2nd ANNUAL CONFERENCE ON CNS CLINICAL TRIALS AND BRAIN METASTASES, CO-SPONSORED BY SNO AND ASCO

Submission Categories and Abbreviations:
BSCI - Basic Science
CLRM - Clinical Research Methods
SPIN - Innovations in Spinal Tumors
LOC - Local Therapies
MMAP - Multimodality Approaches
NEM - Neuroimaging
SPCR - Supportive Care
SYST - Systemic Therapeutics

FINAL CATEGORY: BASIC SCIENCE

BSCI-01
INTRATEHCAL DELIVERY OF DENDRITIC CELL VACCINE ERADICATES TUMOR GROWTH AND PROTECTS AGAINST LEPTOMENINGEAL DISEASE (LMD) RE-INOCULATION IN IMMUNOCOMPETENT HER2+ AND TRIPLE NEGATIVE BREAST CANCER (TNBC) LMD XENOGRAFT MODELS

Vincent Law1, Kenneth Kodumudi2, Colin Sorrell1, Bezn Czerniecki3, Peter Forsyth, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

BACKGROUND: LMD occurs in ~5% of patients with breast cancer (BC) and has a median survival of 2-4 months. We found a loss of the anti-HER2 and anti-HER3 CD4 Th1 immune responses in BC patients. In pre-clinical and clinical trials the administration of class II HER2 peptide-pulsed dendritic cell vaccine (HER2-DCCV) partially restores anti-HER2 Th1 immune responses with pathologic complete responses in HER2+ BC patients. Here, we examined the intrathecal (IT) delivery of HER2/HER3-DCCV in BC-LMD immunocompetent animal models. MATERIALS AND METHODS: Luciferase-labeled HER2+ TUBO BCs were injected into the cisterna magna of BALB/c mice to produce LMD. We used our Murine Ommaya (mimics an Ommaya reservoir clinically in patients) for the IT administration of DCVs into the cerebral spinal fluid (CSF). RESULTS AND DISCUSSION: BC-LMD mice were randomized into following groups: 1) HER2-DCCV IT 2) HER3-DCCV IT 3) HER2/HER3-DCCV IT. The median survival of untreated (control) group was 15 days. All groups given DCCV IT prolonged survival (p<0.001). Interestingly, HER2-/HER3-DCCV IT was able to rescue disease mice (71% in HER2+ BC-LMD and 28% in TNBC-LMD) and showed complete tumor regression. Some surviving mice were immune to subsequent tumor rechallenge. In mice CSF, we found the presence of CD4+ and CD8+ T-cells, and robust IFN- gamma and IL18 response upon DCCV treatment. Collectively, this suggests IT delivery of DCCV elicits immune response in CSF targeting LMD. CONCLUSION: Our preclinical data supported a clinical trial (submitted) of the IT delivery of DCCV in BC patients with LMD.

BSCI-02
CSF PROTEOMICS AS A MINIMALLY INVASIVE STRATEGY FOR DISTINGUISHING BRAIN METASTASES FROM OTHER PRIMARY BRAIN MALIGNANCIES

Alierra Mansouri1, Nicholas Nikolajewicz2, Shabab Khan3, Michael Glantz4, Jason Moffat5, Gielrach Zeled6, Thomas Kistlinger7, 1Penn State Cancer Institute, Hershey, PA, USA; 2University of Toronto, Toronto, ON, Canada; 3University Health Network, Toronto, ON, Canada

BACKGROUND: Accurate diagnosis and prognostication of intra-axial brain tumors hinges on invasive brain sampling, which carries risk of morbidity. Minimally invasive sampling of proximal fluids, also known as liquid biopsy, can mitigate this risk. Although the cerebrospinal fluid (CSF) is the ideal liquid biopsy source, the traditionally high volumes required for meaningful analysis have deterred progress. The objective of this study was to identify diagnostic and prognostic CSF proteomic signatures in glioblastoma (GBM), brain metastases (BM), and central nervous system lymphoma (CNSL). METHODS: CSF samples were retrospectively retrieved from the Penn State Neuroscence Biorepository and profiled using shotgun proteomics with low sample volumes. Proteomic signatures were identified using machine learning classifiers and survival analyses. RESULTS: Using 30kD CSF volumes, we recovered 800 unique peptides across 73 samples [20 normal pressure hydrocephalus (NPH, non-tumor control), 22 GBM, 17 BM, and 14 CNSL]. Externally-validated proteomic-based classifiers identified malignancy with AUCROC of 0.94 and distinguished individual tumor entities from others with AUCROC ≥0.96. More clinically relevant triplex classifiers, comprised of just 3 peptides, distinguished individual tumor entities with AUCROC ≥0.90. Novel biomarkers were identified among the top classifiers, including TFT3 and CACNA2D2, and characterized using single-cell RNA sequencing data. Survival analyses validated previously implicated prognostic signatures, including blood brain barrier disruption. DISCUSSION: Reliable classification of intra-axial malignancies using low CSF volumes is feasible, which has ramifications for longitudinal tumor surveillance. Novel biomarkers identified here necessitate further validation. Based on emerging evidence, upfront implantation of CSF reservoirs in brain tumor patients warrants consideration.

BSCI-03
THE ROLE OF LONPI IN DRIVING ENHANCED PMT IN THE ‘LEADING EDGE’ NICHE IN GliOBLASTOMA

Christopher Douglas1, Naomi Lomeli, Daniela Bota; University of California, Irvine, CA, USA

Glioblastoma (GBM), a high grade brain tumor, possesses poor overall survival with less than 5% surviving past five years. Previously, the TCGA classifications for GBM have included the mesenchymal, proneural, classical and neural subtypes with their own respective expression profiles and survival. Recent omics analysis has revealed other key aspects of GBM pathology, including intratumoral heterogeneity spanning all subtypes and enhanced stemness and treatment resistance. We have observed these hallmarks of proneural mesenchymal transition (PMT) following treatment with first-line standard of care treatment with radiation therapy and temozolomide (TMZ). Invading glioma stem cells (GSC) with high Nestin and hypoxia-inducible factor 1 alpha (HIF-1α) expression have been theorized to contribute to recurrence. HIF-1α acts as a master regulator driving increased stemness, invasiveness and angiogenesis. Interestingly, HIF-1α and nuclear respiratory factor-2 both upregulate Lon peptide 1 (LonP1) in response to increased hypoxia or reactive oxygen species (ROS) production. LonP1 has been shown to drive increased metastasis, tumor growth and epithelial-mesenchymal transition (EMT), an analog of PMT, in colon cancer, melanoma and other cancer types. In a recently elucidated GBM organoid model, we present new findings demonstrating the importance of LonP1 in driving enhanced, transient PMT near the ‘invading edge’. This includes the enhanced expression of several key drivers of PMT and phenotypic hallmarks, such as increased invasiveness, proliferation and poorer survival.

BSCI-04
TARGETING THE PI3K-MTOR PATHWAY TO TREAT UBE2C-DRIVEN BRAIN METASTASES

Fenice Paivano1, Rita Cascão3, Carlos Custódia4, Nan Qien1,2,3, Daniel Picard1, David Pausch1, Eunice Carvalho2,3, Patricia Ruivo1, Rafael Roque1, José Pimentel1, Marc Remke0,2,3, João T. Barata3, Cláudia C. Faria4,5; 1Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal. 2German Cancer Consortium (DKTK), partner site Essen/Düsseldorf, Düsseldorf, Germany. 3Department of Pediatric Oncology, Hematology, and Clinical Immunology, Medical Faculty, Heinrich Heine University, University Hospital Düsseldorf, Düsseldorf, Germany. 4Laboratory of Neuropathology, Neurology Department, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisboa, Portugal. 5Department of Neurosurgery, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisboa, Portugal

Brain metastases (BM) are a devastating complication of advanced cancers associated with poor prognosis. Contrarily to the current improvement in systemic therapies, BMs are still incurable and one of the main causes of death in cancer patients. We analyzed BMs from thirty patients with various primary tumor origins by RNA sequencing and identified the upregulation of UBE2C, a gene involved in the correct transition from metaphase to

© The Author(s) 2022. Published by Oxford University Press, the Society for Neuro-Oncology and the European Association of Neuro-Oncology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc-nd/4.0), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com