

**BIOMEDICAL & VETERINARY SCIENCES
GRADUATE PROGRAM**



ANNOUNCES

The Doctor of Philosophy Seminar and Examination of

Amanda D. Házy

**“Novel Immune-Regulatory Mechanisms in a Mouse
Model of Traumatic Brain Injury”**

Thursday, July 11th, 2019

1:00 pm

Life Sciences 1

Room 101

Bio



Amanda was born in upstate New York and lived in Illinois, Colorado, Vermont and Virginia before settling in Summit Point, West Virginia. She was homeschooled before attending Liberty University in Lynchburg, Virginia. Throughout high school and college, she served at small and large animal vet clinics as well as worked for a horseback riding and training facility in Virginia, developing a strong love of animals and veterinary medicine. At Liberty, she worked on Alzheimer's Disease research in the lab of Dr. Gary Isaacs, gaining experience in neuroscience and molecular genetics. After graduating from Liberty with a B.S. in Cell and Molecular Biology in May 2015, she entered the dual DVM/PhD program at VT in June 2015. As a member of the Theus Lab, she studied the peripheral immune response to traumatic brain injury and attended multiple local and national conferences, publishing several papers from her work under Dr. Theus. Amanda entered the first year of the DVM portion of the dual program in Fall 2018 and will complete the DVM in Spring 2022.

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VT Institute for Critical Technology and Applied Science (ICTAS)

VMCVM Office of Research and Graduate Studies

Lay Language Abstract

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States and worldwide. Following brain trauma, the blood-brain barrier, which normally excludes circulating immune cells from the brain, is compromised and these cells are able to infiltrate the area of injury. These cells can cause significant damage to brain tissue, and better understanding of this process is a critical research target. Our work demonstrates that the protein EphA4 is an important regulator of the circulating immune cell response to TBI. A mouse model lacking EphA4 in bone marrow cells (WTKOBMC) shows improved tissue recovery following TBI compared to mice with wild-type bone marrow cells (WTWTBMC) as well as decreased numbers of circulating cells entering the brain. WTKOBMC mice also show decreased numbers of activated macrophages and of Tie2⁺ immune cells entering the brain compared to WTWTBMC mice. In addition, immune cells that entered the injury area in WTKOBMC mice show a shift toward a pro-recovery gene expression pattern. Gene expression levels of the Tie2 protein and its Angiopoietin protein binding partners were also increased in these cells, indicating a key interaction between the Tie2/Angiopoietin pathway and EphA4. Further experiments with Tie2 inhibition in cultured wild-type macrophages compared to macrophages lacking EphA4 confirmed that the EphA4-Tie2 interaction helps to determine whether macrophages express pro-inflammatory or pro-recovery characteristics. Overall, our work has shown that EphA4 interacts with the Tie2/Angiopoietin pathway to regulate the circulating immune cell response to brain trauma and suggests that EphA4 offers a promising target for TBI therapeutics.

Publications

- A. Hazy**, L. Bochicchio, A. Oliver, E. Xie, S. Geng, T. Brickler, H. Xie, L. Li, I. C. Allen, M. H. Theus, Divergent age-dependent peripheral immune transcriptomic profile following traumatic brain injury. *Scientific reports* 9, 8564 (2019); published online EpubJun 12 (10.1038/s41598-019-45089-z).
- T. R. Brickler*, **A. Hazy***, F. Guilhaume Correa, R. Dai, E. J. A. Kowalski, R. Dickerson, J. Chen, X. Wang, P. D. Morton, A. Whittington, A. Ahmed, M. H. Theus, Angiopoietin/Tie2 Axis Regulates the Age-at-Injury Cerebrovascular Response to Traumatic Brain Injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **38**, 9618-9634 (2018); published online EpubNov 7 (10.1523/JNEUROSCI.0914-18.2018). [*co-first authors]
- T. Brickler, P. D. Morton, **A. Hazy**, M. H. Theus, Age-dependent responses in traumatic brain injury, in *Traumatic Brain Injury*, Nikolai Gorbunov, Ed. (InTech, 2018).
- M. H. Theus, T. Brickler, A. L. Meza, S. Coutermarsh-Ott, **A. Hazy**, D. Gris, I. C. Allen, Loss of NLRX1 Exacerbates Neural Tissue Damage and NF-kappaB Signaling following Brain Injury. *J Immunol* **199**, 3547-3558 (2017); published online EpubNov 15 (10.4049/jimmunol.1700251).
- B. Okyere, K. Giridhar, **A. Hazy**, M. Chen, D. Keimig, R. C. Bielitz, H. Xie, J. Q. He, W. R. Huckle, M. H. Theus, Endothelial-Specific EphA4 Negatively Regulates Native Pial Collateral Formation and Re-Perfusion following Hindlimb Ischemia. *PloS one* **11**, e0159930 (2016)10.1371/journal.pone.0159930).

Presentations

Poster: **Amanda Házy**, Thomas R. Brickler, Fernanda Guilhaume Correa, Rujuan Dai, Elizabeth J.A. Kowalski, Ross Dickerson, Jiang Chen, Xia Wang, Paul D. Morton, Abby Whittington, Ansar Ahmed and Michelle H. Theus. Angiotensin/Tie2 axis regulates the age-at-injury cerebrovascular response to traumatic brain injury. Virginia Tech Institute for Critical Technology and Applied Science Doctoral Scholars Spring Poster Session. Blacksburg, VA. April 2019.

Poster: **Amanda Házy**, Elizabeth Kowalski, Lauren Bochicchio, Michelle H. Theus. A Pro-inflammatory role for peripheral immune-specific EphA4 receptor following traumatic brain injury. Virginia Tech Institute for Critical Technology and Applied Science Doctoral Scholars Spring Poster Session. Blacksburg, VA. April 2018.

Poster: **Amanda Házy**, Elizabeth Kowalski, Lauren Bochicchio, Michelle H. Theus. A Pro-inflammatory role for peripheral immune-specific EphA4 receptor following traumatic brain injury. Central Virginia Chapter of the Society for Neuroscience Conference. Richmond, VA. March 2018.

Poster: **Amanda Házy**, Elizabeth Kowalski, Lauren Bochicchio, Michelle H. Theus. A Pro-inflammatory role for peripheral immune-specific EphA4 receptor following traumatic brain injury. VMCVM Research Symposium. Blacksburg, VA. March 2018.

Oral: **Amanda Házy**. A novel role for Eph signaling in immune-mediated neural injury following trauma. Virginia Tech Biomedical and Veterinary Sciences Research in Progress Seminar. Blacksburg, VA. October 2017.

Poster: **Amanda Házy**, Thomas Brickler, Benjamin Okyere, Daniel Rothschild, Irving C. Allen, Michelle H. Theus. Interrogating the role of peripheral-derived hematopoietic cells in tissue homeostasis following brain trauma. American Society for Neural Therapy and Repair Annual Conference. Clearwater Beach, FL. April 2017.

Poster: **Amanda Házy**, Thomas Brickler, Benjamin Okyere, Daniel Rothschild, Irving C. Allen, Michelle H. Theus. Interrogating the role of peripheral-derived hematopoietic cells in tissue homeostasis following brain trauma. Virginia Tech Institute for Critical Technology and Applied Science Doctoral Scholars Spring Poster Session. Blacksburg, VA. April 2017.

Poster: **Amanda Házy**, Thomas Brickler, Benjamin Okyere, Daniel Rothschild, Irving C. Allen, Michelle H. Theus. Interrogating the role of peripheral-derived hematopoietic cells in tissue homeostasis following brain trauma. VMCVM Research Symposium. Blacksburg, VA. March 2017.

Poster: **Amanda Házy**, Thomas Brickler, Benjamin Okyere, Daniel Rothschild, Irving C. Allen, Michelle H. Theus. Interrogating the role of peripheral-derived hematopoietic cells in tissue homeostasis following brain trauma. Central Virginia Chapter of the Society for Neuroscience Conference. Roanoke, VA. March 2017.

Poster: **Amanda Házy**, Thomas Brickler, Armand Meza, Irving C. Allen, and Michelle Theus. (April 2016) NLRX1 Regulates Inflammatory Signaling Via Modulation of Microglia Activation following Traumatic Brain Injury.

American Society for Neural Therapy and Repair Annual Conference,
Clearwater, FL.

Awards and Academic Achievements

- Inducted into the Honor Society of Phi Kappa Phi, 2017
- American Society for Neural Therapy and Repair Travel Award (\$500), 2017
- Doctoral Scholar of the Institute for Critical Technology and Applied Science at Virginia Tech, 2015-Present

Examination Graduate Committee

Major Advisor/Chair:

Michelle H. Theus, PhD
Associate Professor
Department of Biomedical Sciences and Pathobiology

Graduate Advising Committee Members:

William R. Huckle, MS, PhD
Associate Professor
Department of Biomedical Sciences and Pathobiology

Pamela VandeVord, PhD
Professor
Department of Biomedical Engineering and Mechanics

Gary D. Isaacs, PhD
Associate Professor
Department of Biology and Chemistry, Liberty University

External Examiner

John R. Bethea, PhD

Professor and Department Head
Department of Biology
Drexel University

TNF: A Tale of a Cytokine and Two Receptors in Chronic Neuropathic Pain
Thursday, July 11, 2019
9:30 am
Life Sciences 1 Room 101



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