DEPARTMENT OF

PHARMACOLOGY & PHYSIOLOGY

2020 ISSUE

SPRING 2020 – WINTER 2020

Graduate Program Expansion

SCHOOL OF MEDICINE & DENTISTRY
UNIVERSITY of ROCHESTER

They say,

“Hindsight is 2020.”

I say,

“Bring on 2021!”

–Robert T. Dirksen, Ph.D.

Cover Image: First Year Pharmacology and Physiology Graduate Students
Back row: Wenqi Fu, Miao He, Katherine Edwards, Amanda Bradley; Front row: Michal Shaposhnikov, Maura Connorton, Halima Aweis. Missing: Autumn Helland.
Photographer: Lily Cisco.

Newsletter Editor: Rachel Zapata-Bermudez

Message From The Chair

There is no doubt that this past year was exceptionally challenging for everyone, which was no different for our department. With the surge in COVID-19 positive cases increasing rapidly throughout New York State in March, the Medical Center redesigned all operations with one goal in mind: to keep everyone safe and to provide care for the rapidly growing number of COVID-19 patients in Western New York. The university moved all educational activities to online instruction and research laboratory operations were essentially shut down for the remainder of the semester. In addition, staff moved to remote work and/or were furloughed for the next several months. As a result, our department, once bustling with students, staff and faculty, turned into a veritable ghost town sans tumbleweeds. I cannot express how eerie it was during those days when the lights in the darkened hallways of the department would automatically turn on whenever I would walk the corridors.

Fortunately, with COVID-19 cases in Monroe County coming under control after the initial surge, we were able to ramp-up the research laboratories relatively quickly beginning in mid-May. While we are still getting used to the "new normal" of universal masking, social distancing, and regular hand sanitizing, our faculty, trainees and technical staff are back in the labs moving the research forward. Meanwhile, our graduate and medical education courses were all conducted successfully during the fall semester using a hybrid format including elements of both online and in-person instruction.

In spite of these disruptions, the department realized a number of notable milestones, awards, and achievements in 2020. For example, the department received New York State approval for a new MS degree in Medical Pharmacology (see Medical Pharmacology Spotlight on pg. 3). In contrast to existing MS programs that focus on promoting research careers, this new MS program will couple specialized academic training in medical pharmacology with personalized professional skills development to help students successfully compete in medical (MD), dental (DDS) and pharmacy (PharmD) programs. The Silvio O. Conte Center for Research in Obsessive Compulsive Disorder, led by Dr. Suzanne Haber, completed its first five-year funding cycle and the renewal application for the Center received an encouraging score for a second five years of funding (see Research Spotlight, pg. 4). Several of our trainees received notable awards this past year, including the Graduate Alumni Fellowship Award to Halima Aweis and the Outstanding Postdoctoral Research Award to Dr. Romeo Blanc. In addition, Dr. Robert Freeman received the Outstanding Course Director Award for exceptional leadership of two major interdepartmental graduate-level courses (IND 501 Ethics and Professional Integrity in Research; IND 447 Signal Transduction). Finally, six different trainees (Karl Foley, Jarreau Harrison, Jacob Kallenbach, Jing Liu, Matt Rook, and Chongyang Zhang) received highly competitive independent fellowship awards from the National Institutes of Health, American Heart Association, and the University of Rochester (see Awards on pg. 7).

In addition to recognizing these awards and accomplishments, this newsletter highlights a number of other important department developments and activities. Dr. Denise Hocking was appointed the Department of Pharmacology and Physiology Faculty and Staff Diversity Officer (see Diversity and Inclusion, pg. 2). In this new role, Dr. Hocking will chair a Faculty/Staff Diversity and Inclusion Committee consisting of members from across all segments of the department including faculty, postdoctoral fellows, graduate students, and office staff. This committee is charged with developing and implementing policies/actions to make the department a more inclusive, diverse, and equitable environment for teaching, learning, and working. In addition, the Collaboration Corner section of the newsletter (pgs. 10-11) highlights the long-standing collaborative activities between our department and faculty in the Department of Biomedical Engineering. Finally, the Alumni Career Stories section of the newsletter (pgs. 12-13) highlights four of our distinguished alumni's diverse and successful career paths.

In spite of the many challenges encountered in 2020, the department's accomplishments in our research and education missions over the past year are impressive.

We look forward to an even greater year in 2021! Meliora!

Robert T. Dirksen, Ph.D.

Lewis Pratt Ross Professor
Chair of Pharmacology and Physiology

Recognizing and Harnessing Our Differences

The University of Rochester Medical Center has recently expanded its commitment to equity and inclusion by supporting the formation of departmental Faculty/Staff Diversity and Inclusion Committees. These committees' mission is to enact meaningful and sustained change to the inclusivity of their respective departments by focusing on culture and behavior, workforce and student diversity, and transparency and accountability.

These departmental efforts will be conducted in partnership with the Office of Equity and Inclusion as well as Human Resources. Dr. Denise Hocking is serving as the Faculty and Staff Diversity Officer for the Department of Pharmacology and Physiology and will chair the Faculty/Staff Diversity and Inclusion Committee for the department.

The Faculty/Staff Diversity and Inclusion Committee includes representatives from across the DPP community, including faculty (Drs. Kaye Thomas, Angela Glading, Robert Freeman, and Robert Dirksen), staff (Lisa Adams and Rachel Zapata-Bermudez), postdoctoral fellows (Drs. Emma Norris and Alexander Kotelsky), and graduate students (Miriam Barnett and David Delemos). The committee is charged with developing and implementing policies and actions that will make the department a more inclusive, diverse, and equitable environment for teaching, learning, and working.

Celebrating and drawing upon our rich and diverse backgrounds, viewpoints, and life experiences to create a culture of inclusion and cooperation is fundamental to our individual and departmental success.

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

Medical Pharmacology Spotlight

New Master's Degree Program in Medical Pharmacology

According to a 2019 survey by the American Association of Medical Colleges (AAMC), 65% of newly matriculated medical students begin medical school a full year or more after completing college. While pre-med students utilize these "gap years" in diverse ways, nearly 25% pursue graduate studies.[1] With these students in mind, we are excited to announce New York State approval of a new graduate program leading to an MS degree in Medical Pharmacology!

Overall Program Goal:

The MS degree program in Medical Pharmacology will provide aspiring medical and health sciences professionals with the specialized academic training and professional development skills needed to craft stronger, more competitive applications for gaining entry into professional degree programs in medicine, dentistry, pharmacy, and other health science fields.

This new program aims to achieve this goal through three specific objectives, each carefully matched to corresponding components of the curriculum. First, a newly developed Medical Pharmacology course (PHP 623), together with the existing courses in Human Cell Physiology (PHP 403) and Applied Human Anatomy (BME 459), will provide students with advanced training in basic science disciplines fundamental to all medical school curricula. Second, a new program-specific and individually-tailored Professional Development course, together with our Effective Scientific Communication course (PHP 405), will help ensure students develop the AAMC-defined 15 core competencies that all successful medical school applicants should possess. Third, participation in the weekly student seminar series, other departmental seminars, and a new Special Topics in Medical Pharmacology course (PHP 593) will teach students the critical thinking and quantitative reasoning skills that are necessary for tackling real-world research and clinical problems.

Robert Freeman, Ph.D.

A particularly attractive aspect of the program is that it can be completed in just two semesters of full-time study. The program's steering committee and individual faculty mentors will supplement the students' academic training by helping them attain meaningful extracurricular experiences among the myriad of opportunities available at URMC and in the greater Rochester area. The steering committee will also provide professional school admissions committees with a comprehensive personalized letter of recommendation for each student that encapsulates their unique accomplishments and experiences.

The MS in Medical Pharmacology program will be directed by Bob Freeman, with Rachel Zapata-Bermudez serving as Program Coordinator. Current efforts are focused on marketing the program locally, regionally, and nationally, including to the 150+ pre-medical students who graduate from UR each year. After turning the corner on 2020 and with new graduate student recruitment just a few months away, we look forward to admitting our first class of students and welcoming them here next fall.

www.medpharm.urmc.edu

1 The "AAMC Matriculating Student Questionnaire – 2019 All Schools Summary Report" is available at https://www.aamc.org/data- reports/students-residents/report/matriculating-student-questionnaire-msq.

Research Spotlight

Silvio O. Conte Center
The Neurocircuitry of OCD: Effects of Modulation

Obsessive-compulsive disorder (OCD) is a chronic disorder that affects 2–3% of the population worldwide and, according to the World Health Organization, is one of the top incapacitating neuropsychiatric diseases.

The disease is characterized by persistent, intrusive thoughts (obsessions), and impulses to carry out repetitive intentional behaviors (compulsions). These symptoms persist despite the awareness that they are unproductive, and the individuals' attempts to resist them. Conventional, first-line treatments for OCD are cognitive-behavioral interventions and pharmacological approaches, particularly serotonin reuptake inhibitors (SRIs). These therapies are effective for mild to moderate cases of OCD only 40-60% of the time. Moreover, it is estimated that over 20% of OCD patients are completely refractory to these treatments. These severely affected individuals are unable to hold jobs and are often homebound. Promising new therapies for this population include a combination of invasive (lesions and deep brain stimulation-DBS) and conventional treatments along with non-invasive stimulation therapies (i.e., transcranial magnetic stimulation-TMS). Nonetheless, these approaches are only effective in about 50% of these patients.

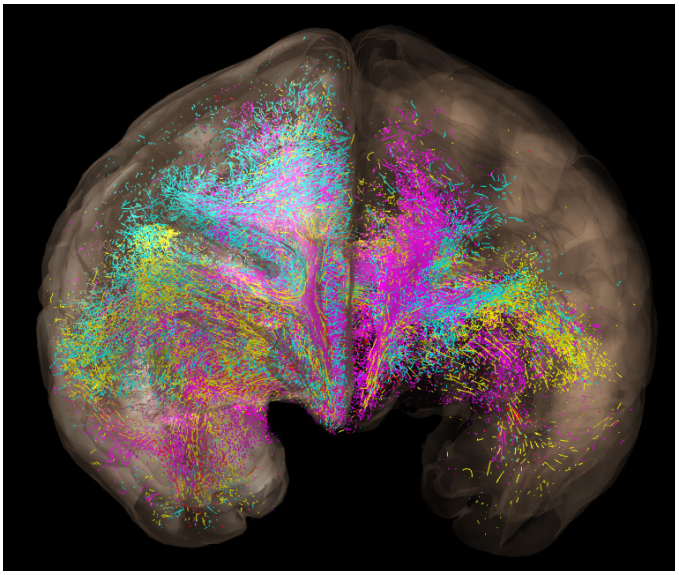


Figure: OCD network connections. Fibers from each node project to multiple brain regions, creating complex circuits that underlie the ability to modulate behaviors based on different outcomes.
Fuscia =ACC fibers, blue=vlPFC fibers, yellow=OFC fibers.

Although the pathogenesis of OCD remains unknown, converging lines of evidence suggest abnormal functioning in specific cortical and subcortically linked brain regions. Human imaging studies demonstrate abnormalities in these areas, and both invasive and non-invasive therapeutic approaches that target them are beneficial in the treatment of highly refractory OCD. We refer to them collectively as the central nodes of the OCD network (Figure). Importantly, this neural network is central to behavioral flexibility and switching goal-directed responses based on environmental changes and expected outcomes. That is, they comprise a network of brain regions central for linking stimuli, actions, and outcomes (positive or negative), thus facilitating learning and the selection of appropriate responses. They accomplish this by coding situations in which the outcome of a response deviates from the expected outcome. This paves the way for behavioral modification in future selections. Flexibility to respond to a changing environment is thus dependent on the normal functioning of the circuits within this network. Thus, this allows for the modification of behaviors based on experience. Under certain circumstances, responses can transition into habits (e.g., driving to work, etc.). A normal balance between goal-directed and habit-driven behaviors allows us to operate efficiently in our environments. However, this balance and the network's flexibility to adjust responses can be hijacked in disease, including, but not limited to, OCD (i.e., addiction). In contrast to addiction, one common feature of OCD is persistent avoidance, in which the individual compulsively avoids situations despite a low probability of an aversive outcome. That is, despite overwhelming evidence that a negative outcome is highly unlikely, an OCD patient continues to behave as if it would and creates rituals to prevent it. This fear-driven anxiety falls into several general categories, i.e., fear of contamination, fear of doing harm to self or others, etc.

Hypothesis and Goals of the Conte Center

Our central hypothesis is that the behavioral inflexibility reflected in persistent avoidance (and, thus, ritualization) in OCD is the result of circuit dysfunction between central nodes in the OCD network. There are three overarching goals. The first is to further our understanding of the brain regions and network connections that are linked to persistent avoidance behavior. This component focuses on the complex circuit interactions between the network nodes. The second is to identify abnormalities within the connections that are associated with impairments in behavioral flexibility, resulting

in persistence avoidance in individuals with OCD. The third goal is to study the effects of neuromodulation on those circuits and on the behavioral inflexibility in OCD. Finally, we use our results to develop non-invasive and invasive therapeutic approaches that target those circuits. Taken together, the Center combines state-of-the-art anatomy, physiology, behavioral assessments, imaging, and innovative advances in computational neuroscience and neural device technology to address the circuit dysfunction underlying OCD. This approach allows us to understand the effects of neuromodulation of these circuits at a level deeper than would be possible with each method alone.


Dr. Suzanne Haber

The Center brings together five interactive projects and three cores from five different Institutions: the Department of Pharmacology and Physiology, University of Rochester (lead institution); the Department of Psychiatry, University of Pittsburgh; the Department of Neuroscience, Harvard University; the Department of Psychiatry, Brown University; and the Department of Neuroscience, University of Puerto Rico. Each project uses novel approaches to address specific questions. Project 1 (UR) combines animal anatomical studies with high-resolution diffusion and functional imaging in humans to identify the connectivity profiles in the OCD network. These data directly link to data in Projects 2 (University of Pittsburgh) and 3 (Harvard) that probe imaging abnormalities in OCD patient populations and in individuals, identifying individual variation in critical network locations. The results from these studies are used to explore novel invasive and non-invasive neuromodulation of the OCD network in Projects 4 (Brown) and 5 (University of Puerto Rico).

The results from the experiments funded through the Center have moved the field forward in several important ways:

1. We developed an animal model of persistent avoidance consistent with behavioral constructs seen in OCD. In particular, the task demonstrates persistent avoidance for choosing an object that, while previously having resulted in a negative outcome, would lead to a reward. In other words, the animal continues to avoid specific stimuli despite the fact that, if selected, it would now result in a reward. This behavior is associated with reduced activity in one of the central nodes of the OCD network, the ventrolateral prefrontal cortex (vlPFC). Importantly, activity between this node and another, the anterior cingulate cortex (ACC), is necessary for overcoming the persistent avoidance.

2. We found a specific region embedded within the ACC that receives input from the other central nodes of the network and functions as a central hub for this behavior.

3. This hub is involved in coding the value and uncertainly of aversive outcomes. It is also active during the time the animal is resolving the problem and selecting a response, supporting the central role of this brain region in avoidance behavior.

4. Testing the persistence avoidance task in a population of OCD patients, we found that they performed less well compared to healthy control subjects. Importantly, they were less able to devalue the negative value of stimuli when those cues no longer resulted in a negative outcome.

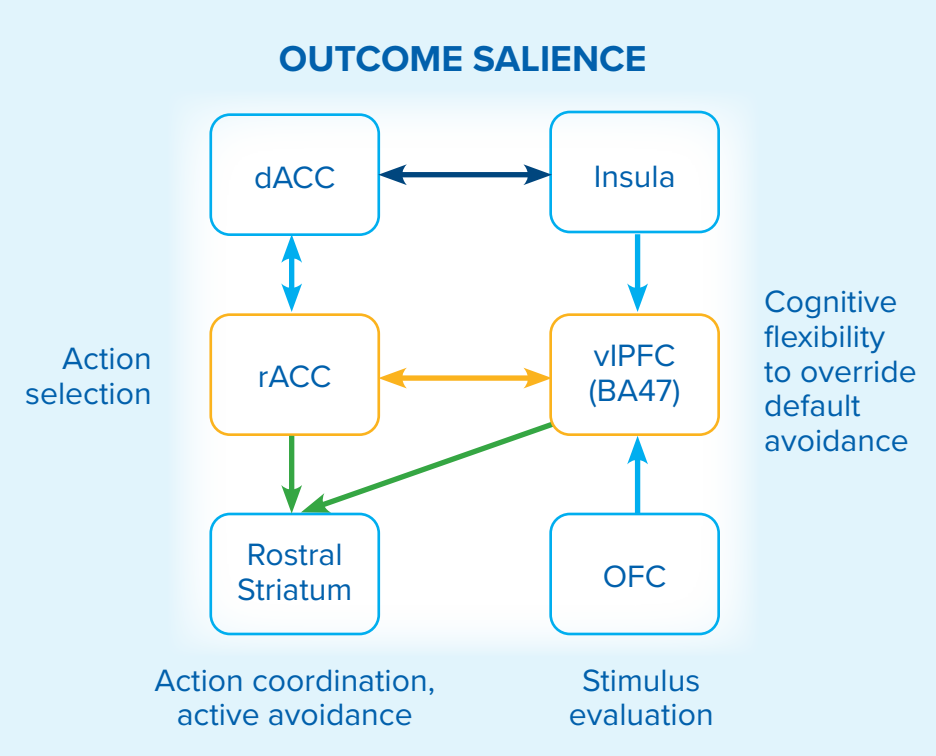
5. White matter connectivity abnormalities are common in many diseases, including OCD. We found that white matter pathways can be segmented based on the position of specific cortical fibers within them, allowing the identification of the specific circuits that are abnormal in OCD.

6. Finally, based on these collective results, we modified the DBS target, repositioning it to better capture the relevant connections in the network. These modifications resulted in better outcomes for the patients. Most recently, the results also have led to proposing new targets that are now under investigation.

Overall, the Center applies a network approach to understand the circuit dysfunctions that explain obsessions and compulsions and the lack of cognitive control over them. The individual projects and between-project collaborations have uncovered fundamental relationships between brain structures in the OCD network that contribute to the abnormalities underlying the ritualization surrounding persistent avoidance in OCD. Importantly, this network, which mediates normal behaviors related to the flexibility of responses, is central not only to OCD, but a wide range of other psychiatric illnesses, including depression, PTSD, and addictions. Thus, our studies have a broad impact on understanding how circuit dysfunction can underlie these other disorders and sets the stage for optimizing targets for neuromodulation for a wide range of psychiatric illnesses.

(continued on next page)

The OCD Network: The ACC sits at the intersection of the motivational and cognitive systems. The ACC is particularly important for both control and evaluation of self-generated actions and the responses to aversive stimuli. The vlPFC is involved in sensory integration, emotional regulation, stimulus-outcome encoding, salience, and cognitive control, which plays an important role in behavioral inhibition and cognitive flexibility. The OFC combines information from highly processed sensory inputs with reward and aversive stimuli through its connections with limbic regions, placing it in an optimal position for value-encoding, stimulus-evaluation and outcome learning. The Insula is part of the salience network. The striatum plays a central role in goal-directed behaviors and habit formation. dACC=dorsal anterior cingulate cortex, OFC=orbitofrontal cortex, rACC=rostral anterior cingulate cortex, vlPFC=ventrolateral prefrontal cortex Arrows indicate direct connections.



Representative Conte Center Publications

The Silvio O. Conte Center for Obsessive Compulsive Disorder Research produced over 50 publications during the current funding cycle (2015-2020). Below is a list of a few of these publications:

1. Rodriguez-Romaguera J, Do-Monte FH, Tanimura Y, Quirk GJ, Haber SN. **Enhancement of Fear Extinction with Deep Brain Stimulation: Evidence for Medial Orbitofrontal Involvement.** Neuropsychopharmacology, 2015.
2. Heilbronner SR, Rodriguez-Romaguera J, Quirk GJ, Groenewegen HJ, Haber SN. **Circuit-Based Corticostriatal Homologies Between Rat and Primate**. Biological Psychiatry, 2016.
3. Choi EY, Tanimura Y, Vage PR, Yates EH, Haber SN. **Convergence of Prefrontal and Parietal Anatomical Projections in a Connectional Hub in the Striatum**. Neuroimage, 2016
4. Coizet V, Heilbronner SR, Carcenac C, Mailly P, Lehman JF, Savasta M, Haber SN. **Organization of the Anterior Limb of the Internal Capsule in the Rat.** Journal of Neuroscience, 37:2539-2554, 2017.
5. Safadi Z, Grisot G, Jbabdi S, Behrens TE, Heilbronner SR, Mandeville J, Versace A, Phillips ML, Lehman JF, Yendiki A, Haber SN. **Functional Segmentation of the Anterior Limb of the Internal Capsule: Linking White Matter Abnormalities to Specific Connections.** Journal of Neuroscience, 38:2106-2117, 2018.
6. Tang W, Jbabdi S, Zhu Z, Cottaar M, Grisot G, Lehman JF, Yendiki A, Haber SN. **A Connectional Hub in the Rostral Cortex Links Areas of Emotion and Cognitive Control.** eLife, 8:e43761, 2019.
7. Haber SN, Tang W, Choi E, Yendiki A, Hesheng L, Jbabdi S, Versace A, Phillips ML. **Circuits, Networks, and Neuropsychiatric Disease: Transitioning from Anatomy to Imaging.** Biological Psychiatry, 87:318-327, 2020.
8. Tang W, Choi EY, Heilbronner SR, Haber SN. **Nonhuman Primate Meso-Circuitry Data: A Translational Tool to Understand Brain Networks Across Species.** Brain Struct Funct, In Press, 2020.
9. Haber SN, Yendiki A, Jbadbi S. **Four Deep Brain Stimulation Targets for Obsessive-Compulsive Disorder: Are They Different?** Biological Psychiatry, In Press, 2020.

Graduate Education

Welcome First Year Students!

Front row: Michal Shaposhnikov, Maura Connorton, Halima Aweis
Back row: Wenqi Fu, Miao He, Katherine Edwards, Amanda Bradley
Missing: Autumn Helland

Degrees Awarded

OCTOBER 2019

Isaac Fisher, Ph.D.

"Understanding Molecular Mechanisms of G-protein Subunit by Activation of Downstream Effectors"

Advisor: Dr. Alan V. Smrcka

NOVEMBER 2019

Manisha Taya, Ph.D.

"Neutrophil Elastase and GPNMB as Novel Potential Therapeutic Targets in aTsc2-null Mouse Model for Lymphangioleiomyomatosis (LAM) Tumor Growth"

Advisor: Dr. Stephen R. Hammes

OCTOBER 2020

Brandon Berry, Ph.D.

"Optogenetic Control of Mitochondria Impacts Cellular Energy Sensing and Hypoxia Resistance"

Advisor: Dr. Andrew P. Wojtovich

Student and Postdoc Awards

Graduate Alumni Fellowship Award

This fellowship, established by gifts from alumni of the PhD, MPH, and MS degree programs in the School of Medicine and Dentistry, annually recognizes incoming first-year students with promise for exceptional accomplishment in graduate study.

Halima Aweis
(First-Year)

Outstanding Postdoctoral Researcher Award

This award, established in 2015, is to recognize a School of Medicine and Dentistry postdoctoral appointee for outstanding research contributions. The selection criteria include originality, creativity, and significance of their research accomplishments.

Romeo Blanc, Ph.D.
(Chakkalakal Lab)

Invited Speaker, European Calcium Society

Based on her recent JBC publication, Lara was invited to present her research at the European Calcium Society General Assembly plenary session in honor of the memory of Mike Berridge. Lara is one of only 6 invited speakers, the others all being past students.

Lara Terry
(Yule Lab)

STEM Catalyst Finalist

This Rochester Museum and Science Center Award recognizes bright minds in our area's educators and organizations that are making a difference and exciting people about opportunities in STEM.

Emma Grygotis Norris, Ph.D.
(Hocking Lab)

Young Investigator and Undergraduate Research Awards

Society for Redox Biology and Medicine Conference

Brandon Berry, Ph.D.
(Young Investigator Award) (Wojtovich Lab)

Tyrone Nieves
(Undergraduate Research Award) (Wojtovich Lab)

Bidlack Lab

Based on her recent publication in Molecular Pharmacology, Miriam was recognized as the October Highlighted Trainee Author by the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Miriam Barnet

Graduate Student Fellowship Awards

American Heart Association Predoctoral Fellowship

1/1/20 – 12/31/21
"Role of MRCKa and Na+/K+-ATPase signaling in alveolar barrier function in the mouse lung"

Jing Liu
(Dean Lab)

SMD Ambassador Program

As an SMD Ambassador, Alex connects current medical students, trainees, and PhD candidates with alumni through events, programs, tours, and other activities.

Alexander Milliken
(Brookes Lab)

Joan Wright Goodman Dissertation Fellowship

7/1/20 – 6/30/21
This UR fellowship was endowed by Joan Wright Goodman, PhD class of 1952, to support doctoral students across disciplines in the sciences.

Matthew Rook
(MacLean Lab)

Wilmot Cancer Institute Predoctoral Fellowship

7/1/20 – 6/30/22
"Targeting CCR2 to mitigate the late effects of juvenile radiation-induced skeletal muscle decline"

Jacob Kallenbach
(Chakkalakal Lab)

American Heart Association Predoctoral Fellowship

1/1/20 – 12/31/21
"The role of PDE1C in vascular smooth muscle cell lysosomal dysfunction and atherosclerosis"

Chongyang Zhang
(Yan Lab)

NIH F31 Ruth L. Kirschstein Individual Predoctoral National Research Service Award F31

9/15/20 – 9/14/23
"The role of HSPB8 (HSP22) in maintaining tau proteostisis"

Jarreau Harrison
(Johnson Lab)

NIH F30 Ruth L. Kirschstein Individual Predoctoral National Research Service Award F30

2/1/20 – 1/31/24
"Protein phopsphatase 1 isoforms and human de novo mutations in synaptic plasticity"

Karl Foley MSTP
(Xia Lab)

Awards And Honors

The department currently manages $10M in extramural research funds annually and has an additional >$9M in pending proposals.

Awarded Tenure 2020
Dr. Joe Chakkalakal

2020-2021 Faculty Senator and SEC Member
Dr. Jean Bidlack

2020 Gold Medal Award the Society of Biological Psychiatry for Research on Mental Disorders
Dr. Suzanne Haber

2020 Outstanding Graduate Course Director Award
Dr. Robert Freemen

2020 Teaching Students to Explore Protein Structures Using the Visual Molecular Dynamics(VMD) program and 3D Printing
Drs. Whasil Lee, Moriana Garcia

2020 Summer Outreach STEM Program
Dr. Whasil Lee

Outstanding Graduate Course Director Award
Dr. Robert S. Freeman


Dr. Joe Chakkalakal


Dr. Jean Bidlack


Dr. Suzanne Haber


Dr. Robert S. Freeman


Dr. Whasil Lee


Dr. Moriana Garcia

SELECTED PUBLICATIONS

Terry LE, Alzayady KJ, Wahl AM, Malik S, Yule DI. Disease-associated mutation. Terry LE, Alzayady KJ, Wahl AM, Malik S, Yule DI. Disease- associated mutations in inositol 1,4,5-trisphosphate receptor subunits impair channel function. J Biol Chem. 2020 Oct 22:jbc.RA120.015683. doi: 10.1074/ jbc.RA120.015683. Online ahead of print. PMID: 33093175

Norris, E.G., Dalecki, D. and Hocking, D.C. (2020) Acoustic fabrication of collagen-fibronectin composite hydrogels accelerates microtissue formation. Applied Sciences, 10(8), 2907.

Tylock K, Auerbach DS, Zhen ZT, Thornton CA, and Dirksen RT. Biophysical mechanisms for QRS- and QTc-interval prolongation in mice with cardiac expression of expanded CUG-repeat RNA. J. Gen. Physiol., 152(2), 2020. PMC7062505

Milliken AS, Kulkarni CA, Brookes PS. (2020) Acid enhancement of ROS generation by complex-I reverse electron transport is balanced by acid inhibition of complex-II: relevance for tissue reperfusion injury. Redox. Biol. 37: 101733. [PMID: 33007502 PMCID: PMC7527751] doi: 10.1016/ j.redox.2020.101733.

Rook M, Williams A, Lueck JD, Musgaard M, MacLean DM.β11-12 linker isomerization governs Acid-sensing ion channel desensitization and recovery. (2020) eLife. Feb 7;9. Pii: e51111. PMCID: PMC7041949.

Blanc S. Roméo, Kallenbach G. Jacob, Bachman F. John, Mitchell Amanda, Paris D. Nicole, and Chakkalakal V. Joe. Inhibition of inflammatory CCR2 signaling promotes aged muscle regeneration and strength recovery after injury. Nat Commun. 2020 Aug 20;11(1):4167.

Barnett, M.E., Knapp, B.I. and Bidlack, J.M. (2020) Unique pharmacological properties of the kappa opioid receptor signaling through Gaz as shown with bioluminescence resonance energy transfer. Mol. Pharmacol. 98: 462-474.

McCullock TW, MacLean DM, Kammermeier PJ (2020). "Comparing the performance of mScarlet-I, mRuby3, and mCherry as FRET acceptors for mNeonGreen." PLoS One 15(2): e0219886.

DiStefano PV, Glading AJ. VEGF signalling enhances lesion burden in KRIT1 deficient mice. J Cell Mol Med. 2020 Jan;24(1):632-639. doi: 10.1111/jcmm.14773. Epub 2019 Nov 20. PubMed PMID: 31746130; PubMed Central PMCID: PMC6933401.

Watkins LR and Orlandi C. Orphan G Protein Coupled Receptors in Affective Disorders. Genes 2020 Jun 24;11(6):694.

White JK, Bromberg-Martin ES, Heilbronner SR, Zhang K, Pai J, Haber SN, and Monosov IE. A neural network for information seeking. Nat Commun. 2019 Nov 14;10(1):5168.

Hou H, Wang L, Fu T, Papasergi M, Yule DI, and Xia H. Magnesium acts as a second messenger in the regulation of NMDA receptor-mediated CREB signaling in neurons. Mol Neurobiol. 2020 57(6):2539-2550.

Peng H, Purkerson JM, Freeman RS, Schwaderer AL, and Schwartz GJ. Acidosis induces antimicrobial peptide expression and resistance to uropathogenic E. coli infection in kidney collecting duct cells via HIF-1Î±. Am J Physiol Renal Physiol. 2020 Feb 1;318(2):F468-F474.

Collaboration Corner

A unique aspect of the research programs in the Department of Pharmacology and Physiology are the number of longstanding collaborative interactions with other departments and centers across the university. Indeed, the overall objective of the Drug Targets and Mechanisms Program of Excellence Pilot Grant program is to organically stimulate and grow these interdepartmental collaborations. These pilot grants have fostered collaborations with the Departments of Pediatrics, Genetics, Environmental Medicine, Biomedical Engineering (BME), and the Center for Oral Biology.

In this section of the newsletter, we highlight our collaborative interactions with the research faculty in the Department of Biomedical Engineering. The collaboration between the two departments dates back to 2001 and includes three basic science faculty (Drs. Glading, Hockings, and Lee) whose labs are located in Pharm/Phys space in the medical center, as well as several clinical research faculty located on the 5th floor. All three basic science faculty members hold secondary appointments in the BME department, their research grants are managed by our department's superior administrative staff, and they are all very active in the Department's teaching and mentoring programs.

Pharmocology & Physiology/Biomedical Engineering Research Group

Angela Glading, Ph.D.
The Angela Glading Lab currently has an ongoing collaboration with Dr. James McGrath, Ph.D. (BME) to test the commercial productin of a new cell culture device that features an UR-developed ultrathin (< 300 nm) and transparent porous membranes to enable high resolution live imaging of barrier tissue on highly permeable substrates. The barrier imaging chamber being developed, called the μSiM (microsystem enabled by a Silicon Membrane), has both tissue engineering and drug development applications. These devices, produced by the UR-founded start-up SiMPore, are being used to develop advanced blood-brain barrier models of Alzheimer's disease and other vascular disorders. This work is supported by a FuzeHub manufacturing grant from New York state.

Dr. Glading also participates in the educational mission of the Biomedical Engineering department through teaching and mentoring activities. Her expertise is featured in lectures in BME265: Intro to Cell Mechanics and Mechanobiology and the first-year introductory course BME402: Research Methods. Dr. Glading is also a past and present advisor to BME Master's and PhD trainees.

Glading Lab


Hocking Lab

Denise Hocking, Ph.D.
Dr. Denise Hocking (Pharmacology and Physiology) and Dr. Diane Dalecki (Biomedical Engineering) have a long- standing collaboration focused on developing innovative therapeutic and diagnostic ultrasound technologies for tissue engineering, wound healing, and regenerative medicine. Together, they have led numerous NIH- sponsored projects as a Multi-PI leadership team. The rationale for this cross-disciplinary collaboration is that mechanical forces associated with ultrasound propagation can be used to alter extracellular matrix protein structure, and thus, stimulate cell functions associated with wound repair, providing new, non-invasive approaches to tissue regeneration.

This collaboration has led to several new technologies, including methods to (1) acoustically pattern endothelial cells to vascularize tissue engineered hydrogels non-invasively, (2) functionalize, characterize, and monitor collagen-based biomaterials in 3-dimensions, and (3) accelerate healing of diabetic skin wounds. The collaborative nature of poster presentations at scientific meetings, publications and joint patents, and a variety of awards and fellowships garnered by graduate and undergraduate students co-mentored by Drs. Hocking and Dalecki.

Lee Lab

Whasil Lee, Ph.D.
The Lee Mechanobiology lab focuses on the roles of mechanosensitive ion channels, Piezo1 and Piezo2, to understand pathogenesis and to find therapeutic strategies for knee arthritis. Dr. Lee has established a multidisciplinary research program for students and scientists in Biomedical Engineering (BME) and Pharmacology and Physiology (PHP) departments. In their laboratory located in SMD 4-8548, Lee lab uses multidisciplinary cutting-edge approaches from engineering to physiology, including Ca2+ imaging microscopy, confocal microscopy, atomic force microscopy (AFM), molecular biology assays, and animal models. The Lee lab has strong collaborations with Dr. Mark Buckley (BME), Dr. Alayna Loiselle (CMSR), Dr. Sandeep Mannava (Orthopaedics) and Dr. Robert Dirksen (PHP; a Co-mentor for postdoc Dr. Kotelsky in ROCMSK T32 program). Teaching: Dr. Lee developed two new courses for upper-level undergraduates and graduate students majoring BME and PHP. In BME465 / PHP465, she teaches the fundamental principles of mechanotransduction and mechanobiology; and in BME468/PHP468, protein structures and human diseases.

Dr. Lee also participates IND501 Ethics course as a Facilitator every year. Her students and trainees, who come with diverse disciplines, learn fundamentals of mechanobiology and their clinical aspects, and propose or examine complex mechanotransduction processes. A student who took BME465/ PHP465 last year, Ms. Nancy Bansbach who focused her class project on 'the microgravity and bone health', acknowledged her research passion and her new job at the Johnson NASA Space Center at Huston. Mentoring: Every semester, 5–10 BME undergrad students take independent study courses and participate our lab projects, and students present at BMES conferences and CMSR symposiums. Dr. Lee proudly noted that two trainees, Ms. Lydia Petricca and Halima Aweis joined graduate programs at the University of Virginia (Bioengineering) and the University of Rochester (CMPP program), respectively.

Furthermore, Dr. Lee is an Academic Advisor of 23 BME undergrads every year, she routinely meets students to discuss curriculum and research. In addition, Dr. Lee also serves as a Senior Design Supervisor and a BME Graduate Admission Committee Member every year. Outreach: Dr. Lee and David T. Kearns Center have developed a piloted a summer STEM program, titled 'Protein Channels Causing Human Disease - Clay Sculpting Your Channel of Interest' for students participating in Upward Bound, a selective program for Rochester City School District (RCSD) high school students who are either potential first- generation college students or from low-income families. Students in BME and DPP departments volunteer and work with an Upward Bound student every year.

In short, Dr. Lee and the Lee lab are in a unique position to research and mentor BME and PHP students both in laboratory and classes. She promotes the excellence in basic science and translational research, and pursues comprehensive understanding of physiology and biomedical engineering, and this has been only possible because of the extraordinary collaborative and environments of the BME and PHP departments. She deeply thanks her department chairs, Dr. Dalecki and Dr. Dirksen, and faculty members in BME and PHP for recruiting her to the University of Rochester.

Alumni Career Stories

Matt Betzenhauser Ph.D. (2008)

What is the most important element in nature? Some might say oxygen because we breathe it, some may say hydrogen because it helps make water, but I came to learn in the Department of Pharmacology and Physiology that calcium is the be all and end all for life. I came to the department because I wanted to learn how cells work, and more specifically, how cells respond to the outside world. After my first day in Dr. David Yule's lab in the summer of 2003 and watching calcium go up and down in some parotid acinar cells, I was hooked. I also went to graduate school because I wanted to learn how to be a scientific leader and through my thesis studies with David and spending time with the faculty, students and staff set me on the path I find myself on now.

After leaving Rochester, I followed calcium into the heart and muscle in the Department of Physiology at Columbia University. I then continued to look at how calcium impacts the aging heart as a Staff Scientist and Assistant Director of Research at the Masonic Medical Research Laboratory in Utica, NY. From there, I moved back to Western NY to start up a cell-based screening team at AMRI at our Integrated Drug Discovery facility in Buffalo. I was able to implement the knowledge of imaging gained during my graduate studies in the department to work leading projects and teams using high content imaging and analyses to identify new drug candidates. In my current position, I am leveraging exciting recent advances in laboratory automation, high content imaging and genome editing to develop novel, physiologically relevant, predictive models of human disease for drug discovery. My greatest thrill at this stage in my career is in managing projects and leading a team of 25 other talented and creative scientists in this effort.

Hoffman Moka Lantum, Ph.D. (2001)

I am the CEO of CheckUp Medical. We operate a tech- enabled medication procurement and delivery service in Kenya and South Sudan that helps patients to get medicines and diagnostics at home and at work as fast as we can and at the best prices. Some people call me the "medicine man" because once you have my number you can save on medicines and health care costs. We use technology to make our services frictionless and efficient. Our operations focus on optimizing rate- limiting steps, just like enzymes do. Though 19-years ago, the work during my training in the DPP seems far removed from the present. I often ask, did I really do a Ph.D. in Pharmacology to start selling medicines?

Drawing a direct line from research in molecular methods in Pharmacology to helping people obtain affordable medicines quickly may not immediately be obvious. Yet looking back, I recall my interest was always focused on ensuring safe access to medicines. My thesis work involved studying how enzymes in the liver and kidney protect against cell damage and cancer. The most frequently used phrase in our lab was "bioactivation" because we were very passionate about the molecular mechanisms that underlie the side effects of drugs and anesthetics. I did a ton of enzyme assays in order to understand how drugs were broken and processed in the body to compounds that were either destined as good byproducts or sometimes destined as bad products that can cause hell in other tissues. It all depended on the rate-limiting step of a metabolic pathway.

While what I do now is not laden with molecular terms nor published in peer journals, my 4.5 years in DPP medicines work to selling medicines was not direct. I was a doctor before joining DPP. The day after defending my thesis at DPP, I was hired as a senior scientist at Eastman Kodak in Rochester. There I learned business and management. After 5 years, I joined Excellus BlueCross BlueShield as Director of Utilization Management from 2006 to 2011, where I used claims data to design cost- efficient heath care pathways. There I learned corporate politics and health financing. In 2011, I began a Masters in Health Care Management at Harvard University. I graduated in 2013 and founded my first company that used technology to monitor medication supply chains in public systems. I exited that business in 2016 and subsequently founded CheckUps Medical.

I have been honored along the way with numerous awards. In 2016, I was nominated by Policy Magazine as a Top-100 Global Thinker alongside Hillary Clinton and Mark Zukerberg. I serve on numerous boards of directors, including the Max and Mariam Charitable Foundation in Rochester. I also serve as an Expert-in-Residence at the Harvard iLab, which allows me to mentor other young entrepreneurs.

I am deeply indebted to Dr. Anders for continuing to be my mentor even to this day. He always believed in me, and because of the training and support he has provided over the years, I am able to sell medicines with a level of molecular understanding that helps me keep patients safe across the globe.

Makaia Papasergi-Scott, Ph.D. (2017)

When I reflect on my time in the pharmacology and physiology department, I am tremendously grateful. The training and experience I received established a well-laid foundation for my career, and the collaborative and supportive environment is an aspect that I increasingly cherish. My fondest memories

all revolve around the people that make the department a unique place: comprised of moments of laughter at department gatherings; acts of kindness and generosity that gave a feeling of belonging; critical and impassioned discussions of research and ethics; and always finding an ear to listen when challenges arose.

Under the guidance of Drs. Greg Tall and Robert Freeman, I completed my thesis work on phosphorylation of the G protein folding chaperone Ric-8 in 2017. I was then fortunate to stay affiliated with the department an additional year as a postdoctoral scholar in Dr. Hugh Xia's lab studying synaptic protein interactions by fluorescent lifetime imaging. I also simultaneously taught evening courses at SUNY Geneseo and Monroe Community College as an adjunct. During this time, however, I realized that I intensely disliked working with rodents, I missed working within the realm of G protein signaling, and I felt drawn to structural biology. When I expressed to Hugh my desire to pursue research that I was passionate about, his support was more than I could have imagined, a demonstration of the department's encouraging environment and the caring nature of the faculty.

I soon arrived at my current postdoctoral position in Dr. Georgios Skiniotis' laboratory at Stanford University. My research here involves mechanistic studies of G protein signaling pathways by leveraging structural information obtained through cryo-electron microscopy (cryoEM) with biochemical and computational methods. My first project focused on structures of the metabotropic GABAB receptor and was recently published in Nature. I was also involved in our lab's collaborative manuscript with the Tall lab on the structure of Ric-8 in complex with G protein alpha. Coincidently, one of the proteins used in that study was Ric-8 that I had personally purified years ago during my thesis work. It was quite a surprise to me on my interview that they had the cryoEM reconstruction, and I was moved to tears upon first seeing the structure of the protein that I prepared. In addition to research, I am also a postdoctoral representative on a pilot committee for the physiology department's "diversity and environmental inclusion program", a member of a subcommittee promoting and highlighting diversity on the department webpage, and I have led a team to develop the Skiniotis lab webpage. I love that my current position combines previously learned techniques with new ones, is on a topic I am passionate about, and that science and art intersect in the visual representation of molecular structures.

Patricia Perez Cornejo, Ph.D. (1996)

I started my science journey in the Department of Physiology at the University of Rochester in the fall of 1990. Not being able to fluently speak the language was the first obstacle I had to overcome. Despite that, I became a student in the Physiology Graduate Program under the superb direction of Dr. Ted Begenisich, who not only taught me about potassium channels but also trained me to be a rigorous scientist. I defended my thesis on "C-type Inactivation in Mutant Shaker Potassium Channels" on May 1996. During those 6 years I benefited from many great teachers and wonderful technicians that help me develop and refine my technical and communication skills. Thanks to their patience and mentoring, my self-confidence grew and I became an independent learner, determined to succeed in academia.

I was fortunate enough to return to Mexico following my defense to begin my independent career at a public university. My return to Mexico was made possible thanks to a Repatriation Program funded by the National Council for Science and Technology. My first task was to set up a lab with the help of one graduate student, one technician and a small grant I received from Funsalud. Setting up the lab and teaching medical students became everyday activities. It was not easy. After a couple of years, I returned to the University of Rochester as a postdoctoral fellow to work alongside Dr. Phil Knauf. I stayed 2 more years as a Research Assistant Professor of Dentistry in Dr. James Melvin's group in the Center for Oral Biology.

Since my subsequent return to Mexico, I have worked in the Physiology and Biophysics Department in the School of Medicine at the Autonomous University of San Luis Potosi. I have published 30 papers, graduated 6 students and trained numerous undergraduates. I have been a member of the National System of Researchers since 1997. In 2010, I was a Visiting Professor at the Cell Biology Department at Emory University. More recently, in 2017, I was a visiting Scholar at the Department Physiology and Pathology of Ion Transport at the Leibniz Institute of Molecular Pharmacology in Berlin, Germany. During my career, I have learned that is never too late to improve my teaching skills. Over the last 8 years, I attended the APS Institute on Teaching and Learning meetings and have become part of the Life Science

Thanks to my rigorous graduate and postdoctoral training at the University of Rochester, I have enjoyed a rich and successful career in science. Learning to do research, attending seminars of leaders in the field, and interacting with my classmates are among the many great memories from my time in Rochester!

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UNIVERSITY of ROCHESTER

Department of Pharmacology and Physiology
University of Rochester
School of Medicine & Dentistry 601 Elmwood Avenue,
Box 711
Rochester, NY 14642-8711

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