prognosis and limited treatment options. A major hallmark of GBM is the rapid and diffused infiltration of tumor cells into the surrounding healthy tissue that contribute to tumor recurrence and therapeutic resistance. However, existing *in vitro* cell culture or *in vivo* xenograft models inadequately recapitulate the inter-tumoral and intra-tumoral heterogeneity which are key features of GBM. For example, common oncogenic drivers of GBM such as epidermal growth factor receptor (EGFR) amplification and EGFRvIII mutation do not persist in traditional *in vitro* models due to selection pressures, thus requires exogenous overexpression. Alternatively, EGFR statuses can be maintained in xenografted mice, but implantation of the primary GBM cells into the flank is required to first establish the tumor prior to secondary injection into the brains. Recently, we have established a novel protocol for culturing GBM tissue as organoids (GBOs) directly from patient tumor resection that retain many distinct cell populations *in vitro* with high fidelity evidenced by histological, whole-exome, bulk and single cell RNA analyses. Compared to prolonged generation time of previously established *in vitro* and xenograft models, our methodology is robust for generating GBOs within 1–2 weeks from initial resection. In addition, these GBOs can be readily xenografted into the adult mouse brains as an intact organoid, exhibit rapid and aggressive infiltration phenotypes, and maintains driver mutation EGFRviii within as little as one month. Consequently, they can be used to test *in vivo* treatment efficacies in a timely fashion. The presence of diverse cell types in this GBO model offers a promising platform for not only understanding of tumor biology, but also more strategic development of new therapies.

TMOD-27. A NEURAL CREST CELL SUBPOPULATION UNDERLIES INTRATUMOR HETEROGENEITY IN MENINGIOMA

Stephen Magill[1], Harish Vasudevan[1], Kyounghee Seo[1], S. John Liu[1], Stephanie Hilz[2], Javier Villanueva-Meyer[1], Abrar Choudhury[1], Benjamin Demaree[1], Daniel Lim[1], Steve Braunstein[1], Nancy Ann Oberheim-Bush[1], Erik Ullian[3], Manish Aghi[1], Philip Theodosopoulos[2], Patricia Sneed[1], Adam Abate[1], Mitchel Berger[1], Mike McDermott[1], Joseph Costello[2], and David Raleigh[1]; [1]University of California, San Francisco, San Francisco, CA, USA, [2]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA, [3]Ophthalmology, San Francisco, CA, USA

BACKGROUND: Meningiomas are the most common primary intracranial tumor, and high grade meningiomas are resistant to most cancer therapies. Intratumor heterogeneity is a recognized source of resistance to treatment in numerous malignancies. Thus, we hypothesized that investigating molecular heterogeneity in meningiomas would elucidate biologic drivers and shed light on tumor evolution and mechanisms of resistance. METHODS: We collected 86 spatially distinct samples at the time of resection from 13 meningiomas. Seven meningiomas were WHO grade I (46 samples), three were grade II (22 samples), and three were grade III (18 samples). Seven meningiomas were sampled at the time of salvage surgery (48 samples), and 6 were sampled at the time of initial diagnosis (38 samples). We performed multiplatform molecular profiling of these samples to identify drivers of intratumor heterogeneity, and validated our results using meningioma cells co-cultured with human cerebral organoids and RNA sequencing of paired primary and recurrent meningiomas. RESULTS: Using bulk RNA sequencing, DNA methylation profiling and phylogenetic analysis of spatially distinct samples, we discovered significant transcriptomic, epigenomic and genomic heterogeneity in meningioma. In particular, we identified chromosomal structural alterations and differences in immune and neuronal signaling that underlie clonal evolution in high grade tumors. Using MRI-stratified bulk RNA sequencing, single nuclear RNA sequencing, RNA sequencing of paired primary and recurrent meningiomas, and live cell microscopy and single cell RNA sequencing of meningioma cells in co-culture with human cerebral organoids, we revealed a rare meningioma cell subpopulation with strong transcriptional concordance to the neural crest, a multipotent embryonic tissue that forms the meninges in development. CONCLUSIONS: These data suggest that misactivation of a developmental cell population underlies intratumor heterogeneity in meningioma and that expression of neural crest and immediate early genes are an important step in meningeal oncogenesis.

TMOD-28. AUTHENTIC HUMAN GLIOMA MODELING USING GENETICALLY ENGINEERED INDUCED PLURIPOTENT STEM CELLS

Tomoyuki Koga[1], Isaac Chaim[2], Sebastian Markmiller[2], Jorge Benitez[3], Alison Parisian[3], Shunichiro Miki[3], Florian Hessenauer[3], Kristen Turner[3], Sriram Venneti[4], Denise Malicki[5], Robert Wechsler-Reya[6], Paul Mischel[3], Clark Chen[1], Gene Yeo[2], and Frank Furnari[3]; [1]Department of Neurosurgery, University of Minnesota, Minneapolis, MN, USA, [2]Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA, USA, [3]Ludwig Cancer Research at UCSD, La Jolla, CA, USA, [4]University of Michigan, Ann Arbor, MI, USA, [5]Rady Children's Hospital San Diego, San Diego, CA, USA, [6]Sanford Burnham Prebys Medical Research Discovery Institute, La Jolla, CA, USA

Many mouse and human glioma models have been utilized to study the genetic alterations involved in the genesis of these tumors, but they have not been fully evaluated for how closely they recapitulate pathobiology, including tumor heterogeneity, which is an inherent feature making patient treatment difficult. Here we present new glioma models using genetically engineered human pluripotent stem cells, in which authentic pathobiology is recapitulated through precision gene editing. Specifically, we show that neural progenitor cells (NPCs) derived from human induced pluripotent stem cells (iPSCs), with different combinations of genetic drivers introduced by CRISPR/Cas9-mediated editing give rise to distinct intracranial tumors recapitulating authentic pathobiology of the disease when engrafted in immunocompromised mice. NPCs deficient in *PTEN* and *NF1*, a genotype associated with the mesenchymal molecular subtype, and NPCs deficient in *TP53* and expressing a *PDGFRA* activating mutation (*PDGFRAΔ8–9*), a genotype associated with the proneural glioblastoma molecular subtype,

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