Title
DDRE-50. INVESTIGATING THE ROLE OF LonP1 IN GLIOBLASTOMA TUMOR PROGRESSION

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Authors
Douglas, Christopher
Bota, Daniela
Di, Kaijun
et al.

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platin when tested in GBM cell lines *in vitro*. Platinum increased by using Pt(IV)-M13 when compared to cisplatin in our *in vitro* BBB-spheroid model (20-fold, p-value=0.0033), in brain tissue (10-fold, p< 0.0001) and GBM tumor-bearing mice models (7.5-fold, p< 0.0001). Bio-distribution of platinum delivered by Pt(IV)-M13 in spleen, heart and blood was significantly different to cisplatin 5hrs. after intravenous injection (p< 0.001). Bi-weekly dose regimes of Pt(IV)-M13 are tolerable in nude mice without toxicity at a similar concentration to reported tolerable cisplatin doses at 5 mg/kg. Finally, Pt(IV)-M13 significantly increased survival in a murine glioblastoma xenograft model compared with controls (median 24 days vs. 29 days, p-value=0.0071). CONCLUSION: Overall, our data support the further development of BBB-crossing peptide-drug conjugates for GBM treatment.

DDRE-48. COMPARTMENT LOCKED IL-12 - INCREASED TISSUE RETENTION AND MINIMAL PERIPHERAL EXPOSURE ALLOW HIGHER TREATMENT EFFICACY AND TOLERABILITY IN LOCAL GLIOBLASTOMA THERAPY

Michal Beffinger[1], Linda Schellhammer[1], Tala Shekarian[2], Sereina Deplazes[1], Ivan Zimmermann[3], Pascal Egloff[3], Thorsten Buch[1], Markus Seeger[3], Gregor Hutter[4], and Johannes Vom Berg[5]; [1]Institute of Laboratory Animal Science, University of Zurich, Schlieren, Zurich, Switzerland, [2]University Hospital Basel, Basel, Switzerland, [3]Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland, [4]University Hospital Basel and University of Basel, Basel, Switzerland, [5]University of Zurich, Schlieren, Zurich, Switzerland

Recent clinical studies in glioblastoma (GBM) highlight the potential of local IL-12 therapy, but they also bring back tolerability concerns due to leakage into the periphery. This leakage might thus hamper exploiting the full potential of local IL-12 therapy. Fusion with an IgG4 Fc portion increases the tissue retention of IL-12; but could also confer export into the blood and subsequent systemic recycling through the neonatal Fc receptor (FcRn), ultimately leading to potentially toxic IL-12 serum levels. We assessed the expression of FcRn in human and murine GBM and its role in IL-12Fc tissue retention and systemic exposure upon local delivery. Human or murine IL-12Fc was injected in GBM-bearing or naïve wt or FcRn-humanized mice continuously or as bolus via convection-enhanced delivery (CED). We screened combinations of amino-acid substitutions at the (IL-12)Fc:FcRn binding interface to abolish this interaction. Brain and blood concentrations were assessed via ELISA or cytokine bead arrays. FcRn affinity was measured by SPR/ELISA and bioactivity tested on PBMCs and human GBM explant cultures. Treatment efficacy and immunological correlates were assessed in GBM bearing mice. FcRn is upregulated in human and mouse GBM and contributes to brain export and subsequent peripheral recycling of IL-12Fc in the blood. IL-12Fc with abrogated FcRn binding due to a unique set of substitutions is fully functional and appears brain compartment locked (CL IL-12) as it exhibits enhanced tissue retention and reduced serum levels upon local injection, reaching up 100x higher brain to serum concentration ratios than regular IL-12. Compared to its non-modified counterpart, murine CL IL-12 shows significantly higher treatment efficacy at negligible systemic footprint in late stage murine GBM. In patient explant cultures, human CL IL-12 leads to successful inflammatory conditioning. Compartment locked IL-12 should thus allow a wide dosing window to fully harness its therapeutic potential for local GBM therapy.

DDRE-49. TRANSIENT OPENING OF THE BLOOD-BRAIN BARRIER BY VASOACTIVE PEPTIDES TO INCREASE CNS DRUG DELIVERY: REALITY VERSUS WISHFUL THINKING?

Matthew Smith-Cohn[1], Nicholas Burley[2], and Stuart Grossman[3]; [1]Johns Hopkins and the National Institutes of Health, Bethesda, MD, USA, [2]Sinai Hospital of Baltimore, Balitmore, MD, USA, [3]Johns Hopkins, Baltimore, MD, USA

BACKGROUND: Drug delivery to treat neurologic disease and cancers of the central nervous system (CNS) is severely limited by the blood-brain barrier (BBB). Vasoactive peptides (VAPs) such as regadenoson, adenosine, and labradimil have been shown in animal studies to transiently open the BBB, and regadenoson is currently under investigation in humans to determine if it might improve CNS drug delivery. There is currently limited information regarding the potential for other VAPs to open the BBB transiently. METHODS: We performed a review of the literature evaluating the physiologic effects of vasoactive peptides on the vasculature of the brain and systemic organs. To assess the likelihood that a vasoactive peptide might transiently disrupt the BBB, we devised a four-tier classification system to organize data available in the literature which factors in alterations in BBB integrity and effects on normal brain vasculature and systemic blood vessels. This data was further sorted based on whether it comes from humans, animals, or in vitro systems. RESULTS: We identified 38 VAPs with potential BBB permeability-altering properties. To date, none of these has been shown to open the BBB in humans. Thirteen VAPs increased BBB permeability in rodents. The remaining 25 had favorable physiologic effects on blood vessels but lack specific information on permeability changes to the BBB. We ranked VAPs in a four-tier ranking system related to their known physiologic actions. CONCLUSION: Rodent studies document that analogs of bradykinin and adenosine transiently disrupt the BBB leading to higher chemotherapy concentrations in the CNS. VAPs remain an understudied class of drugs with the potential to increase drug delivery to the CNS. Dozens of VAPs have yet to be formally evaluated for this important clinical effect. This retrospective review summarizes the available data on VAPs highlighting agents that deserve further *in vitro* and *in vivo* investigations.

DDRE-50. INVESTIGATING THE ROLE OF LONP1 IN GLIOBLASTOMA TUMOR PROGRESSION

Christopher Douglas[1], Daniela Bota[2], Kaijun Di[1], Bhaskar Das[3], and Javier Lepe[1]; [1]University of California, Irvine, Irvine, CA, USA, [2]Department of Neurology, University of California, Irvine, Irvine, CA, USA, [3]Long Island University, Bronx, NY, USA

Glioblastoma (GBM), a WHO grade IV brain cancer, exhibits strong treatment resistance and a high rate of reoccurrence, which gives it a dismal prognosis, a 5% survival rate in the first 5 years. LonP1, a mitochondrial master regulator, can drive metabolic transformation, cytokine production, EMT, and treatment resistance in various cancer types, but its role in GBM remains unexplored. Our research group has previously shown that LonP1 is overexpressed in human malignant gliomas, particularly glioblastoma, and that this is associated with disease prognosis. Here, we present findings that demonstrate that LonP1 seems to drive enhanced tumor progression, invasiveness, angiogenesis in different high grade glioblastomas based on TCGA-subtype. Furthermore, in collaboration with Professor Bhaskar Das, we have validated a lead compound, BT317, with on-target inhibition of LonP1 protease activity. BT317 has enhanced activity against glioma stem cell lines (GSC) and has demonstrated low toxicity and efficacy in an intracranial xenograft model. This preliminary data highlights the potential of using combinatorial, pharmacological LonP1 and proteasome inhibition as a novel strategy for targeting specific subtypes of GBM.

EPIDEMIOLOGY & BIOSTATISTICS

EPID-01. THE EPIDEMIOLOGY OF BRAIN METASTASES IN ADOLESCENT AND YOUNG ADULT (AYA) PATIENTS DISTINCTLY DIFFERS FROM THE ADULT POPULATION

Nayan Lamba[1], and Bryan Iorgulescu[2]; [1]Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA, [2]Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, MA, USA

INTRODUCTION: Few data exist regarding the epidemiology of brain metastases (BMs) in adolescent and young adult (AYA) patients. Herein we use national cancer registry data to dissect their epidemiology and compare to the adult population. METHODS: AYA patients ($15 \leq age \leq 39$) who newly presented with a BM between 2010 and 2017 were identified in the National Cancer Database (comprising >70% of all newly-diagnosed cancers in the U.S.). The epidemiology of BMs was analyzed by primary cancer of origin, and compared between AYA and adult patients. Overall survival was analyzed with multivariable Cox regression. RESULTS: 2,773 AYA patients presenting with BMs were identified (98% with histopathological diagnosis), compared to 156,103 adult patients (94% with histopathological diagnosis). Whereas 39.6% of newly-diagnosed brain tumors with histopathological confirmation were BMs in adults, BMs represented only 5.8% of such tumors in AYA patients. Additionally, the distributions of primary cancer types differed substantially between adults and AYA patients: notably, NSCLC dominated in adults (64.2%) vs representing only 31.6% of BMs in AYA patients. AYA patients were more likely to present with BMs from melanoma (13.0% of AYA BMs vs 3.7% in adult), soft tissue (4.5% vs 0.3%), testicular (in males 26.2% vs 0.1%), and breast (in females 29.5% vs 7.8%) primaries. Among breast BMs in females, AYA patients were less likely to have HR+/HER2- primaries (40.2% vs 47.8%) and more likely to have HER2+ (25.2% vs 20.1%) and triple positive (11.1% vs. 9.8%) primaries than adults. Overall survival was significantly longer for AYA patients with BMs (HR=0.61 compared to adult patients, 95%CI:0.58-0.64, p< 0.001) even after adjusting for primary cancer type, patient sex. CONCLUSIONS: The epidemiology and cancer types of BMs in AYA patients differ substantially from adult patients. Future research aimed at understanding the unique differences in pathophysiology and outcomes of BMs in AYA patients is warranted.