

**BIOMEDICAL & VETERINARY SCIENCES
GRADUATE PROGRAM**



ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Alison Cash

“Endothelial-targeted deletion of EPH receptor A4 ameliorates blood brain-barrier disruption and tissue damage by way of Tie2/Angiopoietin ”

Thursday, April 21st, 2022
9:00am
VetMed VMIA 220

Bio



I'm originally from northeast Ohio and have wanted to be a veterinarian since I was a child. I found a love for research, and more specifically, neuroscience after working in Parkinson's Disease and stroke research for the Cleveland Clinic Foundation. I plan to use my knowledge in biomedical and veterinary sciences in conjunction with a veterinary degree to pursue a government agency career investigating infectious zoonotic diseases. In my spare time, I enjoy doing anything outside like hiking or kayaking. And I like to relax by knitting, reading, or playing guitar.

Funded by

VMCVM Office of Research and Graduate Studies
NIH RO1 Grant

Lay Language Abstract

Traumatic brain injuries (TBIs) impact millions of individuals each year in the United States, making it a significant cause of death and disability. Furthermore, TBI has been linked to other comorbidities such as Alzheimers Disease, mood disorders, and epilepsy. Since the primary impact of a TBI cannot be predicted or prevented, research focuses on the secondary injury response as a therapeutic target to improve the outcomes following brain insult. Blood brain barrier (BBB) disruption is a well described consequence of TBI and has been correlated to a worse prognosis. The BBB normally provides a barrier between the circulating blood and the brain as protection and to maintain homeostasis. It is understood that decreased BBB integrity leads to subsequent edema, inflammatory response, and glial excitotoxicity, however, the mechanisms regulating this response remain to be investigated. Recent focus has been on a family of receptor tyrosine kinases, Eph receptors, that are unregulated following brain injury. Utilizing a mouse model, we can manipulate the temporal and spatial expression of Eph receptors to understand their role in the secondary injury cascade. Findings indicated that ablation of Eph receptors specifically on endothelial cells (ECs) resulted in preservation of BBB integrity at 1-, 4-, and 7- days following injury. Based on these results, we hypothesize that Eph receptor signaling on ECs negatively mediates BBB function and recovery following TBI. To test this hypothesis, we performed a comparative analysis between wild type (WT) and knockout (KO) mice on the expression of genes integral to BBB integrity, functional motor deficits, and loss of tissue in the lesion site following injury. We discovered significant decreases in lesion volume correlating with improvements in motor function in the KO mice compared to the WT. Moreover, KO mice showed increased expression of genes important for BBB maintenance such as Occludin and Tie2. To further discern the mechanism for these effects, we blocked Tie2 in the KO mice and observed similar negative prognostic indicators as in the WT. Future studies are warranted to understand the downstream signaling of Eph receptors on the Tie2 pathway. This data provides evidence that Eph signaling influences the BBB negatively following TBI through the Tie2 pathway and may be exploited for therapeutic means in the future.

Publications

Cash A, Brickler T, de Jager C, Johnson Z, Mills J, Ju J, Sotiropoulos Y, Chen M, Wang X, Xie H, Theus MH. Endothelial-targeted deletion of Eph receptor A4 ameliorates blood brain-barrier disruption and tissue damage by way of Tie2/Ang. PNAS. 2022 March.

Cash A, Theus MH. Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury. Int J Mol Sci. 2020 May 8;21(9):3344. doi: 10.3390/ijms21093344. PMID: 32397302; PMCID: PMC7246537.

Presentations

GSA Annual Research Symposium - *“Insights into a novel regulator of blood brain barrier dysfunction following traumatic brain injury”* VT 2020

National Capital Area Annual Traumatic Brain Injury Conference - *“Endothelial Cell-Specific Eph Signaling: A Novel Mediator of Blood Brain Barrier Disruption Following Traumatic Brain Injury”* Bethesda 2020

BMVS Annual Research Symposium - *“Endothelial Cell-Specific Eph Signaling: A Novel Mediator of Blood Brain Barrier Disruption Following Traumatic Brain Injury”* VMCVM 2019

NVSS Dual Degree Colloquium - *“Endothelial Cell-Specific Eph Signaling: A Novel Mediator of Blood Brain Barrier Disruption Following Traumatic Brain Injury”* VMCVM 2019

VT Neuroscience Summer Symposium - poster VT 2019

BMVS Research in Progress Seminar - *“Novel regulation of blood brain barrier disruption following traumatic brain injury”* VMCVM 2018

NVSS Dual Degree Colloquium - poster Texas A&M 2018

Awards and Academic Achievements

- Saul T. Wilson Jr. Internship and Scholarship - September 2021
- Bente Flatland Resident Award - January 2021
- Conan W. Vaughan Jr. Scholarship - November 2020
- Darlene Dill DVM Scholarship - November 2020
- Tyler J. and Frances F. Young Scholarship - August 2020
- First Place in GSA Annual Research Symposium Oral Presentation Category - April 2020
- Poster Presentation Award – National Capital Area TBI Conference - March 2019
- Invitation to the Society for Collegiate Leadership and Achievement - November 2019
- Honors Scholar in the field of Cancer Biology - April 2016
- Beta Beta Beta National Biological Honor Society Elected Historian and member - 2014-2016
- Choose Ohio First Scholar- awarded to Ohio colleges to exemplary students 2014-2016 in the STEMM fields
- Competitor Scholarship- written essay competition - 2012-2015

Examination Graduate Committee

Major Advisor/Chair:

Michelle H. Theus, PhD
Associate Professor - Molecular and Cellular Neurobiology
Department of Biomedical Sciences and Pathobiology

Graduate Advising Committee Members:

Alicia Pickrell, PhD
Assistant Professor
School of Neuroscience

Paul Morton, PhD
Assistant Professor - Neurodevelopment and Neurobiology
Department of Biomedical Sciences and Pathobiology

John Rossmeisl, DVM, MS, DACVIM
Interim Director, Animal Cancer Care and Research Center
Associate Department Head
Department of Small Animal Clinical Sciences



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