DEPARTMENT OF
PHARMACOLOGY & PHYSIOLOGY

2021 YEAR IN REVIEW

Empire Discovery Institute Medicines Discovery Awards

SCHOOL OF MEDICINE & DENTISTRY
UNIVERSITY of ROCHESTER

Message From The Chair

I write to you all at the end of an incredible year of resilience, transition and accomplishment for our department.

At the start of 2021, COVID-19 positivity rates in Monroe County were at the peak of the pandemic and vaccines were just beginning to become available. As vaccinations increased and the cold weather subsided, positivity rates plummeted to vanishingly low levels over the summer before rebounding with abandon in the fall and early winter. We also celebrated the retirement of Ms. Debra Andreacchi-Roth, who served as the department's Senior Administrator/Research Program Manager for the last 30 years. During all of these transitions, our faculty, trainees and staff remained resilient and indefatigable. With our people vaccinated and universal masking, our courses, seminars, journal club and meetings were able to transition to hybrid in-person/remote formats. Research labs remained open and thriving, while prioritizing safety and flexibility. I continue to be in awe of the remarkable character, drive, and abilities of the individuals in our department.

In spite of these many challenges, the department made many notable accomplishments in 2021, many of which are covered in this newsletter. In the cover story (p. 3–4), two of our faculty members, Drs. Denise Hocking and John Lueck, were each awarded separate Empire Discovery Institute (EDI) Medicines Discovery Awards. The EDI is a 501(c) corporation that is partnership between research laboratories at the University of Rochester, the University at Buffalo, and Roswell Park Comprehensive Cancer Center. The overall mission of the EDI is to convert research discoveries into new medicines for commercialization. The EDI's Medicines Discovery Award program provides incubator and accelerator funds to identify and advance a promising early stage drug discovery into an early "proof of concept." Successful projects then exit the program with either a licensing transaction to a strategic pharmaceutical partner or as an EDI-created startup company. Drs. Hocking's and Lueck's EDI Medicines Discovery Awards, the first two such projects from the University of Rochester, are the focus of our cover story. It will be exciting to see how these exciting new therapeutics develop and advance towards commercialization in the upcoming years.

The department's new Faculty/Staff Diversity and Inclusion Committee, Chaired by Dr. Hocking, worked together to update the committee's mission statement and to develop and refine the department's mission statement (p. 5–6). The committee also organizes a monthly department-wide "Community Conversations" that discusses topical issues designed to deepen our understandings of diversity, equity, and inclusion, and what it means to hold these as central values within our professional work.

Cover Image:
John Lueck, Ph.D. and Denise Hocking, Ph.D.

Newsletter Editor:
Rachel Zapata-Bermudez

In recognition of their outstanding research programs and contributions to the department's education and service missions, Dr. David Yule was reappointed as the Louis C. Lasagna Professor of Experimental Therapeutics (p. 7) and Dr. David MacLean was appointed as the Paul Stark Professor of Pharmacology and Physiology (p. 8). This newsletter also highlights new M.S. and Ph.D. students that joined our graduate programs this year, awards and honors bestowed upon our faculty, postdoctoral fellows and students (p. 9–13), and selected research publications (p. 14–15).

In 2015, the department launched a competitive pilot grant program designed to promote grass-roots collaborations between our faculty and other faculty members across the institution. The Drug Targets and Mechanisms Collaborative Pilot Grant Program has dispersed >$300,000 in pilot grant funds, which enabled collection of key preliminary needed for several successful larger extramural grant applications. For the first time, in 2021 the program funded a new collaboration between two department faculty members (Drs. Orlandi and MacLean) to establish an unbiased mouse behavioral analysis system that allows consistent measurements of free running mice across experiments and investigators (p. 16). This system will not only be useful to the Orlandi and MacLean research programs, but will also be shared with other investigators in the department and across the institution.

As we have done in previous years, the newsletter ends with Career Stories of several of our past alumni (p. 17–18). This year we highlight department alumni (one Physiology Ph.D. and two Pharmacology Ph.D.s) that have enjoyed successful careers in Pharma (Doug Krafte, Ph.D., '86 Physiology), academia (Kristen M.S. O'Connell, Ph.D., '02 Pharmacology) and medical communications (Jesi Anne To, Ph.D., '14 Pharmacology). The success and accomplishments of our alumni continues to be one of the greatest legacies of our department.

I continue to be both humbled and inspired by the outstanding work of our faculty, students, staff and alumni. I am proud to be a part of this family! *Meliora!*

Robert T. Dirksen, Ph.D.

Lewis Pratt Ross Professor
Chair of Pharmacology and Physiology

Department Leadership Team

Jean M. Bidlack, Ph.D.
Professor and Associate Chair

Angela J. Glading, Ph.D.
Associate Professor and
Director of Graduate Studies

Denise C. Hocking, Ph.D.
Professor and Faculty and
Staff Diversity Officer

Two Faculty Members Awarded EDI Medicines Discovery Award

Left to Right: Diane Dalecki, Denise Hocking, Emma Norris, Sarah Wayson, Carol Raeman, Sally Child, Melinda VanderHorst, Sabrina Pan, Megerize Li

Denise Hocking, Ph.D.

Advancing the Chimeric Fibronectin Matrix Mimetic 'Chimectin' as a Wound Biologic

Chronic wounds have become a 'silent epidemic', affecting ~20 million people worldwide, including more than 8 million Americans. Non-healing wounds cause considerable pain and discomfort to patients, with health complications ranging from serious infections to limb amputations to death. Chronic wounds, which include diabetic, venous, and pressure ulcers, impose a significant and growing health care burden worldwide. In the U.S., annual health care costs for treating chronic wounds are conservatively estimated at $32 billion. Diabetes, obesity, and aging are the major underlying causes of chronic wounds. According to a recent report from the Centers for Disease Control and Prevention, 30 million Americans, or 9.4% of the U.S. population, have been diagnosed with diabetes. Foot ulceration is the most common complication of diabetes; between 10-25% of diabetics will develop at least one foot ulcer over the course of their life, incurring yearly health care costs of $30,000 to $60,000 per patient. In the U.S., diabetic foot ulcers are the leading cause of non-traumatic lower extremity amputations, with an annual rate of 5 per 1000 adults with diabetes. Treatment approaches for chronic wounds include surgical debridement, moist dressings, engineered skin substitutes, compression therapy, negative pressure therapy, skin grafts, and recombinant growth factors. Yet, none of these approaches has proven to be an efficient and effective therapy.

Tissue repair occurs or normally through a series of complex and highly regulated events that are mediated through interactions between various cell types and extracellular matrix (ECM) proteins. Fibronectin fibrils are a principal component of the wound ECM and plays a key role in tissue formation. The Hocking lab has developed a series of soluble, recombinant fragments of fibronectin, termed "fibronectin matrix mimetics", that "mimic" the structural and functional properties of insoluble fibronectin fibrils. Fibronectin matrix mimetics were produced by first removing several amino acids from FNIII1 to expose the matricryptic heparin-binding site and thus, produce a fragment that mimics the active conformation of fibronectin in tissues (referred to as "FNIII1H"). FNIII1H was then coupled directly to various portions of fibronectin's integrin-binding domain (modules FNIII8-10). Fibronectin matrix mimetics promote cell adhesion, proliferation, migration and contractility, modulate extracellular matrix composition, and induce local vasodilation - all of which contribute to effective tissue regeneration. Topical application of fibronectin matrix mimetics to full-thickness dermal wounds in diabetic mice accelerates wound closure and epithelial maturation, and promotes granulation tissue deposition, remodeling, and re-vascularization. Thus, a primary target of the fibronectin matrix mimetics is chronic diabetic wounds. The goal of this EDI

Denise Hocking, Ph.D.

project is to produce a tag less version of one of the fibronectin matrix mimetics, FNIII1H,8,10 (“Chimectin”) and identify effective dosing and application protocols for full thickness dermal wounds in diabetic male and female mice. This information will then be used to test Chimectin’s efficacy in a diabetic porcine wound model, laying the ground work to advance Chimectin to clinical trials to test its ability to stimulate wound healing in patients with diabetes.

John Lueck, Ph.D.

Development of Engineered tRNAs for Treatment of Nonsense Mutations

Nonsense mutations change an amino acid codon to a premature termination codon (PTC) generally through a single-nucleotide substitution. The generation of a PTC results in a defective truncated protein and often in severe forms of disease. Nonsense mutations account for 10-15% of all genetic lesions leading to disease and causing nearly 1000 genetic disorders including cancer. Because of the exceedingly high prevalence of nonsense-associated diseases and a unifying mechanism, there has been a concerted effort to develop PTC therapeutics. Our research focuses on the use of suppressor tRNAs (sup-tRNAs) as possible therapeutics for correcting PTCs that result in disorders where the target gene is too large for conventional gene replacement approaches. Indeed, sup-tRNAs have many attractive qualities as therapeutic agents which include their inherent compact size and ability to be delivered as naked DNA, RNA and encoded in viruses.

The overarching goal of our EDI project is to develop and advance therapeutic sup-tRNA delivery technologies with a focus on mini-vectors and adeno-associated virus (AAV). The Lueck Lab has generated a suite of mini vectors that express sup-tRNAs in eukaryotic cells that are as small as 200 base pairs in size, making them the smallest known expression vector to date. The benefit of this technology is that they exhibit persistant robust expression in non- dividing cells for > 6 months and can be paired with burgenoning nucleotide delivery technologies for efficient delivery. With support of EDI funding, we will audition two different nucleotide delivery technologies through collaboration with both academic and industry laboratories. These technologies will first be delivered to cultured cells engineered to express PTC interrupted luminescence and fluorescent reporters to determine DNA delivery efficiency and PTC suppression efficacy. These technologies will then be delivered to mouse models with nonsense-associated diseases. In parallel, the Lueck Lab will generate a platform of novel sup- tRNA expression cassettes to be delivered to mouse models with nonsense-associated diseases by AAV. The purpose of this research is to advance two sup-tRNA cargo technologies that can be utilized for treatment of nonsense-associated diseases that affect different tissues. In theory the therapeutic promise of sup-tRNAs is agnostic to the genetic context of nonsense mutations and the gene size in which the mutations are harbored, therefore can be used for many nonsense disorders. However, different modes of delivery will likely be needed to target specific tissues. The end goal of our EDI funded research is to advance our sup-tRNA technology and shorten the timeline for its realization as a nonsense disorder therapeutic.

John Lueck, Ph.D.

Back row, Left to Right: Matthew Sipple, Joseph Porter, John Lueck, Christina Heil, Emily Sorensen, Wooree Ko, Guy Azriel, Lily Cisco, Meghan Martin, Julie Hyatt, Katie Edwards, Ben Lupia; Front row, Left to Right: Nernst Lueck, Ubiquitous Martin

Diversity and Inclusion Committee Report

Mission Statement

The Diversity and Inclusion Committee is made up of a diverse group of individuals representing all stakeholders in the department. The committee is charged with supporting and advancing the department's commitment to providing a diverse and inclusive environment for all students, staff, and faculty. The ongoing mission of the committee is to evaluate departmental policies, actions and resources, and solicit input from the departmental community on issues surrounding diversity and inclusion. In turn, the committee will develop and implement tangible and quantifiable approaches and tools that can be utilized by various stakeholders to produce meaningful and sustained change in the department's culture and behavior, workforce and learner diversity, and transparency and accountability.

DPP Diversity and Inclusion Statement

The Department of Pharmacology and Physiology is deeply committed to fostering an inclusive and welcoming environment where a diverse group of unique individuals feel valued and respected.

We strive to create a climate of trust, openness, advocacy for others, and mutual respect, free from bullying, harassment, or any other type of harmful behavior, so that our students, faculty, and staff can engage fully in their academic and scientific pursuits.

We recognize and affirm that a rich variety of social and cultural identities enhances the strength of our shared community and is essential for attracting, promoting and retaining talented individuals.

With this in mind, we endeavor to create a climate of collegiality, belonging, and acceptance by acknowledging and honoring the diverse histories and life experiences of our community members, with the expectation that such an environment will provide equal opportunities for individual success while cultivating a collaborative setting for scientific discovery and innovation.

DPP Anti-Racism Statement

Racism leverages racial prejudice with social and institutional power to marginalize and discriminate against individuals based on race, skin color or ethnicity. We strive to be better than that. We, the members of the Department of Pharmacology and Physiology, acknowledge that racism is embedded in our society, in science, and in our systems of higher education. We emphatically and unequivocally reject racism in all forms and support the implementation of the University's Anti-racism Action Plan. As scientists and educators, we acknowledge that race is a social construct that is not based on biology, and are committed to interrupting racial disparities by developing and implementing holistic approaches to combat racism and ethnic oppression. We aspire to be a community where all individuals are equally valued and respected, and will work to actively promote anti-racism and to overcome individual, interpersonal and institutional racism.

D/I Committee Members

Back row (left to right)) Alexander Milliken, Angela Glading, Kaye Thomas, ex officio Robert Dirksen, Robert Freeman, David Delemos; Front Row (left to right) Rachel Zapata-Bermudez, Denise Hocking (Chair), Amra Mujcic, Emma Norris. Missing: Lisa Adams, Jarreau Harrison

We aspire to be a community where all individuals are equally valued and respected, and will work to actively promote anti-racism and to overcome individual, interpersonal and institutional racism by:

Examining implicit bias and systemic oppression, and aligning our policies, practices, behavior, and attitudes to be anti-racist. Our shared responsibilities include:

- Learning about implicit bias and identifying our own individual biases
- Ensuring that departmental policies and practices adhere to equity and inclusion principles
- Engaging in difficult conversations on race and racism in our community
- Periodically reviewing and revising the department's curriculum to be culturally inclusive
- Practicing self-awareness and self-reflection

Educating ourselves on white privilege and developing a deeper understanding of the experiences of racialized people and the struggle for racial justice. These efforts include:

- Providing online and in-person training to all faculty, staff and students
- Taking part in different groups and educational forums, including the Department's Diversity and Inclusion Journal Club
- Visiting the University's website of relevant anti-racism materials and resources
- Attending UR-sponsored workshops and forums on diversity and racism

Practicing anti-racism consciously and engaging in efforts to eliminate power imbalances between racialized and non- racialized/White people in academia. Our individual and departmental commitments include:

- Being an advocate for others in lab meetings, social gatherings, and group settings
- Speaking up when we witness racism and hate speech
- Knowing how to access the University's reporting process
- Notifying the Diversity and Inclusion Officer when policies are breached
- Partnering with Human Resources to ensure equity in hiring, promotion and retention practices
- Valuing individual contributions to diversity and inclusion efforts
- Implementing UR's Best Practices in Hiring and providing faculty and lab managers with anti-racism training

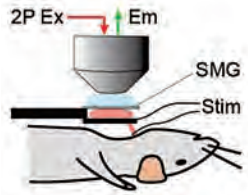
Recently Reappointed Endowed Professor

Louis C. Lasagna Professor of Experimental Therapeutics

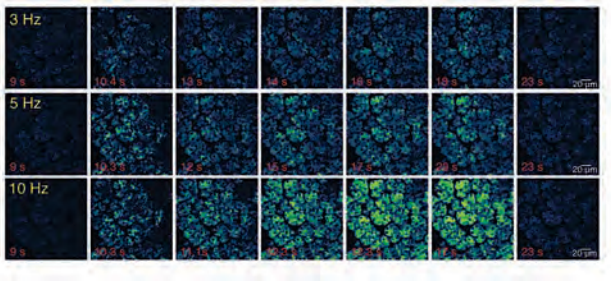
David Yule, Ph.D.

David Yule, Ph.D.

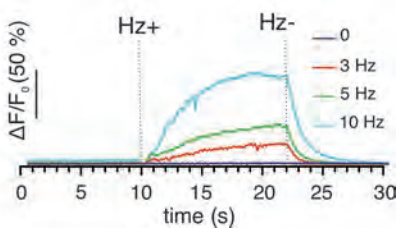
Research in the Yule lab focuses on understanding mechanisms in secretory cells that control changes in intracellular calcium concentration, together with alterations in these processes that occur in diseases associated with altered fluid and protein secretion. Using a variety of imaging, biochemical and electrophysiology techniques we interrogate calcium and secretory events, with the aim of gaining a better understanding of these events at multiple spatial scales. Data is generated both in disease models and under physiological conditions at the level of single ion channel activity, to the resulting subcellular calcium changes measured in vivo and culminates in measuring secretion in the intact animal. The overarching goal of these studies is to gain insight, that can be leveraged to understand these mechanisms in disease processes. Resources provided by the endowment continues to facilitate our development of mouse models expressing genetically encoded calcium indicators in particular cell types in the glands and at specific subcellular localizations. We believe these studies will provide unparalleled insight into these processes observed in vivo with minimal disruptive experimental intervention.



A. Cartoon of the experimental set-up allowing multi-photon imaging of calciumin dicator expressed in the salivary glands of a living mouse.



B. Images of the gland following neural stimulation at the indicated frequency where blue colors represent low calcium and hellow indicates higher calcium levels.



C. Graphical depiction of the changes in flourescence obtained from the images in B.

Left to Right: Jim Chaffer, Amanda Wahl, Kai Ting Huang, Sundeep Malik, Vikas Arige, David Yule, Maria Rojas Tawil, Lara Terry, Takahiro Takano and Larry Wagner

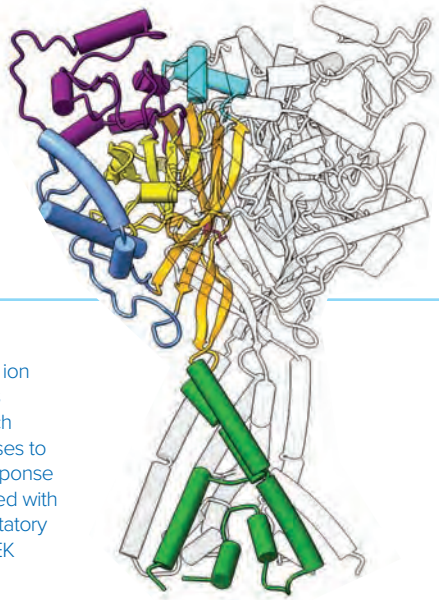
Recently Appointed Endowed Professor

Paul Stark Professor of Pharmacology

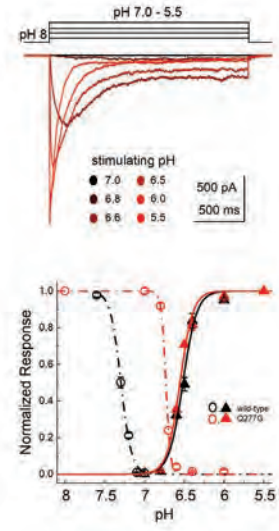
David MacLean, Ph.D.

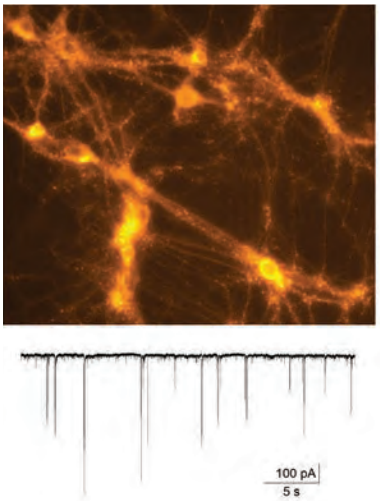
David MacLean, Ph.D.

The focus of the MacLean lab is neurotransmitter-gated ion channels; receptors in the brain that open an ion channel in response to neurotransmitter binding. We study two classes of neurotransmitter-gated ion channels: ionotropic Glutamate receptors (iGluRs) and acid-sensing ion channels (ASICs). Our goal is to understand the relationships between these receptor's form, function and physiology. How does the receptor's structure bestow certain biophysical properties? How do those biophysical properties enable physiological or pathophysiological processes? Can we leverage our biophysical knowledge to advance disease treatment? Over the last few years, we have coupled functional measurements of receptor activity with kinetic and molecular modelling to elucidate the core mechanism of ASIC desensitization. We have used patch clamp fluorometry, combined with simulations, to generate the first glimpse of the important but unresolved ASIC intracellular domains. We have developed critical insights into where and how specific toxins bind these channels, potentially opening new avenues for drug development. In the coming years, we will continue to explore these questions. The resources provided by the Paul Stark Professor of Pharmacology endowment provides the freedom and resources needed to push these studies further, to explore related questions in iGluRs, as well as to pursue new avenues such as non-canonical amino acid incorporation in neuron-HEK co-cultures, development of genetically encoded voltage sensors, and machine learning approaches to behavioral analysis.



Resting state structure of acid-sensing ion channel (ASIC) with individual domains of single subunit colored. Excised patch recording of ASIC1a functional responses to pH steps (upper) and summary pH response curves (lower). Cultured neurons stained with PSD-95 (upper) and spontaneous excitatory postsynaptic currents from neuron- HEK co-cultures (lower).





David MacLean, Matthew Rook, Maddison McClelland, Tyler Couch, Kyle Berger.

New Graduate Students

CMPP Ph.D. and PHP M.S. Students
Front row: Anya Wang, Xiaoxuan Lin, Ei Tun, Lori White (Program Coordinator)
Back row: :Nada Ahmed Selim, Rhodalyn Essien, Grant Grieble, Bryce West, Rana Alabdali. (Missing: Katyana Collins, Fatemeh Alimohammadi, Alireza Mousaei, and Angela Glading, Program Director)

Medical Pharmacology M.S. Students: Joshua Agyarko, Rachel Christie, Vivienne Tucker, Megan Berntsen, Vabby Baker, Himal Subramanya, Winni Gao, and Robert Freeman, Program Director. (Missing: Kate French)

Degrees Awarded

MARCH 2021

Vivian Si Chen, Ph.D.
"Regulation, Function and Mechanism of Phosphodiesterase 10A in Pathological Cardiac Remodeling and Dysfunction"
Advisor: Dr. Chen Yan

JUNE 2021

Lara Terry, Ph.D.
"Functional Analysis of disease-associated Mutations in the Inositol 1,4,5-Trisphosphate Receptor"
Advisor: Dr. David Yule

JULY 2021

Miriam Barnett, Ph.D.
"Differential Regulation of Opioid Receptor Signaling via Ga Proteins"
Advisor: Dr. Jean Bidlack

AUGUST 2021

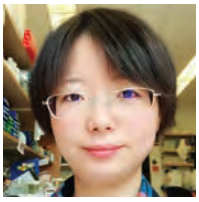
Louben Dorval, Ph.D.
"FGF21 Reduced Morphine Preference and the Development of Acute Antinociceptive Tolerance and Physical Dependence"
Advisor: Dr. Jean Bidlack

DECEMBER 2021

Harsha Swamy, Ph.D.
"Regulation of Endothelial Cell Behavior via KRIT1 Localization and Function"
Advisor: Dr. Angela Glading

DECEMBER 2021

Chongyang Zhang, Ph.D.
"Cyclic Nucleotide Phosphodiesterase and Abdominal Aortic Aneurysm"
Advisor: Dr. Chen Yan



Student Awards

Melinda Vander Horst, M.S.
Recipient, 1st place, Student Paper Competition (Biomedical Acoustics) at the Annual Meeting of the Acoustical Society of America, Therapeutic effects of ultrasound on dermal wound healing in diabetic mice
Hocking Lab

Jacob Kallenbach, M.S.
Finalist in the University of Rochester's Three Minute Thesis (3MT) an academic competition that challenges doctoral students to describe their research within three minutes to a general audience
Chakkalakal Lab

Alexander Milliken, M.S.
Recipient of a two-year AHA Predoctoral Fellowship Award entitled, "Succinate dynamics and pH in cardiac ischemia-reperfusion injury"
Brookes Lab

Amanda Wahl, M.S.
Recipient of a three-year Ruth L. Kirschstein NRSA NIH F31 entitled, "Elucidating the mechanisms of salivary gland dysfunction following gamma-irradiation utilizing an experimental and computational approach"
Yule Lab

Lara Terry, M.S.
Co-recipient of the First Place Prize at the Ca Signaling Meeting
Yule Lab

Matthew Rook, M.S.

Recipient of a three-year Ruth L. Kirschstein NRSA NIH F31 entitled, "Optical interrogation of acid-sensing ion channel activation and desensitization through genetic code expansion". Recipient of the Joan Wright Goodman Dissertation Fellowship for Academic Year 2020-2021

First place in the CMPP Retreat Poster Competition winner (June 2021) CMPP Inquisitive Award: Recipient of the Student Research Achievement Awarding Channels, Receptors and Transporters Subgroup at the 2021 Biophysical Society Annual Meeting

MacLean Lab

Lily Cisco, M.S.

Winner of the University of Rochester Graduate Women in Science (GWIS) Mentoring-Up Challenge

Lueck Lab

Emma Grygotis Norris, Ph.D.

12th Annual Lung Research & Trainee Day, Selected Postdoctoral PresentationWhat is the title for?? "Receptor Binding Domain of SARS-CoV-2 is a functional avβ3 integrin ligand that supports cellular adhesion and phosphotyrosine signaling"

Hocking Lab

Brandon Berry, Ph.D.

Recipient of the Wallace O. Fenn Award given annually to a graduating student judged to have performed meritorious research and presented an excellent Ph.D. thesis.

Wojtovich Lab

Miriam Barnett, M.S.

ASPET Award chosen for the 2021 American Society for Pharmacology and Experimental Therapeutics (ASPET) Washington Fellow. The mission of the ASPET Washington Fellows Program is to enable developing and early career scientists interested in science policy to learn about and become more engaged in public policy issues.

Bidlack Lab

Karl Foley, M.S.

Trainee, Professional Development Award from the Society for Neuroscience. This award recognizes trainees who demonstrate scientific merit and excellence in research.

Xia Lab

Sanjib Guha, Ph.D.

Recipient of the Career Enhancement Award. The annual Career Enhancement Award was created to support the professional development of postdocs as part of the UR PDA's mission. Invited speaker at the Global Tau2020 symposium, and Cell and Experimental Biology conference

Johnson Lab

Vikas Arige, Ph.D.

Vikas Arige and Co authors (Lara Terry and other members of the Yule Lab) on their new paper in the Journal of Cell Science paper

Yule Lab

Tyrone Nieves

Recipient of the Barry Goldwater Scholarship and Excellence in Education Foundation Award. The most prestigious undergraduate scholarship in the natural sciences, mathematics, and engineering in America

Wojtovich Lab

Awards and Honors 2021

Empire Discovery Institute (EDI) Medicines Discovery Awards
Drs. Denise Hocking and John Lueck

Outstanding Graduate Program Director Award
Dr. Angela Glading

Neuroscience Pilot Awards
Drs. Jean Bidlack, Cesare Orlandi and Hugh Xia (2 Awards)

DTM Collaborative Pilot Award
Drs. Cesare Orlandi and David MacLean

Elected office of Secretary for Medical Faculty Council
Dr. Paul Kammermeier

Work featured in *Chemical Engineering News*
Dr. John Lueck

University's Student Supervisor of the Year
Dr. Andrew Wojtovich

First Place prize at the Ca Signaling Meeting
Dr. Takahiro Takano

Board of Scientific Counselors, National Institutes of Health
Drs. Suzanne Haber and David Yule


Dr. Denise Hocking


Dr. John Lueck


Dr. Angela Glading


Dr. Andrew Wojtovich


Dr. Takahiro Takano


Dr. David Yule


Dr. Cesare Orlandi


Dr. Houhui Xia


Dr. Paul Kammermeier


Dr. Jean Bidlack


Dr. David MacLean


Dr. Suzanne Haber

SELECTED TRAINEE PUBLICATIONS

Rook M, Ananchenko A, Musgaard M, MacLean DM. 2021. Molecular investigation of chicken ASIC1 B11-12 linker isomerization and channel kinetics. Frontiers in Cellular Neuroscience. In press.

Couch T, Berger K, Kneisley D, McCullock TW, Kammermeier P, MacLean DM. 2021. Topography and motion of the acid-sensing ion channel intracellular domains. eLife (e68955)..

Rook M, Miaro M, Couch T, Kneisley D, Musgaard M, MacLean DM. 2021. Mutation of a conserved glutamine residue does not abolish desensitization of acid-sensing ion channel 1. J General Physiol., 153(8):e202012855.

Rook M, Musgaard M, MacLean DM. 2021. Coupling structure with function in acid-sensing ion channels: Challenges in pursuit of proton sensors. J Physiol. 599(2):417-430..

Zhang C, Zhao H, Cai Y, Xiong J, Mohan A, Lou D, Shi H, Zhang Y, Long X, Wang J, Yan C. 2021. Cyclic Nucleotide Phosphodiesterase 1C Contributes to Abdominal Aortic Aneurysm. Proc Natl Acad Sci U S A. Aug 3;118(31):e2107898118..

Guha, S., S. Fischer, G.V.W. Johnson, and K. Nehrke. 2020. Tauopathy-associated tau modifications selectively impact neurodegeneration and mitophagy in a novel C. elegans single-copy transgenic model. Mol Neurodegener. 15(1).

Guha, S., G.V.W. Johnson, and K. Nehrke. 2020. The Crosstalk Between Pathological Tau Phosphorylation and Mitochondrial Dysfunction as a Key to Understanding and Treating Alzheimer's Disease. Mol Neurobiol. 57(12).

Guha, S., S. Fischer, A. Cheng, G.V.W. Johnson, and K. Nehrke. 2020. A T231E Mutant that Mimics Pathologic Phosphorylation of Tau in Alzheimer's disease Causes Activation of the Mitochondrial Unfolded Protein Response in C. elegans touch neurons. MicroPubl Biol. .

Dorval, L., Knapp, B.I., Majekodunmi, O.A., Eliseeva, S., and Bidlack, J.M. (2021) Mice with high FGF21 serum levels had a reduced preference for morphine and an attenuated development of acute antinociceptive tolerance and physical dependence. Neuropharmacology doi: 10.1016/j.neuropharm.2021.108858

SELECTED FACULTY PUBLICATIONS

Watkins LR and Orlandi C. 2021. In vitro profiling of orphan G protein coupled receptor (GPCR) constitutive activity. Br J Pharmacol. Mar 30.

McCullock, TW And Kammermeier, PJ, 2021. The Evidence for and Pharmacological Consequences of Metabotropic glutamate receptor heterodimerization, Neuropharmacology, Nov1;199:108801.j.neuropharm.2021.10 8801. Epub 2021 Sep 20. P.

Norris, E.G., Dalecki, D. and Hocking, D.C. (2020) Using Acoustic Fields to Fabricate ECM-Based Biomaterials for Regenerative Medicine Applications. Recent Progress in Materials 2(3):24. .

Vander Horst, M., Raeman, C.H., Dalecki, D, and Hocking, D.C. (2020) Time and dose-dependent effects of pulsed ultrasound on dermal wound repair in diabetic mice. Ultrasound in Medicine and Biology, 148, 2776.

Tang, W., Choi, EY, Heilbronner, SR, Haber, SN. 2021. Nonhuman primate meso-circuitry data: a translational tool to understand brain networks across species. Brain Structure and Function.226:1–11.

Yendiki A., Aggarwal, M., Axer, M., Howard, ARD., van Cappellen van Walsum, AM., Haber, SN. 2021. , Post mortem mapping of connections anatomy for the validation of diffusion MRI. . NeuroImage, In Press. bioRxiv preprint .

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2021 Drug Targets & Mechanisms Collaborative Pilot Project Award

Cesare Orlandi Ph.D. & David MacLean Ph.D.

DeepLabCut for analysis of mouse behavior

A principal challenge of neuroscience is linking the molecular maneuverings of proteins to animal behavior and ultimately diseases. This is generally attempted by recreating specific molecular deficits in animals that are known or thought to lead to a human disease, i.e. generating knockout animal models or administering drugs acting on the central nervous system targets.

Experimenters can then measure quantifiable observables in well- defined and very focused behavioral tests ,i.e. how long did the mouse spend in one arm of a maze. While these behavioral tests are tremendously useful,

they are limited to tasks or behavioral aspects that the experimenter anticipated measuring. Moreover, many behavioral tests often have issues of reproducibility between labs, members of the same lab, strain of animals, and treatments. To solve these issues, machine-learning methods or deep learning strategies have been recently developed to allow for faster, more efficient and more reproducible measurements of animal behavior. Using machine learning to quantify action patterns and sequences maximizes consistency while minimizing human bias and cost. Therefore, this approach provides a more time and labor-efficient means of comparing phenotypes with greater consistency and power. It may serve as are placement, or supplement, to existing behavioral tests or simply run in parallel depending on the specific test. With the recently awarded Drug Targets and Mechanisms DTM Program of Excellence, the laboratories of Dr. Cesare Orlandi and Dr. Dave MacLean will implement one of these methods based on the freely available algorithm DeepLabCut. After establishing and validating this approach using pre- recorded videos and sets of available training data, the Orlandi lab will apply this technology to explore the role of the orphan Gprotein coupled receptor GPRC B in retinoic acid-induced depression. While the MacLean lab will adopt this apparatus to investigate in detail the phenotype of a mouse model of anxiety ASIC KO. Data collected using DeepLabCut will complement the results obtained with traditional tests and will possibly reveal features otherwise impossible to quantify. Gaining access to a dedicated machine learning system for unbiased analysis of animal behavior will be an asset for the Department and the entire University of Rochester potentially enabling researchers interested in behavioral studies to increase the depth and rigor of their analysis obtaining extremely high content data in a fast and accurate way.

3D camera

Open field arena

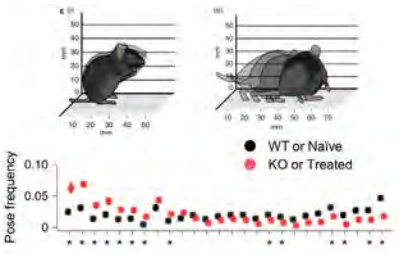
A, Movements and pose used by each mouse will be recorded for 20 minutes.

Post-processing

B, Videos will be post-processed using DeepLabCut.

Data analysis

C, the output will consist in the quantification of the frequency of usage of each post elaborated by DeepLabCut.



Alumni Career Stories

Doug S. Krafte, Ph.D.

Senior Vice President at Ligand Pharmaceuticals

I look back very fondly on my time at Rochester in what was then the Physiology Department led by Paul Horowicz where I had the opportunity to work with great mentors and do science from the ground up based on first principles. This education has proven to be foundational in helping me establish and maintain a positive career trajectory over the past 35 years. My dissertation work in the laboratory of Dr. Rocky Kass focused on cardiac electrophysiology when the patch clamp technique had just been invented. Rocky was incredibly supportive, and I learned so much from him as well as other members of the talented faculty including Peter Shrager, Ted Begenisich, and Camillo Peracchia. From Rochester I left to do a postdoctoral fellowship at Caltech in molecular neurobiology continuing to study ion channels with various heterologous expression systems and biophysical methods. Gene cloning and expression of ion channels had just begun, and it was an exciting time to be working in the area. As I completed my fellowship, I had a career decision to make between academia and industry and decided to explore opportunities in both areas. Ultimately this strategy led to interviews scheduled with various universities and job offers on my desk from pharma and I decided to take the plunge into industry where I have been ever since. In the early part of my career, I managed a lab and focused on initiating and running drug discovery programs in multiple therapeutic areas including cardiovascular, CNS, and immunological and inflammatory diseases. This typically involved building confidence-in-rationale for a molecular target to enter a drug discovery program, developing the necessary reagents, assays, and tools to prosecute a program and then identifying modulators that could affect the function of that molecular target in a way that would translate to clinical benefit; ultimately leading to clinical candidates. In those days the work was primarily small molecule-based but now has expanded to cover all modalities. As time progressed my responsibilities extended beyond the lab in the role of CSO, Site Head and currently Senior Vice President at Ligand Pharmaceuticals where I run the Icagen business unit. Scientific oversight of the drug discovery portfolio remains an important aspect of the job but my responsibilities also extend to strategic planning, finance, legal, HR, business development and other operational areas. The goal ultimately remains the same, though, and that is to apply science to identify meaningful therapeutics for people in need. Looking back to those early years at Rochester my memories include happy random snippets about writing code for my refrigerator-sized computer, a DEC PDP11/23, squid lunches when the Woods Hole crew brought their experimental leftovers back home, soft ball games and Jeremiah's chicken wings. Mostly, though, it is the great people I met during that time. I wish all the students, faculty, and staff of today's department great success.

Jesi Lee Anne To, Ph.D.

Senior Medical Writer at McCann Health Medical Communications

During my graduate studies in the pharmacology and physiology department, I was under the guidance and mentorship of Dr. Alan Smrcka with a primary interest in inflammatory signaling mechanisms using small molecule inhibitors. My research interests were focused on identifying and targeting inflammatory signaling mechanisms downstream of chemokine receptors, specifically G protein α and βγ subunits. Using small molecule G protein βγ (Gβγ) inhibitors, we collaborated with Dr. Jennifer Anolik and observed that G protein βγ was critical in autoimmune disease such as systemic lupus erythematosus (SLE). Before I was ready to defend my thesis and with Alan's approval, I joined GE Global Research in Niskayuna, NY for 10 weeks as a biosciences research fellow to gain industry research experience. The industry experience cemented my interest in pursuing a career outside of academia and in the world of the pharmaceutical industry. I gained invaluable skills and friendships in the pharmacology and physiology department. I formed wonderful lifelong friendships and learned important skills including collaboration, critical thinking and analysis, project management, scientific writing, story telling and presentation, to name a few. I continue to apply all these skills in my professional career to this day. After graduate school, I joined a pharmaceutical company in Princeton, New Jersey as a medical affairs associate. I learned the importance of compliance regulations with the FDA, OIG, and PhRMA that governs scientific exchanges between pharmaceutical companies, healthcare providers, and patients. Since then, I've worked as a medical communications professional, and I have joined a global medical communications agency as a senior medical writer. In this role, I help our clients, pharmaceutical companies, develop scientific storylines and materials to scientifically communicate their data to healthcare

professionals and patients. These materials can range from slide decks, animations, scripts, e-learning modules, websites, and apps. Even now, my interest and work continue to be about chronic inflammatory diseases including multiple sclerosis, axial spondylarthritis, psoriasis, and diabetic macular edema. I truly love and enjoy the diverse disease areas I can immerse myself as a medical writer. It's encouraging to know that my work as a medical writer will in some way help improve the quality of life of patients.

Kristen O'Connell, Ph.D.

Associate Professor, The Jackson Laboratory

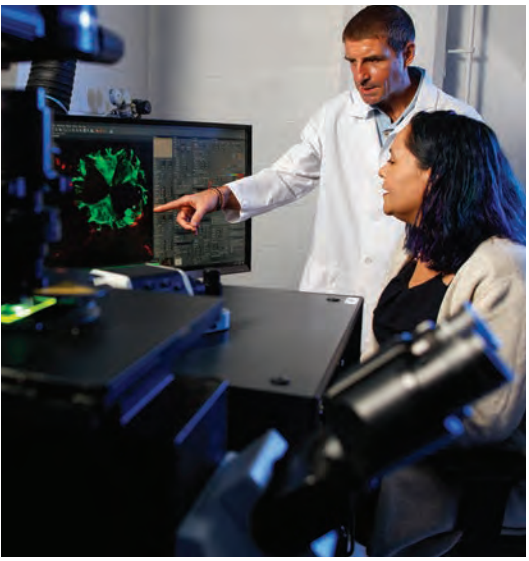
I received my Ph.D. from the Department of Pharmacology and Physiology in 2002 in the lab of Dr. Robert Dirksen – I was his first Ph.D. student! After leaving Rochester, I was a postdoc in the lab of Dr. Michael Tamkun at Colorado State University, where I was fortunate enough to be part of the first cohort to receive the NIH's K99/R00 Pathway to Independence Award. This facilitated the transition to my first independent faculty position at the University of Tennessee Health Science Center in Memphis, TN, where I was awarded tenure in 2016. That same year, I had the opportunity to move my lab to The Jackson Laboratory for Mammalian Genetics in Bar Harbor, ME, where I am an Associate Professor. While the move to JAX represented a transition away from a traditional university setting, the chance to leverage the resources at JAX to create more translational, genetically diverse, preclinical models for human diseases such as Alzheimer's and obesity and understand the role of environmental factors and comorbidities on disease susceptibility has been a boon for my research program. Best of all, I still have the opportunity to interact with trainees through the education programs here at JAX and my affiliate faculty positions at Tufts University and the University of Maine. In addition to running my own NIH-funded lab, I am also part of the leadership teams for the JAX Center for Alzheimer's and Dementia Research and the Center for Addiction Biology. True to my roots in pharmacology, I am also excited to be part of a team leading the development of small molecule therapeutics to enhance resilience to Alzheimer's disease.

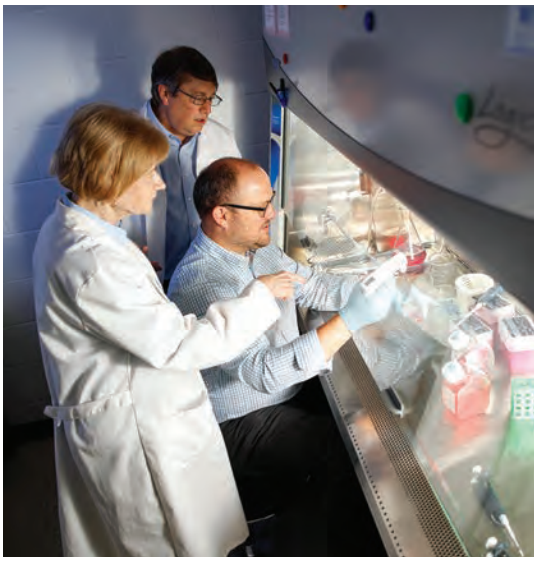
My career has been marked by an ability to pivot my research program to take full advantage of the resources and opportunities that have come my way to address the scientific questions that excite me. But it has always been defined by a fundamental interest in the mechanisms underlying cellular excitability – an interest that was nurtured and developed at URMC in Bob's lab. I credit my time at Rochester for a solid scientific foundation that left me well-prepared for the challenges of a career in biomedical research and continues to serve me well.

Debra Andreacchi-Roth, M.S., Retires

Debra Andreacchi-Roth (Debe), Senior Administrator and Research Program Manager for the department for the past 30 years, retired in September. Debe began her career at the University in 1976, and made significant contributions to the University and to the Departments of Pharmacology & Physiology and Anesthesiology & Perioperative Medicine. Debe provided oversight for all fiscal and operational activities of the Department of Pharmacology and Physiology, and was responsible for all proposal submissions and grant post-award activities for both the Department of Pharmacology and Physiology and the Department of Anesthesiology and Perioperative Medicine. Debe served on numerous committees and special interest groups over the years and used her extensive experience to contribute to multiple University initiatives. In recognition of her outstanding service to the department and university, Debe was awarded the 2019 Witmer Award for Distinguished Service, the highest staff award given by the institution. Debe always created a friendly and welcoming work environment for everyone in the department, and was deeply supportive of the professional growth of her staff. Debe, thank you for all you have done for everyone in our department over the years. Congratulations on your much-deserved retirement!

Collaborative Research-in-Action





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2021 Year in Review