



Doctoral Dissertation Defense Announcement

“Keratinocyte Piezo1 mediates touch sensation and touch hypersensitivity”



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Cell and Developmental Biology
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Committee in Charge:

Cheryl L. Stucky, PhD (Mentor)

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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
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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:

1. **Mikesell AR**, Isaeva E, Schulte ML, Menzel AD, Sriram A, Prahll MM, Shin SM, Sadler KE, Yu H, Stucky CL. Keratinocyte Piezo1 drives paclitaxel-induced mechanical hypersensitivity. *bioRxiv* [Preprint]. 2023 Dec 13:2023.12.12.571332. doi: 10.1101/2023.12.12.571332. PMID: 38168305; PMCID: PMC10760029. **(2024 in review at Science Translational Medicine)**
2. Brandon Itson-Zoske, Uarda Gani, **Alexander R. Mikesell**, Chensheng Qiu, Fan Fan, Cheryl L. Stucky, Quinn H. Hogan, Seung Min Shin, and Hongwei Yu. Selective RNAi-silencing of Schwann cell Piezo1 alleviates mechanical hypersensitization following peripheral nerve injury, *Gene Therapy*, 2024 **(in review)**
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
4. **Alexander R Mikesell**, Olena Isaeva, Francie Moehring, Katelyn E Sadler, Anthony D Menzel, Cheryl L Stucky (2022) Keratinocyte PIEZO1 modulates cutaneous mechanosensation *eLife* 11:e65987
5. Cheryl L. Stucky, **Alexander R. Mikesell**, Chapter 16 - When soft touch hurts: How hugs become painful after spinal cord injury, Editor(s): Christine N. Sang, Claire E. Hulsebosch, *Spinal Cord Injury Pain*, Academic Press, 2022, Pages 341-351
6. Sadler KE*, Moehring F*, Shiers SI, Laskowski LJ, **Mikesell AR**, Plautz ZR, Brezinski AN, Mecca CM, Dussor G, Price TJ, McCorvy JD, Stucky CL (2021) Transient receptor potential canonical 5 (TRPC5) mediates inflammatory mechanical and spontaneous pain

in mice. Science Translational Medicine 13: eabd7702. PMID: 34039739. (*co-first authors).

7. Stucky CL, **Mikesell AR**. Cutaneous pain in disorders affecting peripheral nerves. Neurosci Lett. 2021 Nov 20;765:136233. doi: 10.1016/j.neulet.2021.136233. Epub 2021 Oct 1. PMID: 34506882; PMCID: PMC8579816.

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.
2. “Keratinocyte Piezo1 mediates touch sensation and touch allodynia” Poster Session, Society for Neuroscience, San Diego CA, November 2022.
3. “Keratinocyte Piezo1 mediates touch sensation and touch allodynia “, 2022 US Association for the Study of Pain: Poster Session and Oral Presentation, Cincinnati, OH, May 2022.
4. “Keratinocyte Piezo1 mediates innocuous and noxious touch sensation”, MCW Departmental Seminar (CBNA) Oral Presentation, Milwaukee, WI, March 2022.
5. 31st Annual Graduate School Poster Session, MCW, March 2021.
6. “The Role of Keratinocytes in Heat Sensation, Cold Sensation, and Mechanosensation” Oral Presentation, Pain Research Forum Seminar Series, international virtual seminar, August 2020.