PUBLIC DEFENSE OF DOCTORAL DISSERTATION TRANSLATIONAL BIOLOGY, MEDICINE, AND HEALTH GRADUATE PROGRAM

## **OCTOBER 15, 2020**

"EFFECTS OF CONSTITUTIVE AND ACUTE CONNEXIN 36 DEFICIENCY ON BRAIN-WIDE SUSCEPTIBILITY TO PTZ-INDUCED NEURONAL HYPERACTIVITY"



ALYSSA BRUNAL PAN LAB CENTER FOR NEUROBIOLOGY RESEARCH FRALIN BIOMEDICAL RESEARCH INSTITUTE AT VTC





### TRANSLATIONAL BIOLOGY, MEDICINE, AND HEALTH GRADUATE PROGRAM

Virginia Tech's Translational Biology, Medicine, and Health (TBMH) program is a researchintensive, integrative, and multidisciplinary doctoral program in the biomedical and health sciences. The program brings together students and faculty from the life, behavioral, physical, engineering, mathematical, and computational sciences to consider today's major challenges in health and disease. The program seeks to develop a new generation of research scientists and thought leaders, who are prepared to identify and tackle the complex challenges for improving human health, by making and translating discoveries into preventions, diagnostics, treatments, cures, and healthier behaviors.



CONTACT THE TRANSLATIONAL BIOLOGY, MEDICINE, AND HEALTH GRADUATE PROGRAM:

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- HOMETOWN: Charlottesville, VA
- UNDERGRADUATE DEGREE: Psychology

Virginia Tech

• MENTOR: Y. Albert Pan, Ph.D.

#### • COMMITTEE MEMBERS:

Y. Albert Pan, Ph.D., Chair James W. Smyth, Ph.D. Susan Campbell, Ph.D. Michelle Olsen, Ph.D.

#### • EX OFFICIO COMMITTEE MEMBERS:

Michael J. Friedlander, Ph.D. Michelle Theus, Ph.D. Steven Poelzing, Ph.D.

#### HONORS:

- Graduate Student Commitment to Diversity and Inclusion, Honorable Mention, Virginia Tech Office of Student Engagement and Campus Life, April 2020
- Neuroscience Scholars Program Associate, Society for Neuroscience, May 2019- May 2021

#### PRESENTATIONS:

**Brunal-Brown, A.**, Pan, Y. Albert (October 2019) Neuronal Connexin 36 in Seizure-like Activity, poster presented at the Diversity poster session at the 2019 Society for Neuroscience Annual Conference, Chicago, IL.

**Brunal-Brown, A**., Pan, Y. Albert (April 2019) Neuronal Connexin 36 is regulated by and contributes to the susceptibility of PTZ-induced seizures, poster presented at the 2019 Triangle Zebrafish Research Symposium, Duke University, Durham, NC.

**Brunal-Brown, A.**, (August 2018) Building a Brain: How your neurons make you, public oral presentation as part of the Science Museum of Western Virginia's STEM Tavern series.

#### PUBLICATIONS:

Scientific Publications

Brunal, A. A., Clark, K. C., Ma. M., Pan, Y. A. (October/November 2020) Effects of constitutive and acute Connexin 36 deficiency on brain-wide susceptibility to PTZ-induced neuronal hyperactivity

Newspaper Op-Eds

Brunal, A., (August 2020) Diets and weight loss: What new insights do we have?, The Roanoke Times, Roanoke, VA



Connexins are transmembrane proteins that form hemichannels allowing the exchange of molecules between the extracellular space and cell interior. Two hemichannels from adjacent cells dock and form a continuous gap junction pore, thereby permitting direct intercellular communication. Connexin 36 (Cx36), expressed primarily in neurons, is involved in the synchronous activity of neurons and may play a role in aberrant synchronous firing, as seen in seizures. To understand the reciprocal interactions between Cx36 and seizure-like neural activity, we examined three questions: a) does Cx36 deficiency affect seizure susceptibility, b) does seizure-like activity affect Cx36 expression patterns, and c) does acute blockade of Cx36 conductance increase seizure susceptibility. We utilize the zebrafish pentylenetetrazol (PTZ; a GABA(A) receptor antagonist) induced seizure model, taking advantage of the compact size and optical translucency of the larval zebrafish brain to assess how PTZ affects brain-wide neuronal activity and Cx36 protein expression. We exposed wild-type and genetic Cx36deficient (cx35.5-/-) zebrafish larvae to PTZ and subsequently mapped neuronal activity across the whole brain, using phosphorylated extracellular-signal-regulated kinase (pERK) as a proxy for neuronal activity. We found that cx35.5-/- fish exhibited region-specific susceptibility and resistance to PTZinduced hyperactivity compared to wild-type controls, suggesting that genetic Cx36 deficiency may affect seizure susceptibility in a region-specific manner. Regions that showed increased PTZ sensitivity include the dorsal telencephalon, which is implicated in human epilepsy, and the lateral hypothalamus, which has been underexplored. We also found that PTZ-induced neuronal hyperactivity resulted in a rapid reduction of Cx36 protein levels. 30 minutes and one-hour exposure to 20 mM PTZ significantly reduced the expression of Cx36. This Cx36 reduction persists after one-hour of recovery but recovered after 3-6 hours. This acute downregulation of Cx36 by PTZ is likely maladaptive, as acute pharmacological blockade of Cx36 by mefloquine results in increased susceptibility to PTZ-induced neuronal hyperactivity. Together, these results demonstrate a reciprocal relationship between Cx36 and seizure-associated neuronal hyperactivity: Cx36 deficiency contributes region-specific susceptibility to neuronal hyperactivity, while neuronal hyperactivity-induced downregulation of Cx36 may increase the risk of future epileptic events.

# SERVICE

- Collaborative Conversations: Empowering a Culture of Respect: Organized and planned a full day workshop surrounding the issue and providing access to resources for sexual harassment and implicit bias in STEM. Conducted pre- and post-workshop evaluative measures. August 2019-March 2020
- Annual Biomedical Research Conference for Minority Students (ABRCMS): Panelist "Putting Your Best Foot Forward in Graduate School Interviews" Webinar, February 2019
- West Salem Elementary STEM Night: Had a Zebrafish booth and spoke to ~300-400 elementary school students, November 2018 and March 2018
- STEAM Day at the Taubman Museum of Art: Had a Zebrafish booth and spoke to ~ 300 elementary school students, September 2018, had a booth titled "How scientists use light!" and spoke to ~900 elementary school students, October 2017
- Public lecture as a part of the Science Museum of Western Virginia's STEM Tavern Series titled "Building a Brain: How your neurons make you," August 2018