Boston University Pharmacology & Experimental Therapeutics – Biogen Symposium

Innovations in Neuroscience Drug Discovery

Friday, November 16th, 2018







Dear Colleagues,

Welcome to the symposium "Innovations in Neuroscience Drug Discovery" organized by the Boston University Department of Pharmacology & Experimental Therapeutics - Biogen Ph.D. Program and the university-wide NIGMS Program in BioMolecular Pharmacology at Boston University. Our industry-academia collaboration provides a unique training opportunity to support the aspirations and scientific advancement of BU Pharmacology and Biogen scientists who jointly pursue a Ph.D. degree in Pharmacology & Experimental Therapeutics. Hard work and dedication by many Biogen employees and BU faculty over the past five years have cultivated the success of the training program, bringing us to today - our first joint symposium – a reflection of the mutual dedication of Boston University and Biogen to doctoral education.

The objective of the BU-Biogen Symposium is to enhance the research training of prospective and current doctoral students and their mentors at BU and Biogen . The symposium focuses on innovative and cutting-edge advances that are driving drug discovery, particularly related to neuroscience. In planning this program, we wanted to capture the energy and optimism surrounding the elucidation of new and emerging technologies and areas of research that would be of interest to our broad range of scholars and industrial scientists. We are excited to bring together a diverse group of thought leaders to share their insights and expertise with students, faculty, industrial scientists and guests. It is our hope that their sharing of leading-edge science will motivate and inspire, foster creativity and collaboration, and ultimately contribute to the discovery of breakthrough therapies for those who suffer from debilitating neurological diseases.

We hope you enjoy the day as a celebration of our mutual enthusiasm for research and training of students!

Sincerely,

David H. Farb, Ph.D., Professor & Chair, Department of Pharmacology & Experimental Therapeutics, NIGMS Program in BioMolecular Pharmacology, Boston University

Anabella Villalobos, PhD., Senior Vice President, Biotherapeutic & Medicinal Sciences, Biogen Anirvan Ghosh, Ph.D., Senior Vice President, Research & Early Development, Biogen







Friday, November 16th

- 8:00 9:00 Check-in and Breakfast
- 9:00 9:10 Academia-Industry Alliances: Catalyzing Discovery Science David H. Farb, Ph.D., Chair, Department of Pharmacology & Experimental Therapeutics, Boston University
- 9:10 9:20 Biogen Vision and Industry Academia Alliances Anabella Villalobos, Ph.D., Senior Vice President, Biotherapeutic & Medicinal Sciences, Biogen
- SESSION 1 HARNESSING CUTTING-EDGE TECHNOLOGY TO ENABLE DRUG DISCOVERY Moderator: Richelle Sopko, Ph.D., Scientist, Biotherapeutic & Medicinal Sciences, Chair, BU-Biogen Ph.D. committee, Biogen Jeremy Burns, current BU-Biogen Ph.D. student
- 9:20 9:40 *CryoEM Insights into GPCR Activation and Signaling* Georgios Skiniotis, Ph.D., Professor of Molecular & Cellular Physiology and Professor of Structural Biology, Stanford University School of Medicine
- 9:50 10:10 Untangling Neurodegenerative Diseases Using Patient-Based Structural Biology

Anthony W. P. Fitzpatrick, Ph.D., Assistant Professor of Biochemistry, and Molecular Biophysics, Mortimer B. Zuckerman Mind Brain Institute, Columbia University

- 10:10 10:25 BREAK
- 10:30 10:50 *Optical Analysis of Biological Neural Networks Across Scales* Xue Han, Ph.D., Associate Professor of Biomedical Engineering and Pharmacology, Boston University
- 11:00 11:20 JAK/STATs and the Brain: A Pharmacological Window on the BDNF Transcriptome of Neurological Disease

Shelley J. Russek, Ph.D., Professor of Pharmacology & Experimental Therapeutics and Biology, Boston University

11:30 – 11:50 *Cell Type Classification and Circuit Mapping in the Brain: Mapping a Path to Discovery*

Hongkui Zeng, Ph.D., Executive Director, Structured Science, Allen Institute for Brain Science

12:00 – 1:00 BUFFET LUNCH

Friday, November 16th

1:00 - 1:10 Afternoon Introductory Remarks Anirvan Ghosh, Ph.D., Senior Vice President, Research & Early Development, Biogen **NEUROINFLAMMATION AT THE NEXUS OF CNS DISEASES SESSION 2** *Moderators:* Terry Fang, Ph.D., Scientist, Research and Early Development, Biogen Kate Henry, current BU-Biogen Ph.D. student 1:10 - 1:30 Neuroimmune Interactions in Development: Implications for Health Throughout the Lifespan Staci Bilbo, Ph.D., Associate Professor of Pediatrics and Program in Neuroscience, Harvard Medical School/Mass General Hospital Microglial Phagocytic Mechanisms Governing Brain Plasticity in 1:40 - 2:00Health and Disease Dori P. Schafer, Ph.D., Assistant Professor, Department of Neurobiology, University of Massachusetts Medical School 2:10 - 2:30Proteomic and Neuropathological Characterization of Extracellular Vesicles in Alzheimer's Disease Tsuneya Ikezu, M.D., Ph.D., Professor of Pharmacology & Experimental Therapeutics and Neurology, Boston University 2:40 - 3:00Membrane-Less Organelles and RNA Binding Proteins as Targets for Therapy of Neurodegenerative Diseases Benjamin Wolozin, M.D., Ph.D., Professor of Pharmacology & Experimental Therapeutics and Neurology, Boston University 3:10 - 3:25 BREAK **SESSION 3** PHARMACOLOGY, MODELS AND BIOMARKERS: BENCH TO BEDSIDE Moderator: Danielle Graham, Ph.D., Director, Discovery Biomarkers, Research and Early Development, Biogen Trip Anderson, current BU-Biogen Ph.D. student Therapeutic Insights into Repeat Expansion Disorders 3:30 - 3:50

Friday, November 16th

Alzheimer's Disease: The Brain Disease or the Peripheral System-4:00 - 4:20Brain Axis Disease? Wendy Qiu, M.D., Ph.D., Professor of Psychiatry and Pharmacology & Experimental Therapeutics Boston University School of Medicine

4:30 - 4:50 Animal Models in Neuroscience Drug Discovery: The Good, the Bad, and the Ugly

Thomas Kornecook, Ph.D., Senior Director, Translational In Vivo Sciences, Biogen

- Application of Pharmacokinetic and Pharmacodynamic Modeling in 5:00 - 5:20Drug Development Himanshu Naik, Ph.D., Director, Clinical Pharmacology, Biogen
- 5:30 5:35 **CLOSING REMARKS**
- 5:35 6:30 RECEPTION

Georgios Skiniotis, Ph.D.



Georgios Skiniotis is Professor of Molecular & Cellular Physiology and of Structural Biology at Stanford University. He is also co-Director of the Stanford-SLAC Cryo-EM Center at Stanford University. Dr. Skiniotis is a structural biologist with expertise in electron cryomicroscopy (cryoEM). Dr. Skiniotis has exploited the power of cryoEM to study a wide range of important biological "machines" or macromolecular assemblies. His main interests are on the mechanisms of transmembrane signal instigation with a particular focus on G protein-coupled receptors and cytokine receptors. The application of cryoEM to such systems has also driven him to explore and refine approaches for resolving technically challenging problems. Dr. Skiniotis' honors include the Earl and Thressa Stadtman Scholar Award from the American Society for Biochemistry and Molecular Biology (2016), and a Presidential Early Career Award for Scientists and Engineers awarded by the White House/NIH (2012). Dr. Skiniotis was a Pew Biomedical Scholar (The Pew Charitable Trusts).

Anthony W.P. Fitzpatrick, Ph.D.



Anthony W.P. Fitzpatrick is a structural biologist and Assistant Professor of Biochemistry and Molecular Biophysics at the Mortimer B. Zuckerman Mind Brain Institute affiliated with Columbia University. Previously, he was a Marie Curie International Outgoing Fellow at the Laboratory of Molecular Biology, University of Cambridge (2015-2017) and the California Institute of Technology (2012-2014). Research in the Fitzpatrick lab is focused on determining the structure and behavior of patient-derived amyloid fibrils and, more generally, understanding the role of protein aggregation in vivo by identifying the cellular changes that occur in response to the formation, clearance and spread of fibrillar inclusions. The methods employed by his lab are largely experimental and include cryo-electron microscopy. mass spectrometry, microfluidics, and optical super-resolution microscopy. Dr. Fitzpatrick's honors include the Thermo Fisher Scientific Young Investigator Award (2017-2018) and the American Association of Neuropathologists Terry Award for best paper on neurodegenerative diseases (2017).

Xue Han, Ph.D.



Dr. Xue (Shu-eh) Han is Associate Professor of Biomedical Engineering and Pharmacology at Boston University. Her lab focuses on discovering the design principles for novel neuromodulation therapies. They develop and apply various genetic, molecular, pharmacological, optical and nano tools for better understanding of neurological and psychiatric diseases. The ultimate goal of her research is to discover neural network signatures of brain disorders and use such signatures to design next generation neuromodulation strategies. Dr. Han has received a number of awards, including Presidential Early Career Award for Scientists and Engineers (PECASE), NIH innovator award, DARPA Young Faculty Award, Pew Scholarship, and Alfred P. Sloan Fellowship.

Shelley J. Russek, Ph.D.



Shelley Russek is Professor of Pharmacology and Professor of Biology at Boston University where she also directs the university wide Graduate Program for Neuroscience (GPN) that administers the Neuroscience Ph.D. across the Charles River and MED campuses. Dr. Russek received her Ph.D. in Pharmacology from Boston University School of Medicine, a M.S. in Anatomy and Cell Biology from SUNY Downstate College of Medicine and her undergraduate degree in Psychology from the University of California at San Diego. Dr. Russek is most known for her work on the dynamic regulation of inhibitory neurotransmitter receptors in neurons and was the first to identify that their subunit genes were organized in unique clusters in the human genome due to the duplication of an ancestral gene cluster that brought alpha, beta, and gamma subunit genes into proximity for coordinate gene transcription. Through her early insights on the cell biology of GABARs, she demonstrated that a major component of changes in the inhibitory tone of the injured brain comes from the activation of gene regulatory programs that directly impact the transcription of GABAR subunit genes, countering a long-held assumption that GABAR subunit diversity played a minor role in brain disorders. More recently her laboratory has been instrumental in elucidating a unique role for brain derived neurotrophic factor in the activation of the JAK/STAT pathway in neurons. Using techniques of transcriptomics and genomics, the major goal of their research is to untangle the mechanisms that underlie dysregulated plasticity in the injured brain, with an emphasis on the neurologic and neuropsychiatric disorders of epilepsy, Alzheimer's disease, and depression. A new area for her laboratory is the development of molecular tools that can serve as in vivo fluorescent sensors for the activation or inhibition of gene regulatory pathways in animal models of disease. Dr. Russek was an elected member of the Society for Neuroscience Committee on Departments and Programs and Chair of the SFN Committee on Best Practices in Neuroscience Training where she helped organize webinars for the SFN community to engage other institutions in the development of novel training mechanisms, sensitivity to student issues, and strong programs in professional development.

Hongkui Zeng, Ph.D.



Hongkui Zeng is Executive Director of Structured Science at the Allen Institute for Brain Science. She is leading the Structured Science Division to develop and operate high-throughput pipelines to generate large-scale, open-access datasets and tools to accelerate neuroscience discovery. Dr. Zeng received her Ph.D. in molecular and cell biology from Brandeis University, where she studied the molecular mechanisms of the circadian clock in fruit flies. Then as a postdoctoral fellow at Massachusetts Institute of Technology, she studied the molecular and synaptic mechanisms underlying hippocampus-dependent plasticity and learning. Since joining the Allen Institute, Dr. Zeng has led several research programs, including the Transgenic Technology program, the Human Cortex Gene Survey project, the Allen Mouse Brain Connectivity Atlas project and the Cell Types program. She is also leading a BRAIN Initiative effort to create a Brain Cell Atlas in the mouse. Dr. Zeng has broad scientific experience and a keen interest in using a combined anatomical and physiological approach molecular. to unravel mechanisms of brain circuitry and potential approaches for treating brain diseases. Her current research interests are in understanding neuronal diversity and connectivity in the visual cortical circuit and how different neuronal types work together to process and transform visual information. Dr. Zeng has received many honors including AWIS Award for Scientific Advancement and Gill Transformative Investigator Award.

Staci Bilbo, Ph.D.



Dr. Staci Bilbo is the Lurie Family Associate Professor of Pediatrics and Neuroscience at Harvard Medical School and Director of Research for the Lurie Center for Autism at Massachusetts General Hospital for Children. Her research is broadly focused on the mechanisms by which the immune and endocrine systems interact with the brain to impact health and behavior. Current research in her laboratory focuses on understanding the consequences of early life events, including infection, stress, environmental toxins, and maternal obesity on neural and immune system development, with an emphasis on autism spectrum disorder. A particular focus of her work is on the resident immune cells of the brain, microglia, including their development and function in response to early life inflammatory signals. Dr. Bilbo received her B.A. in Psychology and Biology from the University of Texas at Austin and her Ph.D. in Neuroendocrinology at Johns Hopkins University. She was on the faculty at Duke University from 2007-2016 before she joined the faculty at Harvard in 2017. Dr. Bilbo was the recipient of the Robert Ader New Investigator Award from the Psychoneuroimmunology Research Society (PNIRS) in 2010, and the Frank Beach Young Investigator Award from the Society for Behavioral Neuroendocrinology (SBN) in 2011. Dr. Bilbo has served on the Board of Directors for the PNIRS and was the Invited Mini-Review Editor for Brain, Behavior and Immunity from 2012-15. She has served on the Editorial Board since 2010.

Dori P. Schafer, Ph.D.



Dr. Dorothy (Dori) Schafer is Assistant Professor of Neurobiology, Brudnik Neuropsychiatric Research Institute at the University of Massachusetts Medical School, Worcester, Massachusetts. Dr. Schafer received her bachelor's degree in Neuroscience from Mount Holyoke College in 2001 and her Ph.D. in Biomedical Science from the University of Connecticut Health Center in 2008. She then began her postdoctoral training at Boston Children's Hospital/Harvard Medical School in Dr. Beth Stevens' laboratory. Here, she made the discovery that microglia, the resident CNS macrophages, sculpt neural circuits in the developing brain by engulfing a subset of less active synapses. Dr. Schafer joined UMass Medical School in 2015 as an Assistant Professor in the Neurobiology Department of and she ioined the Brudnik Neuropsychiatric Research Institute at UMass in 2018. Dr. Schafer is considered a pioneer in the field of microglia-mediated synapse elimination. Her earlier postdoctoral work showing microglia engulf and eliminate synapses via the classical complement cascade has served as a foundation for the field to understand new roles for microglia in regulating synaptic connectivity in health and disease. Her laboratory utilizes a combination of cutting-edge molecular genetic approaches and imaging to uncover novel roles for microglia in assembly and plasticity of neural circuits under steady-state conditions and applies these mechanisms to neurological disease. As a result of the work she has done in the field, Dr. Schafer was a recipient of a NIH R00 Pathway to Independence Award (NIMH), Charles H. Hood Child Research Award, a NARSAD Young Investigator Grant, and she was a finalist for the Chan Zuckerberg Initiative Acceleration Award.

Tsuneya Ikezu, M.D., Ph.D.



Dr. Tsuneya Ikezu is Professor of Pharmacology and Neurology at Boston University School of Medicine and has led the Laboratory of Molecular NeuroTherapeutics since 2010. He has been investigating Alzheimer's disease (AD) over 20 years and has performed pioneering research into how modulation of neuroinflammation or neurogenesis enhances hippocampal function and ameliorates AD-like neuropathology through viral gene transfer. He originally discovered caveolae as a platform of APP processing, cloned tau-tubulin kinase-1 as a neuron-specific tau kinase, characterized anti-inflammatory cytokine modulation of hippocampal neurogenesis and cognitive enhancement, microglia-neural stem cell interactions, and recently discovered new roles of microglia and exosomes for spreading of pathogenic tau protein in the brain. Dr. Ikezu received his M.D. and Ph.D. from the University of Tokyo School of Medicine, completed postdoctoral trainings at Massachusetts General Hospital and Cleveland Foundation, and was Professor of Pharmacology Clinic and Experimental Neuroscience at University of Nebraska Medical Center prior to joining Boston University in 2010. Over his career, Dr. Ikezu has received the Vada Kinman Oldfield Alzheimer's Research Award (2000), Inge Grundke Igbal Award from the Alzheimer's Association (2016) and recently the Jack Spivack Distinguished Scientist in Neuroscience Award (2018). He has authored more than 80 papers, edited the textbook Neuroimmune Pharmacology (Springer Nature) and served on several editorial boards.

Benjamin Wolozin, M.D., Ph.D.



Benjamin Wolozin, is Professor of Pharmacology, Neurology and the Program in Neuroscience at Boston University School of Medicine. Dr. Wolozin's research investigates pathophysiology the of neurodegenerative diseases. Current work of the Wolozin lab addresses the roles of "regulated protein aggregation and membraneless organelles" on proteostasis, RNA metabolism, neuronal function and neurodegeneration. A growing body of evidence, including work from the Wolozin laboratory, increasingly highlights the important contributions of RNA binding proteins (RBPs) and translational regulation in the pathophysiology of neurodegenerative disease. The work of the Wolozin lab addresses the roles of "regulated protein aggregation and membraneless organelles" on proteostasis, RNA metabolism, neuronal function and neurodegeneration. Investigating the biology of RNA granules (with a particular focus on stress granules), provides a theoretical framework for understanding the biology of neurodegenerative disease, as well as new directions for therapeutic intervention for tauopathies and other neurodegenerative diseases. Dr. Wolozin has developed methods to analyze the pathological RNA granules and stress granules that accumulate in brain diseases. Dr. Wolozin earned his M.D. and Ph.D. degrees from Albert Einstein College of Medicine (1988), and his B.A. from Wesleyan University (Magna cum laude). He joined Boston University in 2004. Dr. Wolozin is a fellow of the AAAS and has received awards including the Donald B. Lindsley Prize, Society for Neuroscience, the A. E. Bennett Award from the Society for Biological Psychiatry, the Zenith Award from the Alzheimer Association, and the Boston University Spivack award for distinguished research in neuroscience. Dr. Wolozin is also co-founder and Chief Scientific Officer of the biotechnology company, Aguinnah Pharmaceuticals, Inc., which is using the biology of RNA binding proteins to develop new therapies for amyotrophic lateral sclerosis and Alzheimer's disease.

Leonard Petrucelli, Ph.D.



Leonard Petrucelli, is Professor and Chair of Neuroscience at the Mayo Clinic in Jacksonville, Florida. His laboratory has been at the forefront of investigating the cellular mechanisms research that cause neurodegeneration in diseases characterized by abnormal protein aggregation, such as amyotrophic lateral sclerosis (ALS), and frontotemporal lobar dementia (FTLD). Expanding upon a commitment to understand the mechanisms of disease progression and neuronal death, his lab emphasizes translational research to identify biomarkers and develop therapies for treatment and prevention. His lab combines expertise in cell and molecular biology, animal and patient cell modeling, and drug discovery, to design and optimize selective and potent compounds that can be developed into therapies for patients suffering from tau-, TDP-43-, and C9ORF72-related disorders. For instance, a primary focus of his research program is to determine the mechanisms by which the G4C2 repeat expansion in C9ORF72 causes ALS and FTLD-TDP (collectively referred to as c9FTD/ALS). His group recently reported that sense and antisense RNA transcribed from the repeat expansion may cause neurodegeneration via the accumulation of these transcripts into discrete structures in the nucleus, termed RNA foci, and by serving as a template for the synthesis of aggregation-prone "c9RAN proteins" by repeat-associated non-ATG (RAN) translation. The work demonstrated that poly(GA) c9RAN proteins cause neurodegeneration and behavioral deficits in mice, features that are associated with the sequestration of proteins involved in proteasomal degradation and nucleocytoplasmic transport. Moreover, his lab designed small molecule binders of G4C2 RNA that block foci formation and RAN translation, validating the use of such compounds as a potential therapeutic strategy for c9ALS/FTD, and discovered that poly(GP) c9RAN proteins are detected in cerebrospinal fluid (CSF) of c9ALS patients and may thus serve as a pharmacodynamic biomarker. The first mouse model to exhibit both neuropathological and behavioral defects associated with c9FTD/ALS was generated by Dr. Petrucelli's group. In addition to developing RNA foci and c9RAN protein pathology, these (G4C2)66expressing mice develop endogenous TDP-43 pathology. In addition, treatment of these mice with antisense oligonucleotides that target G4C2 RNA causes decreases in poly(GP) in CSF, and this mirrors decreases in levels of G4C2 RNA and c9RAN proteins in the brain. As these findings attest, his research program has had an impact on the field of C9ORF72-associated neurological diseases.

Wendy Qiu, M.D., Ph.D.



Wendy Qiu is an Associate Professor in Department of Psychiatry, Department of Pharmacology & Experimental Therapeutics, Alzheimer's Disease Center at Boston University School of Medicine. Dr. Qiu received her M.D from Peking University School of Medicine and her Ph.D from Weill Cornell Medicine. Dr. Qiu is a board-certified psychiatrist and a physician-scientist. She has been involved both in conducting translational research on neurodegenerative diseases and taking care of patients who have dementia. Using both human studies and animal models, her research has been focused on diagnoses and therapeutics of Alzheimer's disease (AD). Her research career began with the first identification that the insulin-degrading enzyme (IDE) plays a key role in the clearance of amyloid beta peptides (A β), a major component of AD pathology in the brain. This initial finding extended her research themes on genetic vulnerabilities and their interactions with chronic peripheral diseases such as diabetes for the risk of AD. She and her team have been identifying and studying the communication between peripheral biomarkers and brain abnormalities in aging and the prodromal stage of AD. Recently they discovered that a gut-brain axis hormone, amylin, has impacts on AD pathology in the brain. Her research has implication that amylin can be used as a diagnostic tool and a therapeutic target for AD.

Thomas Kornecook Ph.D.



Tom Kornecook joined Biogen in 2017 and currently serves as Senior Director of Translational In Vivo Sciences (TIVS), Research and Early Development at Biogen. The TIVS team supports Biogen's disease area scientists and project leaders in formulating, implementing, and executing on appropriate in vivo pharmacology strategies to support preclinical drug discovery efforts across the portfolio. Dr. Kornecook received his Ph.D. in Neuroscience from the University of British Columbia in Vancouver, Canada in 1998 and his undergraduate degree from McGill University in Montreal in 1991. His doctoral dissertation focused on developing translational assays to explore the neuroanatomical basis of recognition memory in rodents. Dr. Kornecook completed a postdoctoral fellowship in Professor Remi Quirion's lab at the McGill-affiliated Douglas Hospital Research Center studying the neurochemical and neuroinflammatory processes associated with basal forebrain cholinergic system dysfunction in Alzheimer's disease. Dr. Kornecook's industry experience has involved stints in both small biotech (Memory Pharmaceuticals) and large pharma (Merck Research Labs) organizations. A consistent theme during this time has been his long-standing interest in developing and validating novel animal models with enhanced translational strength and predictive human validity to improve on the probability of success in the drug discovery space. More recently, he held multiple positions within Amgen's Neuroscience Department, leading programs in pain, neuropsychiatric, and neurodegenerative disease indications from early-stage target validation to first-in-human studies.

Himanshu Naik, Ph.D.



Himanshu Naik joined Biogen in 2015 and is currently Director, Clinical Pharmacology, Research and Early Development. He serves as the clinical pharmacology and pharmacometrics lead for multiple sclerosis, neuropathic pain and lupus programs. Dr. Naik received his bachelor's degree in pharmacy from Jadavpur University, Calcutta, India. He received his Master's in clinical pharmacy followed by a Ph.D. in pharmacokinetics from the University of Iowa in 2007. For his Ph.D. dissertation, Dr. Naik worked on clinical development of combination therapy (Artisunate + Pyronaridine) for Malaria, a project funded by Medicine for Malaria venture (MMV), a non-profit organization based in Switzerland. As a part of his thesis work, Dr. Naik developed pharmacokinetic models to describe the pharmacokinetics of artesunate and Pyronaridine. Dr. Naik joined Takeda pharmaceutical company based in Chicago in 2007 following completion of his Ph.D. work where he was involved in development of therapies for diabetes, major disorders. anemia. He clinical depressive gout and was pharmacology/pharmacometrics lead for submission and successful approval of drugs like Vortioxetine, Alogliptin, Peginesatide and Febuxostat. Dr. Naik have published or presented over 50 articles in reputed journals and scientific conferences and he is an active member of the American Society of Clinical Pharmacology and Therapeutics and International Society of Pharmacometrics.