Doctoral Dissertation Defense Announcement

“Keratinocyte Piezo1 mediates touch sensation and touch hypersensitivity”

Alexander R. Mikesell
Candidate for Doctor of Philosophy
Cell and Developmental Biology
School of Graduate Studies
Medical College of Wisconsin

Committee in Charge:
Cheryl L. Stucky, PhD (Mentor)
Brian A. Link, PhD
Michele A. Battle, PhD
Jonathan S. Marchant, PhD
Allison D. Ebert, PhD
Daniela M. Menichella, MD, PhD
Date: Wednesday, May 8, 2024
Time: 9:00 AM (CST)
Defense Location: Kerrigan Auditorium
Zoom: Email amikesell@mcw.edu for zoom link

Graduate Studies:
Biochemistry of the Cell
Molecular and Cellular Biology
Reading and Research
Mechanism Cellular Signaling
Fundamentals of Neuroscience
Graduate Neuroanatomy
Neuroscience Journal Club
Ethics & Integrity in Science
Advanced Systems Neuroscience
Advanced Cell Biology
Research Ethics Discussion Series
Statistics for Basic Science
Ion Channels and Signal Transduction
Neurobiology of Pain
Doctoral Dissertation
Dissertation

“Keratinocyte Piezo1 mediates touch sensation and touch hypersensitivity”

Epidermal keratinocytes mediate touch sensation by detecting and encoding tactile information to sensory neurons. However, the specific mechanotransducers that enable keratinocytes to respond to mechanical stimulation are unknown. Additionally, it is unknown if keratinocyte mechanical signaling contributes to the mechanical hypersensitivity and pain that develops after tissue injury. In this dissertation, I demonstrate that the mechanically-gated ion channel PIEZO1 is a key keratinocyte mechanotransducer. Keratinocyte expression of PIEZO1 is critical for normal sensory afferent firing and behavioral responses to mechanical stimuli in mice. Furthermore, I used optogenetic and chemogenetic techniques to specifically inhibit keratinocytes to determine the extent to which keratinocyte mechanical signaling contributes to the severe neuropathic pain that accompanies treatment with the chemotherapeutic drug paclitaxel. I found that keratinocyte inhibition largely alleviates paclitaxel-induced mechanical hypersensitivity. Furthermore, I found that paclitaxel exposure sensitizes mouse and human keratinocytes to mechanical stimulation through Piezo1. Finally, deletion of keratinocyte Piezo1 protects against the development of paclitaxel-induced touch hypersensitivity. My findings demonstrate that keratinocyte Piezo1 contributes to both normal touch sensation and the touch hypersensitivity that develops after neuropathic injury. These findings pave the way for the development of new pain-relief strategies that target epidermal keratinocytes and Piezo1.
Curriculum Vitae

Alexander R. Mikesell, BS
Graduate Student
amikesell@mcw.edu
Department of Cell Biology, Neurobiology & Anatomy
Medical College of Wisconsin
8701 Watertown Plank Road, Milwaukee, WI 53226

Education and Training

Bachelor of Science (BS) in Neuroscience: Brigham Young University, Provo, UT, 2015-2018
- Neuroscience Major
- Worked in the laboratory of Dr. Shawn Gale as a research volunteer studying the effects of visual priming on pattern recognition in humans

Neuroscience Doctoral Program: Medical College of Wisconsin, Milwaukee, WI, 2018-present
- PhD program, Qualifying Exam passed 12/2019, completion expected Spring of 2024
- Working in the laboratory of Dr. Cheryl Stucky, PhD
- Funded by NINDS Individual NRSA for PhD students (F31)
- Projects
  - Identifying novel non-opioid treatments for neuropathic pain
  - Investigating how non-neuronal epidermal cells contribute to normal touch, cold, and heat sensation and how this contribution is altered following neuropathic injury

Publications:

3. Dianise M. Rodríguez García; Aniko Szabo; Alexander R. Mikesell; Samuel J. Zorn; Ulrich Kemmo Tsafack; Anvitha Sriram; Tyler B. Waltz; Jonathan D. Enders; Christina M. Mecca; Cheryl Louise Stucky; Katelyn E. Sadler. High-speed imaging of evoked rodent mechanical behaviors yields variable results that are not predictive of inflammatory injury, Pain, 2024


**Funding**

NRSA Predoctoral Fellowship (F31). February 2022-January 2024

- “Epidermal keratinocytes mediate mechanical pain following neuropathic injury”. NINDS

**Academic and Professional Honors:**

2016: Half-tuition scholarship, Brigham Young University

**February 2021:** Won “Best Poster” at the MCW 30th Annual Graduate School Research Poster Session.

**May 2022 and February 2023:** Awarded a travel award from USASP to attend the 2022 and 2023 conference.

**November 2022:** Awarded a travel award from the MCW graduate school to attend the 2022 SFN meeting.

**April 2023:** Awarded a travel award from the MCW graduate school to attend the 2023 USASP meeting.

**Other Experience and Professional Development:**

1. Keratinocyte Piezo1 mediates touch sensation and touch allodynia” Poster Session, USASP, Durham NC, April 2023.
5. 31st Annual Graduate School Poster Session, MCW, March 2021.