BRAIN BARRIERS RESEARCH CENTER
(BBRC)
INAUGURAL SYMPOSIUM

Drug Delivery to the Brain:
Rationale, Resources, Collaboration

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Wednesday, October 26, 2016
10:00 AM to 5:00 PM
The Commons Hotel, Minneapolis
Meridian Ballroom

The objective of this symposium is to stimulate collaboration across various departments and institutions on issues related to brain barriers, especially the blood-brain barrier (BBB), that interconnect both central nervous system (CNS) drug delivery and CNS pathophysiology.

INTRODUCTION AND KEYNOTE

10:00-10:10 **Dr. William Elmquist, Distinguished Professor**
University of Minnesota, Department of Pharmaceutics
Introduction to the Symposium and the Brain Barriers Research Center (BBRC)

10:10-10:40 **Dr. Les R. Drewes, Professor**
University of Minnesota Duluth, Department of Biomedical Sciences
Overview of the Neurovascular Unit (NVU)

10:40-11:40 Keynote Presentation
Dr. Eric Shusta, Howard Curler Distinguished Professor
University of Wisconsin-Madison, Department of Chemical and Biological Engineering
The Blood-Brain Barrier: An Obstacle and an Opportunity

11:40-1:00 **Lunch, Poster Presentations, and Networking**

BRAIN BARRIERS AND BRAIN TUMORS

1:00-1:20 **Dr. Jann Sarkaria, Professor**
Mayo Clinic Rochester, Translational Neuro-Oncology Laboratory
The Blood-Brain Barrier is Disrupted in All GBM: Debunking the Myth

1:20-1:40 **Dr. William Elmquist, Distinguished Professor**
University of Minnesota, Department of Pharmaceutics
Blood-Brain Barrier Transport and Drug Delivery/Efficacy in Primary and Metastatic Tumors in the Brain

1:40-2:00 **Dr. Ben Hackel, Assistant Professor**
University of Minnesota, Department of Chemical Engineering and Materials Science
Engineering Synthetic Ligands for Molecular Imaging and Therapy

2:00-2:15 **Break**

BRAIN BARRIERS AND NEUROPATHOPHYSIOLOGY

2:15-2:35 **Dr. Aaron Johnson, Associate Professor**
Mayo Clinic Rochester, Departments of Immunology and Neurology
Contribution of Dendritic Cells and Macrophages in Eliciting CD8 T Cell Responses to Brain Tumors

2:35-2:55 **Dr. Carolyn Fairbanks, Professor**
University of Minnesota, Department of Pharmaceutics
Central Nervous System Delivery of Gene Therapeutics

2:55-3:15 **Dr. Karunya Kandimalla, Associate Professor**
University of Minnesota, Department of Pharmaceutics
Blood-Brain Barrier Dysfunction: A Critical Determinant of Alzheimer's Disease Pathophysiology

3:15-4:00 **Break, Poster Presentations, and Networking**

IMAGING AND MODELING OF BRAIN BARRIERS

4:00-4:20 **Dr. Silvia Mangia, Associate Professor**
University of Minnesota, Center for Magnetic Resonance Research, Department of Radiology
Imaging the Neurovascular Unit with Magnetic Resonance Imaging (MRI)

4:20-4:40 **Dr. Samira Azarin, Assistant Professor**
University of Minnesota, Department of Chemical Engineering and Materials Science
Stem Cell-Based Models of the Human Blood-Brain Barrier

4:40-5:00 **Dr. David Odde, Professor**
University of Minnesota, Department of Biomedical Engineering
Mechanics of Cell Migration in the Brain

5:00 **Closing Remarks**

POSTER PRESENTERS

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1) **Grant Anderson, Associate Professor and Department Head**
University of Minnesota Duluth, Department of Pharmacy Practice and Pharmaceutical Sciences
Iron Deficiency During Brain Development Alters the Developing Cerebrovasculature

2) **Poulami Barman, Senior Statistician**
Xiaojia Tang, Research Fellow
Krishna Rani Kalari, Associate Professor
Mayo Clinic Rochester, Department of Health Sciences Research, Division of Biostatistics and Bioinformatics
Blood Brain Barrier Response to Insulin Exposure — Genomics and Proteomics Perspective

3) **Paige Borst, Graduate Student**
University of Minnesota Medical School Duluth, Department of Biomedical Sciences
Monocarboxylate Transporter 1 Deficiency Genetic Testing and Clinical Manifestation

4) **Kristina Burrack, Post-Doctoral Fellow**
University of Minnesota, Department of Laboratory Medicine and Pathology
IL-15 Complex-Stimulated NK Cells Protect Mice from Cerebral Malaria

5) **Les Drewes, Professor**
University of Minnesota Duluth, Department of Biomedical Sciences
Brain Barrier Research Center (BBRC): A Multidisciplinary Approach to Advancing Brain Barriers Research

6) **Gautham Gampa, Graduate Student**
University of Minnesota, Department of Pharmaceutics
Active Efflux and Brain Delivery of Novel pan-RAF Inhibitors

7) **Minjee Kim, Graduate Student**
University of Minnesota, Department of Pharmaceutics
Antitumor Activity of SAR405838, an MDM2 Inhibitor, in the Brain is Limited by Delivery Across the BBB

8) **Janice Laramy, Graduate Student**
University of Minnesota, Department of Pharmaceutics
Implications of Tissue-Differential Binding and Distribution of Ponatinib, a Multi-Kinase Inhibitor, for the Treatment of Brain Tumors

9) **Patricia Maglalang, Undergraduate Student**
University of Minnesota, Department of Chemistry
A Diazepam Prodrug/Enzyme Combination for Treatment of Seizure Emergencies: Pharmacokinetics Following Intranasal Administration in Rats

10) **Courtney Malo, Graduate Student**
Mayo Clinic Rochester, Department of Immunology
A Critical Role for Dendritic Cells in Priming a Robust Anti-Glioma CD8 T Cell Response

11) **Abhijit Nirwane, Post-Doctoral Associate**
Xuanming Zhang, Undergraduate Student
University of Minnesota Duluth, Department of Pharmacy Practices and Pharmaceutical Sciences
The Role of Pericytic Laminin in Blood-Brain Barrier Integrity Maintenance

12) **Davin Rautiola, Graduate Student**
University of Minnesota, Department of Pharmaceutics
High Supersaturation and Rapid Transcellular Permeation of Benzodiazepines Using Prodrugs

13) **Vidur Sarma, Graduate Student**
University of Minnesota, Department of Pharmaceutics
Alzheimer's Disease Amyloid Beta Peptides Inhibit Insulin Signaling/Trafficking at the Blood-Brain Barrier

14) **Suresh Swaminathan, Researcher**
University of Minnesota, Department of Pharmaceutics
Insulin Differentially Affects the Distribution Kinetics of Alzheimer's Disease Abeta Peptides in Plasma and Brain

POSTER 1 ABSTRACT

Iron deficiency during brain development alters the developing cerebrovasculature

Thu An Nguyen, Carl E. Anderson, and Grant W. Anderson
University of Minnesota Duluth, Department of Pharmacy Practice and Pharmaceutical Sciences

Objective: Iron deficiency anemia (IDA) is a global health problem with profound effects on pregnant women and young children. IDA largely impacts the developing brain, leading to poor cognitive outcomes. We recently demonstrated that iron deficiency induces vasculogenesis in the developing neonatal rat brain. Our current hypothesis is that neonatal iron deficiency activates hypoxia-inducible factor 1 alpha (Hif1-alpha) leading to induced expression of several genes associated with vasculogenesis.

Method: In this study, we assessed the impact of fetal and neonatal iron deficiency on the rat brain vasculature at birth, and postnatal days 7, 14 and 30. We assessed the protein levels of Hif1-alpha, the expression of genes associated with vasculogenesis, the expression of endothelial cell marker genes, and vascular density in the developing brain.

Results: mRNA analyses revealed increases in endothelial cell marker and vasculogenesis associated gene expression in the iron deficient neonatal rat brain at birth, and postnatal days 7 and 14. Iron repletion on postnatal day 7 normalized mRNA levels by postnatal day 14. Western Blot densitometry results indicated a possible increase in Hif1-alpha expression in iron deficient brains compared to control at postnatal days 7 and 14. Immunohistochemical assessment of vascular density revealed significant increases in density at postnatal day 14 in the iron deficient brain.

Implication: Our data reveal that iron deficiency induces vasculogenesis throughout late brain development. These findings raise the possibility that nutrient and drug delivery across the blood-brain barrier may be altered in the face of developmental iron deficiency

POSTER 2 ABSTRACT

Blood Brain Barrier response to insulin exposure — Genomics and proteomics perspective

Xiaojia Tang[1*], Poulami Barman[1*], Suresh K. Swaminathan[2], Vidur Sarma[2], Val J. Lowe[3], Karunya K. Kandimalla[2], and Krishna R. Kalari[1]

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Background: The Blood Brain Barrier (BBB) is a monolayer of endothelial cells lining the brain capillaries. The BBB nourishes brain parenchyma by transporting glucose and growth factors like insulin that are critical for brain function, and serves as a main signaling portal between the cerebral vasculature and neuronal tissue. The BBB also protects brain by blocking the entry of harmful substances from blood and shielding the brain from peripheral fluctuations in hormones, fatty acids, and electrolytes. Owing to the physiological importance of the BBB, and the role cerebrovascular dysfunction plays in the pathogenesis of several neurological diseases, including the Alzheimer's disease, substantial effort has been invested in investigating the BBB physiology in health and disease. However, the currently available in-vivo and in-vitro BBB models do not provide a sufficient landscape to study its complex molecular mechanisms. Polarized monolayers of human cerebrovascular endothelial cells (hCMEC/D3) described in the current work serves as one such *in vitro* model that can be easily cultured and manipulated in the lab. Thus, far, the genomic data for hCMEC/D3 cell lines have been generated using array-based approaches. With the advancement in next generation sequencing technology, our study provides deep RNA sequencing, microRNA sequencing, protein and phosphoprotein data of human BBB, thus, unveiling the full potential of systems biology approaches to resolve cellular and molecular interaction networks that regulate the functional integrity of the BBB. We have also made our database publicly available in BBBomics hub that encompasses coding (gene expression, alternate splice forms, and expressed single nucleotide variants -eSNVs) and non-coding (microRNA, LincRNA, circular RNA) counts and are in the process of analyzing protein and phosphoproteins for hCMEC/D3 cell lines. Our BBBomics database is publically available at http://bioinformaticstools.mayo.edu/bbbomics/.

Materials and Methods: We have recently treated five hCMEC/D3 cell lines with insulin. RNA-Seq data were obtained for paired control and insulin treated BBB cell lines at 10 min, 20 min, 40 min, 180 min and 300 min time points. RNA was extracted from the 10 samples and sequenced with Illumina HiSeq 2000. The RNA-Seq data were processed using RNA-Seq pipeline for read alignment (against human genome hg19) and gene expression characterization. Gene expressions of the 5 time-series paired insulin treated and control samples were normalized through CQN (conditional quantile normalization) method. The difference between treated/control paired samples for each gene was calculated to identify possible response patterns to the insulin treatment, the time-series profile of expression changes of genes were clustered with Short Time-series Expression Miner (STEM). For each significant cluster, GO enrichment test was performed.

Results and Conclusions: We have identified 11 significant gene clusters (p-value < 0.05) through the expression changing profile at 5 time points. GO enrichment analysis on genes clustered in early response pattern revealed that neurological system process that response to stimulus, G-protein coupled receptor signaling pathway and neurogenesis were activated. Although not significant, vesicle transportation and synaptic vesicle exocytosis were associated with early response of insulin. Further analysis of genomic and proteomic landscapes in BBB cell lines are being conducted.

MCT-1 GENTAC
MONOCARBOXYLATE TRANSPORTER 1 DEFICIENCY GENETIC TESTING AND CLINICAL MANIFESTATION

Seth Heikkila, Paige Selvey, and Lester R. Drewes
Department of Biomedical Sciences, University of Minnesota Medical School Duluth

Abstract: Monocarboxylate Transporter 1 (MCT1, SLC16A1) is a proton-coupled membrane transporter protein (Figure 1). It is essential for transport of lactate, pyruvate, ketone bodies and other monocarboxylates across the plasma membrane. Only two genetic causes of recurrent ketoacidosis are currently known. They are Succinyl CoA Oxoacid Transferase (SCOT) deficiency and Mitochondrial Acetoacetyl-CoA Thiolase (ACAT1) deficiency. Both of these inborn errors are metabolism would result in ketoacidosis symptoms. MCT-1 deficiency, as being explored in this study, has plausibility to be another genetic cause. Our primary objective is to characterize MCT-1 deficiency in the context of the phenotypes/symptoms listed. Secondly, we will explore whether or not MCT-1 is a prototype for other brain barrier transport deficiencies such as the case with ACAT1 and SCOT.

POSTER 4 ABSTRACT

IL-15 complex-stimulated NK cells protect mice from cerebral malaria

Kristina S. Burrack, Sara E. Hamilton, and Stephen C. Jameson
University of Minnesota Department of Laboratory Medicine and Pathology

Abstract: Cerebral malaria (CM) is one of the most lethal complications of *Plasmodium falciparum* infection, responsible for a large fraction of the roughly 500,000 malaria-related deaths annually. Infection of susceptible mouse strains such as C57BL/6 with *Plasmodium berghei* ANKA (PbA) induces a fatal neurological syndrome from 6-10 days post-infection (dpi) that recapitulates many aspects of the human disease. We found that prophylactic or therapeutic treatment of C57BL/6 mice with interleukin (IL)-15 complexes (IL-15C; IL-15 bound to an IL-15Rα-Fc fusion protein) prevented the development of PbA-induced CM. Rescue from CM was not associated with reduced parasitemia levels on day 6 pi but was associated with reduced edema in the CNS. IL-15C treatment stimulates natural killer (NK) cells and CD8 T cells. Interestingly, adoptive transfer of IL-15C-stimulated NK cells, not CD8 T cells, prevented CM. IL-15C treatment resulted in reduced CD8 T cell activation and cytokine production in the brain at 6 dpi, suggesting that IL-15C-stimulated NK cells limit the CD8 T cell-mediated pathology in CM. Indeed, following IL-15C treatment, a large subset of NK cells in the spleen, blood, and brain produced the immunoregulatory cytokine IL-10. These data indicate that NK cells – which are typically involved in promoting inflammatory responses – can restrain damaging immune responses. A mechanistic understanding of CM pathogenesis and the process of cytokine complex perturbation will provide an important foundation for the identification of new therapeutic targets and aid in the development of adjunctive therapies for treating severe malaria.

POSTER 5 ABSTRACT

Brain Barrier Research Center (BBRC): A Multidisciplinary Approach to Advancing Brain Barriers Research

William Elmquist, Lester Drewes, Karunya Kandimalla, Matthew Hunt, Yao Yao, Grant Anderson, et al.
University of Minnesota College of Pharmacy and Medical School

Purpose: The mission of the Brain Barriers Research Center (BBRC) is to improve delivery of therapy to the CNS and enhance the treatment of brain disorders by fostering interdisciplinary brain barriers research. The Brain Barriers Research Center (BBRC) is a distinctive, cutting edge University of Minnesota research group involving members in the College of Pharmacy and the Medical School in the Academic Health Center (Duluth & Twin Cities).

We are dedicated to:

- Providing a research environment for leading scientists
- Sharing unique strategies within the scientific community
- Developing novel drug therapies
- Vigorously pursuing an academic research agenda
- Transferring scientific knowledge
- Designing and developing new medicines to benefit human populations worldwide
- Supporting the interaction of many disciplines and areas of study
- Creating a focal point for research

Current projects include:

- Brain tumor (primary, metastatic)
- Alzheimer's disease
- Stroke
- Muscle development/regeneration
- Epilepsy
- Anti-tumor drug development
- Parkinson's disease
- Nutrient transporter deficiency syndromes
- Brain vasculogenesis

POSTER 6 ABSTRACT

Active Efflux and Brain Delivery of Novel pan-RAF Inhibitors

Gautham Gampa[1], Karen Parrish[1], Minjee Kim[1], Ann Tuma[2], David Calligaris[3], Yuk Sham[4], Nathalie Agar[3], Jann Sarkaria[2], and William Elmquist[1]
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Purpose: Melanoma brain metastases (MBM) develop in up to 75% of patients with metastatic melanoma and are associated with a median overall survival of less than 6 months. The FDA has recently approved molecularly-targeted small molecule agents (e.g., vemurafenib, dabrafenib, trametinib and cobimetinib) and immune-modulators for the treatment of metastatic melanoma. However, development of resistance to small molecule therapy and restricted ability to distribute to the brain are key limitations to achieving a durable response. The recently developed pan-RAF inhibitors, capable of inhibiting all isoforms of RAF, have great potential in melanoma treatment and may also overcome the problem of resistance. However, the clinical efficacy of these agents for treating MBM, especially early micro-metastases, depends on their ability to get across the BBB and distribute throughout the brain at therapeutic levels. The purpose of the current study is to determine the distribution of pan-RAF inhibitors to the brain and determine mechanisms that may be responsible for limiting brain delivery.

Methods: In-vitro intracellular accumulation assays were performed for three pan-RAF inhibitors in MDCKII cells that overexpress human P-gp to determine substrate status. In-vitro drug potency assays were conducted using a melanoma cell line (M12) generated from patient MBM samples. Brain distribution studies were conducted in non-tumor bearing FVB wild-type (WT) and triple-knockout (TKO; Mdr1a/b(-/-)Bcrp1(-/-)) mice after oral doses of BRAFV600E inhibitors (25 mg/kg for vemurafenib, dabrafenib and PLX4720) or pan-RAF inhibitors (10 mg/kg for MLN2480 and LY3009120; 5 mg/kg for CCT196969). Plasma and brain samples were harvested one-hour post dose and the concentrations of drugs were determined by LC-MS/MS.

Results: The in-vivo brain distribution studies indicate that BRAFV600E inhibitors have limited distribution to the brain. Dabrafenib has better brain distribution among the three BRAFV600E inhibitors. Brain distribution of dabrafenib and vemurafenib improved in the TKO mice whereas that of PLX4720 is not altered in mice lacking P-gp and Bcrp. In-vitro potency assays indicate that the pan-RAF inhibitors are potent against the M12 melanoma cell line at low nanomolar concentrations. LY3009120 is the most potent of the three inhibitors. The results of the in-vitro intracellular accumulation assays indicate that pan-RAF inhibitors are not substrates of P-gp. The in-vivo brain distribution studies conducted after oral administration of pan-RAF inhibitors indicates that they have limited brain distribution. MLN2480 has better brain distribution among the three pan-RAF inhibitors. The brain concentrations of MLN2480 and LY3009120 were enhanced in TKO mice, whereas those of CCT196969 were not increased in mice lacking P-gp and Bcrp.

Conclusions: The brain delivery of the novel molecularly-targeted pan-RAF inhibitors is limited. They do not appear to be substrates of P-gp at the BBB based on the results of in-vitro intracellular studies and in-vivo brain distribution studies. Devising strategies to improve the brain delivery of the pan-RAF inhibitors, or suitable analogs of these agents, will be important to achieve durable enhancements in the treatment of melanoma brain metastases.

POSTER 7 ABSTRACT

Antitumor activity of SAR405838, an MDM2 inhibitor, in the brain is limited by delivery across the BBB

Minjee Kim[1], Gautham Gampa[1], Janice Laramy[1], Shuangling Zhang[1], Daniel J. Ma[2], Katrina K. Bakken[2], Brett L. Carlson[2], Nathalie Agar[3], Jann Sarkaria[2], and William F. Elmquist[1]
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Purpose: SAR405838, a recently developed and optimized inhibitor targeting MDM2-p53 interaction, has been shown to have strong anticancer activity in solid tumors. The CNS delivery of the compound is a crucial limitation in treating brain tumors. Therefore, the objective of the current study was to examine the brain distribution kinetics of SAR405838, and correlate the observed changes in delivery with its efficacy in glioblastoma (GBM) models.

Method: VEGFA overexpressed GBM cell line (G108) generated with lentiviral transduction with either an empty vector or a vector containing VEGFA transcript was used. Expression level of VEGFA was measured with Human VEGF Quantikine ELISA kit (R&D Systems). In vivo efficacy studies were performed with intracranial xenografts of patient derived glioblastoma cells. Mice were randomized and treated with placebo or SAR405838 (50mg/kg/d). Texas Red Images were obtained in tumor-bearing mice injected with Texas Red conjugated to 3kD dextran via tail vein. The plasma and brain samples were harvested at pre-determined time points after single oral dose of SAR405838 in wild-type (WT) and transgenic FVB mice including Mdr1a/b-/- (PKO), Bcrp1-/- (BKO), and Mdr1a/b-/-Bcrp1-/- (TKO). Steady-state samples were harvested after a 48-hour continuous infusion post intraperitoneal implantation of osmotic pump in mice. The concentrations in the samples were analyzed using LC-MS/MS.

Result: The level of VEGFA expression in G108 cell lines with VEGFA overexpression (G108-VEGFA) and with empty vector (G108-EV) was significantly different according to results from ELISA. The distribution of SAR405838 was much higher and homogeneous in G108-VEGFA based on the results of MALDI-Mass Spectrometry Imaging. The survival study with orthotopic mouse models showed a significant survival benefit in G108-VEGFA tumor bearing mice treated daily with 50mg/kg SAR405838 p.o. over empty vector group. Texas Red image showed that the integrity of BBB was disrupted in G108-VEGFA. Pharmacokinetic parameters and partition coefficients of brains were determined by full time course pharmacokinetic experiments. The half-lives in PKO and TKO were longer than in WT and BKO. The partition coefficients of brain (calculated by AUCbrain over AUCplasma) and brain to plasma ratio acquired from steady-state experiment showed that the accumulation of SAR405838 in the brain was much higher in PKO and TKO mice compared to WT and BKO mice.

Conclusion: Brain delivery of SAR405838is limited due to the active efflux by P-gp at the BBB. The survival studies conducted in orthotopic mouse models show that SAR405838 has great efficacy in GBM if the drug is sufficiently available in tumor as in VEGFA overexpressed models lacking an intact BBB. Drug delivery to the brain across the BBB is critical to have desired efficacy in intracranial tumors and efflux transporters at BBB play a significant role in limiting brain delivery. By understanding the mechanism by which drugs are being excluded from brain, we intend to find a way to overcome this barrier and find a better treatment for tumors located in the brain.

POSTER 8 ABSTRACT

Implications of tissue-differential binding and distribution of ponatinib, a multi-kinase inhibitor, for the treatment of brain tumors

Janice K. Laramy[1], Karen Parrish[1], Katrina K. Bakken[2], Brett L. Carlson[2], Ann C. Mladek[2], Dan J. Ma[2], Minjee Kim[1], Gautham Gampa[1], Jann N. Sarkaria[2], and William F. Elmquist[1]
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Purpose: Targeted drug delivery across the blood-brain barrier (BBB) is a major challenge in the treatment of malignant brain tumors, including glioblastoma (GBM). Ponatinib is a multi-kinase inhibitor known to inhibit oncogenic RET (Rearranged during Transfection) and platelet-derived growth factor (PDGFR alpha). The objectives of this study were to 1) evaluate preclinical efficacy of ponatinib in GBM patient-derived xenograft (PDX) mice and 2) quantitatively investigate the tissue binding and distribution of ponatinib in the brain and tumor.

Methods: Preliminary efficacy of ponatinib was tested in GBM patient-derived xenograft (PDX) mice (n=10) with an implanted flank or intracranial tumor, GBM6 that expresses RET and PDGFR alpha, after a daily oral dose. The efficacy end points were time to reach tumor volume exceeding 1500 mm3 for the flank study and time for survival for the orthotopic (intracranial tumor) study. The log-rank test was performed to compare the duration to reach the tumor volume or survival endpoints between the treatment and placebo groups. In a separate cohort (n=4-6) of GBM6 PDX mice, flank tumor was harvested on Day 104 after tumor implantation in order to measure drug concentrations in the plasma, brain, and tumor. In vivo pharmacokinetic assessment was conducted in wild-type and transgenic Bcrp1(-/-), Mdr1a/b(-/-), and Mdr1a/b(-/-)Bcrp1(-/-) FVB mice to investigate brain penetration of ponatinib. Plasma and brain samples were harvested at several time points after a single oral dose (30 mg/kg) or a steady-state intraperitoneal drug infusion (48 hours) in order to determine the steady-state brain-to-plasma ratio. Total drug concentrations in plasma, brain and tumor samples were determined by LC/MS. The unbound fractions of ponatinib in plasma, brain homogenate, and GBM6 flank tumor homogenate were determined using a rapid equilibrium dialysis device.

Results: Ponatinib significantly suppressed flank tumor growth compared to placebo (p-value =0.0012), demonstrating efficacy in the flank tumor. However, it lacked efficacy in the intracranial tumor (p-value= 0.42). The unbound fraction of ponatinib significantly differed between plasma (0.2%), brain homogenate (0.03%), and GBM6 flank tumor homogenate (0.11%). The unbound brain-to-plasma ratio (Kp,uu) was estimated to be 0.2 in the wild-type mice, and the unbound flank tumor-to-plasma ratio was 4.8 in the PDX mice. The tissue partition coefficient was 7.3-fold higher in the flank tumor compared to the brain, indicating drug distribution advantage in the flank tumor. Ponatinib was determined to be a substrate of the efflux transporters, P-gp and Bcrp, based on the in vivo pharmacokinetic experiments. The brain-to-plasma ratios (AUC ratio or steady-state concentration ratio) were about 16, 4, and 2- fold higher in Mdr1a/b(-/-)Bcrp1(-/-), Mdr1a/b(-/-), and Bcrp1(-/-) mice compared with the wild-type mice, respectively.

Conclusions: Ponatinib, a highly brain penetrating multi-kinase inhibitor, is effective in suppressing GBM6 flank tumor growth but not effective in the intracranial tumor. We observed the lower drug distribution and drug free fraction in the brain compared to the G6 flank tumor, which corresponds to the region-specific preclinical efficacy of ponatinib. Efflux transporters play a role in restricting brain drug disposition of ponatinib, so that increased brain partitioning of the drug is possible if efflux is reduced.

POSTER 9 ABSTRACT

A Diazepam Prodrug/Enzyme Combination for Treatment of Seizure Emergencies: Pharmacokinetics Following Intranasal Administration in Rats

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Rationale: Seizure emergencies (SE) are defined as either seizure clusters or episodes lasting at least 5 minutes. For the last 2 decades, rectal diazepam has been the mainstay of out-of-hospital SE management, but many older children and adults object to this mode of therapy. Development of intranasal (IN) diazepam (DZP) and midazolam (MDZ) formulations is underway. These products have the potential to offer safe, effective, and more socially acceptable treatment options. However, first generations IN therapies have limitations such as suboptimal rates of absorption, variable bioavailability, and reliance on organic solvents. Our group is developing a novel intranasal drug delivery system involving the synthesis of water-soluble benzodiazepine prodrugs that are admixed with converting enzymes at the time of administration. As a first iteration, avizafone (AVF), a water-soluble DZP prodrug, was synthesized and combined with Aspergillus oryzae protease (AOP), which rapidly converts AVF to DZP resulting in supersaturated concentrations of the active drug in the nasal mucosa. The aim of the present pilot study was to evaluate the pharmacokinetics (PK) of our system in rats.

Methods: Six rats received an intranasal (IN) dose of an admixture of AVF (1.6mg/kg, which is equivalent to 1.1mg/kg DZP) and AOP (3.6 Units) prepared just prior to administration. Three rats were sacrificed at 5 min post-dose and brain and blood samples were collected. Blood samples were also collected from the other animals at specified times ranging from 15 to 90 min post-dose. Plasma and brain DZP concentrations were measured by a validated HPLC-UV method. PK parameters were determined using non-compartmental analysis.

Results: The mean (± SD) maximum DZP concentration, 450 ng/mL (± 53.7 ng/mL), was attained at 5 min post-dose. Brain and plasma DZP concentrations at 5 min post-dose were similar with a mean brain to plasma ratio of 0.88 ± 0.08. Distribution volume, elimination half-life, and clearance were 5 L/kg, 40 minutes, and 5.4 L/hr/kg, respectively.

Conclusions: This pilot study demonstrates the feasibility of a novel delivery system as a rescue therapy. Following IN dosing of the water-soluble prodrug/enzyme combination, DZP concentrations were similar to those reported after a 1mg/kg intravenous DZP dose in rats (Paramjeet et al., Int J of Pharmaceutics, 2008). This indicates that a high percentage of the prodrug is converted to DZP and absorbed through the nasal mucosa. This prodrug/enzyme system obviates the need for organic solvents, hence reducing the risk of adverse effects. Further, the supersaturated DZP concentrations produced at the site of administration result in very rapid absorption, offering the potential of a faster onset of action. The ease of use and social acceptability of this alternative rescue therapy should result in a greater acceptability by patients leading to fewer emergency room visits and an improved quality of life. In future studies, we plan to characterize the safety and toxicity of DZP and MDZ prodrugs in rodents and, subsequently, their PK and efficacy in dogs with seizures.

Sources of Funding: Clinical and Translational Science Institute, Academic Health Center, and College of Pharmacy, University of Minnesota, American Epilepsy Society, and Epilepsy Foundation

POSTER 10 ABSTRACT

A critical role for dendritic cells in priming a robust anti-glioma CD8 T cell response following picornavirus vaccination

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Abstract: Vaccine strategies to treat central nervous system (CNS) cancers hold great promise. However, the mechanisms leading to generation of an immune response to CNS cancers are unclear. Specifically, the antigen presenting cell (APC) required to activate a CNS tumor antigen-specific T cell response is unknown. To address this question, we generated a novel cell-type specific deletion of the H-2Kb MHC I molecule in C57BL/6 mice. By deleting H-2Kb on proposed APCs, including dendritic cells (DCs), macrophages, and microglia, we can define which APCs are required to result in effective vaccination for the murine GL261-quad cassette glioma model, which expresses the chicken ovalbumin peptide SIINFEKL as a model antigen. We hypothesized that DCs are required for generation of a natural adaptive immune response to SIINFEKL, and that DC-specific deletion of H-2Kb would abrogate efficacy of a picornavirus vaccination encoding SIINFEKL. We assessed tumor burden and immune infiltration in GL261-quad cassette bearing mice that had a complete deletion of H-2Kb (CMV-cre Kb cKO), DC-specific deletion of H-2Kb (CD11c-cre Kb cKO), or littermate controls. We demonstrated that DC-specific deletion of H-2Kb increases the proportion of animals bearing gliomas, suggesting a role for DCs in induction of a natural anti-tumor immune response. Additionally, we determined that vaccination of CD11c-cre Kb cKO mice resulted in an intermediate level of efficacy as measured by immune infiltration and tumor size. Thus, DCs are critical for generation of a complete anti-glioma T cell response, but they are not the sole APC in the context of a CNS tumor. Importantly, because DCs are modulated by many standard-of-care therapies, understanding their role in anti-tumor responses in the CNS is critical for vaccine development. Furthermore, because DC-specific deletion of H-2Kb resulted in an intermediate phenotype, a critical future direction will address the role of other candidate APCs, including macrophages and microglia.

POSTER 11 ABSTRACT

The role of pericytic laminin in blood brain barrier integrity maintenance

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Abstract: Laminin, a major component of the basement membrane, plays an important role in blood brain barrier regulation. At the neurovascular unit, brain endothelial cells, astrocytes, and pericytes synthesize and deposit different laminin isoforms into the basement membrane. It has been shown that laminin α4 (endothelial laminin) regulates vascular integrity at embryonic/neonatal stage, while astrocytic laminin maintains vascular integrity in adulthood. Here, we investigate the function of pericyte-derived laminin in vascular integrity. Using a conditional knockout mouse line, we report that loss of pericytic laminin leads to hydrocephalus and BBB breakdown in a small percentage (10.7%) of the mutants. Interestingly, BBB disruption always goes hand-in-hand with hydrocephalus in these mutants, and neither symptom is observed in the rest 89.3% of the mutants. Further mechanistic studies show that reduced tight junction proteins, diminished AQP4 expression, and decreased pericyte coverage are responsible for the BBB disruption. Together, these data suggest that pericyte-derived laminin is involved in the maintenance of BBB integrity and regulation of ventricular size/development.

POSTER 12 ABSTRACT

High Supersaturation and Rapid Transcellular Permeation of Benzodiazepines using Prodrugs

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Purpose: Seizure emergencies, such as status epilepticus, can be life threatening and require immediate medical attention. The primary rescue medications to treat seizure emergencies are benzodiazepines (BZDs), most commonly intravenous (IV) lorazepam or rectal diazepam (DZP).1 However, the delivery routes for these BZDs are not ideal considering that a skilled caregiver must be present for IV administration and that there is social stigma associated with rectal administration. Intranasal delivery of BZD is a desirable alternative due to the rapid onset of therapeutic action and ease of administration. The low aqueous solubility of BZDs presents a challenge to formulating BZD nasal sprays without organic solvents. Herein we describe an enzyme/prodrug system that produces supersaturated aqueous solutions of BZDs and demonstrate the feasibility of co-administering the enzyme with the prodrug for intranasal delivery of DZP or midazolam (MDZ).2,3

Methods: Water soluble prodrugs of DZP (avizafone, AVF) and MDZ (MDZ-pro) were synthesized by derivatizing open ring forms of DZP and MDZ with lysine. Enzymes were screened for their ability to catalyze the hydrolysis of lysine from prodrug as well as their compatibility with epithelial cells. MDCKII-wt cell monolayers were used as a model for nasal epithelium in transwell assays to demonstrate the transcellular permeability of drug generated in situ. Prodrug and drug concentrations were monitored by HPLC.

Results: Aspergillus oryzae protease (AOP) was found to efficiently convert both AVF and MDZ-pro to their active constituents (AVF: KM = 3.38 ± 0.34 mM, Vmax = 0.518 ± 0.030 mM/min with 0.25 U/mL AOP and MDZ-pro: KM = 5.86 ± 0.83 mM, Vmax = 0.233 ± 0.022 mM/min with 4.0 U/mL AOP). MDCKII-wt cell monolayers exposed to AOP remained confluent. Clearance and permeability of MDZ across the monolayers were found to be CL = 0.11 ± 0.01 mL/hr and Papp = 2.65 x 10-5 cm/s. The MDZ-pro/AOP system showed greater than 25-fold increase in absorption rate across monolayers compared to saturated MDZ.

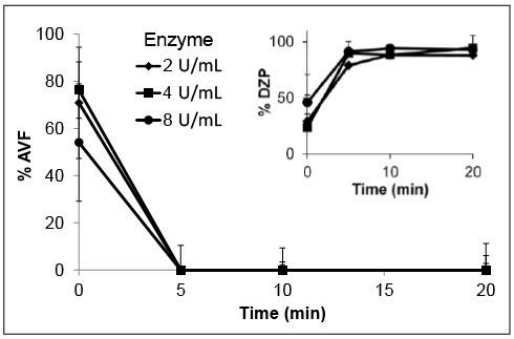

Figure 1. Complete conversion of 480 µM AVF by 2, 4, or 8 U/mL *AOP* at 32 oC pH 7.4 in less than 5 min (main), producing a supersaturated solution of DZP (inset).

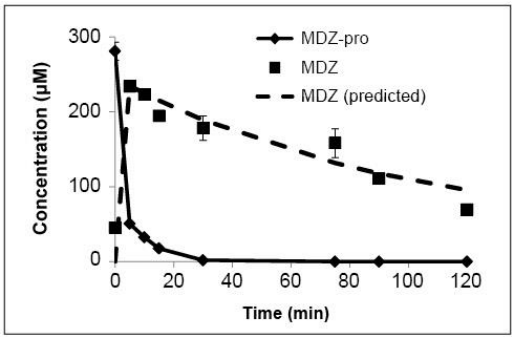

Figure 2. Rapid conversion of MDZ-pro to MDZ by 16 U/mL *AOP* in apical well of transwell assay. Predicted MDZ concentration based on two compartment model.

Conclusions: BZD prodrug co-administered with converting enzyme is a viable platform for the intranasal delivery of BZD. Furthermore, supersaturated DZP and MDZ generated enzymatically from prodrugs at the point of administration may be absorbed more rapidly than saturated formulations utilizing organic solvents.

References:

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POSTER 13 ABSTRACT

Alzheimer's disease Aß peptides impair the dynamics of insulin transport at the blood-brain barrier

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Purpose: Insulin levels in the brains of Alzheimer's disease (AD) patients are known to be significantly reduced compared to the brains of non-demented individuals of similar age. We have been investigating mechanisms triggering insulin scarcity in AD brains by employing transgenic mice (APP/PS1) and age-matched wild-type (WT) mice. Our in-vivo investigations led to the hypothesis that the brain uptake of insulin in APP/PS1 mice is inhibited by amyloid-beta peptides, primarily Aß40 and Aß42, which accumulate in AD brain as amyloid plaques. Appearance of systemic insulin in the brain parenchyma is contingent upon its transcytosis via the blood-brain barrier (BBB), which is mediated by insulin receptors (IR) expressed on the BBB endothelium. Since the exacerbation of AD pathology is associated with BBB dysfunction caused by the anomalous accumulation of Aß peptides, it was imperative to investigate the dynamics of the insulin transport process, as a function of Aß exposure.

Methods: Single-Photon Emission Computed Tomography (SPECT) was conducted to dynamically measure the rate of elimination and uptake of insulin from the brains of WT and APP/PS1 mice. Moreover, the permeability of insulin across the polarized human cerebral microvascular endothelial cell (hCMEC/D3) monolayers in the luminal-to-abluminal (L-A) or in the abluminal-to-luminal (A-L) directions was measured with and without Aß exposure. Next, the effect of Aß peptides on the insulin-mediated expression of IR on the hCMEC/D3 surface was imaged through Spinning Disc Confocal Microscopy. Further, Fluorescence Recovery After Photobleaching (FRAP) was employed to measure the lateral diffusion and exocytotic recycling capacity of IR in presence of Aß peptides.

Results: SPECT analyses revealed that the rate constants of uptake and clearance of insulin from the brains of APP/PS1 mice were significantly reduced as compared to WT mice. In hCMEC/D3 monolayers, the uptake and permeability of insulin was significantly inhibited in presence of Aß peptides. Confocal microscopy images demonstrated decreased expression of IR at hCMEC/D3 cell surface after pre-incubation with Aß40 and Aß42. Further, FRAP studies revealed that half-lives of insulin-mediated lateral diffusion and exocytotic mobility of IR in hCMEC/D3 were impaired following Aß40 and Aß42 pre-exposure.

Conclusion: Both in-vivo and in-vitro studies have shown that Aß peptides interfere with insulin trafficking at the BBB. These findings provide mechanistic evidence that Aß peptides inhibit insulin transport across the BBB and starve the brain tissue for insulin. Rectification of motifs resulting in impaired insulin trafficking at the BBB is critical to improving its transport into the brain parenchyma.

POSTER 14 ABSTRACT

Insulin Differentially Affects the Distribution Kinetics of Alzheimer's Disease Abeta Peptides in Plasma and Brain

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Background and Purpose: Impaired brain clearance of amyloid beta (Aß) peptides 40 and 42 is believed to be responsible for toxic amyloid accumulation in Alzheimer's disease (AD) brain. Blood-brain barrier (BBB) is one of the primary portals for Aß brain clearance. Hyperinsulnemia, which is prevalent in type II diabetes, was shown to damage cerebral vasculature and increase Aß accumulation in AD brain. However, there is no clarity on how aberrations in insulin levels impact cerebrovascular dysfunction, Aß distribution kinetics and consequently Aß accumulation in the brain.

Methods: Effect of peripheral insulin administration on the Aß distribution kinetics in plasma and brain was investigated in mice. Insulin-mediated alterations to the intraendothelial trafficking machinery were investigated in polarized hCMEC/D3 monolayers, a human BBB model.

Results: Upon peripheral insulin administration: i) the plasma clearance of Aß40 increased, and that of Aß42 reduced; ii) plasma-to-brain influx and brain accumulation of Aß40 increased, and that of Aß42 reduced; and iii) the clearance of intracerebrally injected Aß40 decreased, and Aß42 brain clearance increased. In the hCMEC/D3 monolayers exposed to insulin, plasma membrane distribution of the putative Aß receptors was affected and the intraendothelial trafficking of Aß peptides was altered.

Conclusions: This study demonstrates, for the first time, the existence of an intricate relation between plasma insulin levels and Aß transport at the BBB. Moreover, Aß40 and Aß42 demonstrate distinct distribution kinetics in plasma and brain compartments, and insulin differentially modulates the distribution of these peptides. This intricate homeostasis is most likely disrupted in cerebrovascular disease and metabolic disorders.

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