Tyr3-Octreotide and demonstrates its value of fluorescent identification of meningioma cells in vivo. Furthermore, the authors established a new experimental animal model for fluorescence meningioma surgery.

OS06.6A INHIBITION OF GBM INVASION BY THE A-AMINO-3-HYDROXY-5-METHYL-4-ISOXAZOLEPROPIONIC ACID (AMPA) GLUTAMATE RECEPTOR ANTAGONIST PERAMPANEL

K. Sarnow[1], G. Kanli[2], O. Keunen[2], R. Bjerkvig[1,3] [1]University of Bergen, Bergen, Norway, [2]Quantitative Biology Unit, Luxembourg Institute of Health, Luxembourg, Luxembourg, [3]NorLux Neuro-Oncology Laboratory, Department of Oncology, Luxembourg Institute of Health, Luxembourg, Luxembourg.

BACKGROUND: Extensive tumor cell invasion within the brain represents a major problem for effective treatment of glioblastomas (GBMs). The invasive processes can be divided into three types: Collective cell invasion, perivascular infiltration and single-cell invasion into the brain parenchyma. It has recently been shown that GBM cells have the ability to form synapses with neural cells pointing at an extensive communication network between brain cells GBM cells. This communication network can be mediated via the metabolites glutamine and glutamate both needed for GBM cell proliferation. In this context, it has been shown in preclinical models that Perampanel, an antiepileptic agent, functioning as non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, has an inhibitory effect on GBM growth. In order to delineate how Perampanel affects GBM invasion, we here utilised a highly characterized 3D GBM-brain organoid invasion model where single-cell invasion was studied in real-time following Perampanel treatment. MATERIAL AND METHODS: A brain coculture model, consisting of rat brain organoids expressing various markers of the human adult brain, where confronted with GFP-labelled tumor cells. By using time-lapse confocal microscopy, we quantified single-cell invasion patterns and speed of invasion using two glioma stem cell models (GSCs; BG5 and BG7). RESULTS: Perampanel treatment significantly reduces tumor cell invasion into the brain organoids with the strongest effect seen in the most invasive GBM (BG5). Here, the single-tumor cell invasion ratio was reduced by 72 % compared to the control group (p=0.0033). In contrast, collective cell invasion was reduced by 19 % (p=0.028). Statistical analysis was performed using an unpaired sample t-test. CONCLUSION: The AMPA glutamate receptor antagonist Perampanel significantly inhibits GBM invasion, suggesting an important role of the glutamate-glutamine cycle between the GBM cells and neurons in the invasion process. Moreover, this communication and exchange of metabolites seems to be more prominent where single GBM cells invade into the brain parenchyma compared to areas where collective invasion take place.

OS06.7A METPLATFORM IDENTIFIES BRAIN METASTASIS VULNERABILITIES AND PREDICTS PATIENT RESPONSE TO THERAPY

L. Zhu[1], C. Blanco-Aparicio[1], L. Bertero[2], R. Soffietti[2], T. Weiss[3], J. Muñoz[1], J. Sepúlveda[4], M. Weller[3], J. Pastor[1], M. Valiente[1] [1]Spanish National Cancer Research Center, Madrid, Spain, [2]University and City of Health and Science Hospital, Turin, Italy, [3]University Hospital Zurich, Zurich, Switzerland, [4]Hospital Universitario Doce de Octubre, Madrid, Spain.

BACKGROUND: The diagnosis of brain metastasis involves high morbidity and mortality and remains an unmet clinical need in spite of being the most common tumor in the brain. Exclusion of these cancer patients from clinical trials is a major cause of their limited therapeutic options. MATERIAL AND METHODS: We report a novel drug-screening platform (METPlatform) based on organotypic cultures which allows identifying effective anti-metastasis agents in the presence of the organ microenvironment. We have applied this approach to clinically relevant stages of brain metastasis using both experimental models and human tumor tissue (by performing patient-derived organotypic cultures - PDOCs -). We have also used METPlatform to perform unbiased proteomics of brain metastases *in situ* to identify potential novel mediators of this disease and explore resistance mechanisms to targeted therapy. Finally, we have exploited METPlatform as "avatars" to predict response to therapy in patients with primary brain tumors. RESULTS: We identified heat shock protein 90 (HSP90) as a promising therapeutic target for brain metastasis. DEBIO-0932, a blood-brain barrier permeable HSP90 inhibitor, shows high potency against mouse and human brain metastases from different primary origin and oncogenomic profile at clinically relevant stages of the disease, including a novel model of local relapse after neurosurgery. Furthermore, *in situ* proteomic analysis of brain metastases treated with the chaperone inhibitor revealed non-canonical clients of HSP90 as potential novel mediators of brain metastasis and actionable mechanisms of resistance driven by autophagy. Combined therapy using HSP90 and autophagy inhibitors showed synergistic effects compared to sublethal concentrations of each monotherapy, demonstrating the potential of METPlatform to design and test rationale combination therapies to target metastasis more effectively. Finally, we show that brain tumor PDOCs predict the response of the corresponding patient to standard of care, thus proving the potential of METPlatform for improving personalized care in cancer. CONCLUSION: Our work validates METPlatform as a potent resource for metastasis research integrating drug-screening and unbiased omic approaches that is fully compatible with human samples and questions the rationale of excluding patients with brain metastasis from clinical trials. We envision that METPlatform will be established as a clinically relevant strategy to personalize the management of metastatic disease in the brain and elsewhere.

OS06.9A DIVERSITY OF CELLULAR COMMUNICATION IN GLIOBLASTOMA

K. Joseph, L. Vollmer, V. M. Ravi, J. Beck, U. G. Hofmann, O. Schnell, D. H. Heiland University Medical Center, Freiburg, Freiburg, Germany.

BACKGROUND: Owing to recent advances in understanding of the active functional states exhibited within glioblastoma (GBM), intra-tumoral cellular signaling has moved into focus of neuro-oncological research. In our study, we aim to explore the diversity of transcellular signaling and investigate correlations to transcriptional dynamics and cellular behavior. MATERIAL AND METHODS: Electrophysiological mapping of primary GBM cultures was performed by planar microelectrodes, in conjunction with calcium imaging in a human neocortical section based GBM model. Exposure to conditions that are physiologically present within the tumor was carried out to identify specific signaling cells of interest and signaling diversity presented as response to specific environmental conditions. Transcriptional dynamics and plasticity were examined by means of scRNA-sequencing with CRISPR based perturbation, spatial transcriptomics and deep long-read RNA-sequencing. RESULTS: Electrophysiological profiles of primary GBM cell lines revealed highly variable network activity. Despite these different characteristics, all profiled primary cell-lines exhibited characteristics of scale-free networks, confirmed in a human neocortical GBM model. When the GBM was allowed to grow in "*in-vivo*" like environment, basal activity was significantly increased, owing to interactions with elements within the neural environment. Cellular signaling was directly correlated to changes in the environment, like hypoxia or glutamatergic activation, and total inhibition of electrical signaling was achieved only with a combination of both gap junction and synaptic inhibitors. Using single-cell sequencing and proteomics, we identified several genes related to synaptogenesis that plays a crucial role in network formation and consequently transcellular signaling. CRISPR based perturbation of these genes resulted in alterations in cellular morphology and decreased cellular connectivity, with electrical signaling being significantly attenuated. Single-cell sequencing of perturbed tumor cells in the GBM model revealed a loss of developmental lineages and significant reduction of cellular stress response state. CONCLUSION: Our findings highlight the role of electrical signaling in glioblastoma. Cellular stressors induce intercellular signaling, leading to transcriptional adaptation suggesting that there exists a highly complex and powerful mechanism for dynamic transcriptional state adaptation.

OS07 COGNITION IN BRAIN TUMORS REVISITED: NEW TECHNOLOGIES TO IMPROVE OUTCOME

OS07.5A DIAGNOSTIC INSTRUMENT FOR MILD APHASIA (DIMA): SENSITIVE AND VALUABLE ADDITION TO STANDARD LANGUAGE ASSESSMENT IN GLIOMA PATIENTS

S. Mooijman[1], A. Vincent[1], E. De Witte[1,2], E. Visch-Brink[1], D. Satoer[1] [1]Department of Neurosurgery, Erasmus MC University Medical Centre, Rotterdam, Netherlands, [2]Centre for Linguistics, Clinical and Experimental Neurolinguistics, Free University, Brussels, Belgium.

BACKGROUND: Low-grade glioma (LGG) patients typically suffer from mild aphasia that often cannot be detected with standard aphasia tests. The Diagnostic Instrument for Mild Aphasia (DIMA) is the first standardized test-battery to assess mild language disorders. We investigate pre- and postoperative linguistic abilities of LGG and high-grade glioma (HGG) patients with the DIMA. METHODS: The DIMA consists of subtests that tap *phonology* (word, compound, non-word, sentence repetition), *semantics* (odd-picture-out), and *syntax* (sentence completion). Additionally, we administered the *B*oston *N*aming *T*est, Category- and Letter Fluency, and the *T*oken *T*est. Patients were assessed before awake surgery (*T1*, N=98), three-months (*T2*, N=69), and one-year (*T3*, N=30) postoperatively. DIMA performance was compared to healthy controls (N=214). Group differences were examined with parametric (t-test) and nonparametric (Mann-Whitney-U, Wilcoxon) tests. RESULTS: *DIMA*: Preoperatively, patients deviated on sentence repetition and sentence completion ($p<0.05$). HGG patients performed worse than LGG on word, non-word, and sentence repeti-