

Doctoral Dissertation Defense Announcement

“Peripheral Neuronal and Non-neuronal Mechanisms of Fabry Disease Pain”



Tyler B. Waltz

Candidate for Doctor of Philosophy in Cell and Developmental Biology

Graduate School of Biomedical Sciences

Medical College of Wisconsin

Committee in Charge:

Cheryl L. Stucky, PhD (Advisor)

Joseph T. Barbieri, PhD

Nancy M. Dahms, PhD

Quinn H. Hogan, MD

Jonathan S. Marchant, MA, PhD

Friday, July 21, 2023

9:00AM (CST)

HRC: H1210/H1230/H1250

Live Public Viewing: <https://mcw-edu.zoom.us/j/2330753368?pwd=MXc3MwVYQWZFTFRWUldQeXhwc2VGUT09>. Meeting ID: 233 075

3368. Passcode: TylerWaltz

Graduate Studies:

Reading and Research

Advanced Systems Neuroscience

Advanced Cell Biology

Biostatistics Health Sciences

Ethics & Integrity in Science

Ion Channels & Signal Transduction

Research Ethics Discussion Series

Doctoral Dissertation

Abstract:

Fabry disease, the most common X-linked lysosomal storage disease, is caused by a deficiency in the enzyme alpha-galactosidase A (α -Gal A) which results in chronic intracellular accumulation of glycosphingolipids and lysosomes in multiple tissues. The most debilitating complication for patients with Fabry disease is childhood onset of severe chronic pain that has neuropathic attributes, described as mechanical allodynia and burning in the hands and feet. Patients also display evidence of peripheral sensory neuropathy including pronounced structural abnormalities of dorsal root ganglia neurons and peripheral glial Schwann cells. However, it has not been established that pain in Fabry disease is specifically attributable to peripheral sensory neuron dysfunction, as pain may be attributed to more central sites including the spinal cord and brain. The pathophysiological mechanisms underlying chronic pain in Fabry disease are poorly understood, and existing treatments for Fabry disease pain are inadequate.

The purpose of this dissertation was to demonstrate whether dysfunction of the peripheral nervous system contributes to chronic neuropathic pain in Fabry disease using a recently characterized genetic rat model that we have previously shown to exhibit mechanically evoked and ongoing pain phenotypes. Using light, electron, and immunofluorescence microscopy, we demonstrated that peripheral sensory nerves of Fabry rats exhibit evidence of peripheral sensory neuropathy, including abnormalities of both myelinated and unmyelinated axons and Schwann cells. Dorsal root ganglia neurons of Fabry rats exhibited pronounced hyperexcitability and spontaneous activity as assessed using both *in vivo* and *in vitro* electrophysiology. Denervated Schwann cells were observed in sensory nerves from Fabry rats, and we hypothesized that this cell type may contribute to the hyperexcitability of Fabry sensory neurons. We cultured Schwann cells from Fabry rats and found that application of released mediators from these cells induced spontaneous activity and hyperexcitability in naïve sensory neurons. We examined putative algogenic mediators using unbiased proteomic analysis and found that Fabry Schwann cells release elevated levels of the protein p11 (S100-A10) which induces sensory neuron hyperexcitability and enhances voltage-gated sodium channel currents. We then demonstrated that p11 mechanistically contributes to excessive neuronal excitability caused by Fabry Schwann cells through depolarization of the resting membrane potential.

In summary, we demonstrate that peripheral sensory neuron dysfunction underlies chronic pain in Fabry disease. We show that release of the putative algogen p11 induces hyperexcitability in peripheral sensory dorsal root ganglia neurons through altered function of neuronal membrane ion channels including voltage-gated sodium channels. These findings suggest novel analgesic targets to treat pain associated with this understudied and debilitating genetic disorder.

TYLER B WALTZ

Curriculum Vitae

618 North 90th Street, Milwaukee WI 53226

twaltz@mcw.edu

EDUCATION:

- 2017 – present Medical College of Wisconsin, Milwaukee, WI
MD/PhD Candidate, Medical Scientist Training Program
- 2011 – 2015 Arcadia University, College of Arts and Sciences, Glenside PA
B.A with Honors in Biology; Minor in History

RESEARCH EXPERIENCE:

- 08/2019 – present Graduate Program in Cell & Development Biology
Medical College of Wisconsin Graduate School, Milwaukee, WI
Mentor: Cheryl L. Stucky PhD
- 06/2018 – 08/2018 Medical Student Summer Research Fellowship
Clinical & Translational Science Institute of Southeast Wisconsin, Milwaukee, WI
Mentor: Cheryl L. Stucky PhD
- 03/2016 – 03/2017 Postbaccalaureate Intramural Research Traineeship Award Fellowship
National Institute on Aging (NIA), Baltimore MD
Mentor: Vilhelm A Bohr, MD PhD
- 03/2014 – 05/2015 Undergraduate Senior Capstone Project, Department of Biology
Arcadia University, College of Arts and Sciences, Glenside, PA
Mentor: Chad D. Hoefler, PhD
- 06/2013 – 08/2013 Public Health Research Intern
Penn State College of Medicine, Hershey, PA
Mentor: Nasrollah Ghahramani, MD MS

PUBLICATIONS: Published

1. Burand AJ Jr, **Waltz TB**, Manis AD, Hodges MR, Stucky CL. HomeCageScan analysis reveals ongoing pain in Fabry rats. *Neurobiol Pain*. 2023 Jan 5;13:100113. doi: 10.1016/j.ynpai.2022.100113. PMID: 36660199; PMCID: PMC9843259.
2. **Waltz TB**, Burand AJ Jr, Sadler KE, Stucky CL. Sensory-specific peripheral nerve pathology in a rat model of Fabry disease. *Neurobiol Pain*. 2021 Sep 2;10:100074. doi: 10.1016/j.ynpai.2021.100074. PMID: 34541380; PMCID: PMC8437817.

3. Sadler KE, Lewis TR, **Waltz TB**, Besharse JC, Stucky CL. Peripheral nerve pathology in sickle cell disease mice. *Pain Rep.* 2019 Jun 27;4(4):e765. doi: 10.1097/PR9.0000000000000765. PMID: 31579856; PMCID: PMC6728004.
4. Mitchell SJ, Bernier M, Aon MA, Cortassa S, Kim EY, Fang EF, Palacios HH, Ali A, Navas-Enamorado I, Di Francesco A, Kaiser TA, **Waltz TB**, Zhang N, Ellis JL, Elliott PJ, Frederick DW, Bohr VA, Schmidt MS, Brenner C, Sinclair DA, Sauve AA, Baur JA, de Cabo R. Nicotinamide Improves Aspects of Healthspan, but Not Lifespan, in Mice. *Cell Metab.* 2018 Mar 6;27(3):667-676.e4. doi: 10.1016/j.cmet.2018.02.001. PMID: 29514072; PMCID: PMC5854409.
5. **Waltz TB**, Fivenson EM, Morevati M, Li C, Becker KG, Bohr VA, Fang EF. Sarcopenia, Aging and Prospective Interventional Strategies. *Curr Med Chem.* 2018;25(40):5588-5596. doi: 10.2174/0929867324666170801095850. PMID: 28762310; PMCID: PMC5792375.
6. Fang EF*, **Waltz TB***, Kassahun H, Lu Q, Kerr JS, Morevati M, Fivenson EM, Wollman BN, Marosi K, Wilson MA, Iser WB, Eckley DM, Zhang Y, Lehrmann E, Goldberg IG, Scheibye-Knudsen M, Mattson MP, Nilsen H, Bohr VA, Becker KG. Tomatidine enhances lifespan and healthspan in *C. elegans* through mitophagy induction via the SKN-1/Nrf2 pathway. *Sci Rep.* 2017 Apr 11;7:46208. doi: 10.1038/srep46208. PMID: 28397803; PMCID: PMC5387417. **These authors contributed equally to this work.*
7. Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, Iser WB, Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, **Waltz TB**, Tian J, Sinclair DA, Mattson MP, Nilsen H, Bohr VA. NAD⁺ Replenishment Improves Lifespan and Healthspan in Ataxia Telangiectasia Models via Mitophagy and DNA Repair. *Cell Metab.* 2016 Oct 11;24(4):566-581. doi: 10.1016/j.cmet.2016.09.004. PMID: 27732836; PMCID: PMC5777858.

PUBLICATIONS: Pending

1. **Waltz TB**, Chao D, Prodoehl EK, Ehlers VL, Dharanikota BS, Dahms NM, Isaeva E, Hogan QH, Pan B, Stucky CL. Schwann cell release of p11 induces sensory neuron hyperactivity in Fabry disease. *bioRxiv [Preprint].* 2023 May 28:2023.05.26.542493. doi: 10.1101/2023.05.26.542493. PMID: 37292928; PMCID: PMC10245981. *In revision: JCI Insight, 2023.*
2. Sadler KE, Atkinson SN, Ehlers VL, **Waltz TB**, Hayward M, Rodríguez García DM, Salzman NH, Stucky CL, Brandow AM. Gut microbiota and metabolites drive chronic sickle cell disease pain. *bioRxiv [Preprint].* 2023 Apr 28:2023.04.25.538342. doi: 10.1101/2023.04.25.538342. PMID: 37163080; PMCID: PMC10168372.
3. Rodríguez García DM, Szabo A, **Waltz TB**, Mikesell AR, Sriram A, Mecca CM, Tsafack UK, Stucky CL, Sadler KE. High-speed imaging of evoked rodent mechanical behaviors yields variable results that are not predictive of inflammatory injury. *In revision: PAIN, 2023.*

HONORS AND AWARDS

- | | |
|------|--|
| 2022 | Individual National Research Service Award (F31, NINDS, NS122380-01) |
| 2018 | Medical Student Summer Research Fellowship: T35, NHLBI, NIH |
| 2016 | Postbaccalaureate Intramural Research Training Award, NIH |

- 2015 Arcadia University Departmental Award in Biology
- 2013 Arcadia University Pay It Forward Scholarship
- 2011 The Arcadia University Achievement Award

PRESENTATIONS:

National:

- *“Peripheral Neuron Excitability Is Mediated by Schwann Cells in Fabry Disease “*, 2022 US Association for the Study of Pain: **Poster Session and Oral Presentation**, Cincinnati, OH, May 2022.
- *“Peripheral Neuron Excitability Is Mediated by Schwann Cells in Fabry Disease”*, 33rd Annual National MD/PhD Student Conference **Poster Session**, Copper Mountain Resort, CO, July 2022.

Regional:

- 32nd Annual Graduate School **Poster Session**, MCW, October 2022.
- *“Peripheral Neuron Excitability Is Mediated by Schwann Cells in Fabry Disease”*, MCW Departmental Seminar (CBNA) **Oral Presentation**, Milwaukee, WI, March 2022.
- *“Peripheral Neuron Excitability Is Mediated by Schwann Cells in Fabry Disease”*, MCW MD/PhD (MSTP) Research in Progress **Oral Presentation**, Milwaukee, WI, November 2021.
- 31st Annual Graduate School **Poster Session**, MCW, March 2021.
- ‘Tomatidine enhances lifespan and healthspan in worms through mitophagy induction via the SKN-1/Nrf2 pathway’, **Oral Presentation**, The Baltimore Worm Club, University of Maryland, MD, 2016

MENTORSHIP AND TEACHING EXPERIENCES:

- 2023 Bradey Stuart, M2 MD/PhD student
- 2022 Sam Zorn, M2 MSTP student
- 2021 Lexi Kazen, G1 Neuroscience student

LEADERSHIP & COMMUNITY ENGAGEMENT:

- 2023 – present Mentor, MCW MSTP Diversity and Inclusion Mentorship
- 2018- 2022 Community Outreach Coordinator, MCW Sex Education for All (SEA)
- 2018- 2019 MCAT Tutor, StEP-UP, MCW
- 2016 Volunteer, Baltimore Rescue mission, Baltimore MD
- 2014 Tutor, Gateway to Success, Arcadia University, PA