Title: Defining how neurons and astrocytes execute quality control in response to proteotoxic stress in neurodegenerative disease

Goal for proposal: To investigate how quality control pathways are regulated within (Aim 1) and between (Aim 2) neurons and astrocytes in response to proteotoxic stress associated with Parkinson’s disease (PD) (Fig. 1). Proteotoxic stress will be induced by adding exogenous pre-formed fibrils (PFFs) of α-synuclein (α-syn).

Team:
- Dr. Sandra Maday, Assistant Professor in the Department of Neuroscience, PSOM. Dr. Maday’s lab has expertise in primary neuron-astrocyte co-cultures to investigate the mechanisms of autophagy and endolysosomal pathways in physiological conditions and in neurodegenerative disease.
- Dr. Kelvin Luk, Research Associate Professor in the Department of Pathology and Laboratory Medicine, PSOM. Dr. Luk’s lab has expertise in the pathogenic mechanisms of PD and related synucleinopathies. Dr. Luk’s lab will generate pathogenic fibrils of α-syn to be used in the cellular assays that will be performed in Dr. Maday’s lab.

SIGNIFICANCE. How do neurons and astrocytes, two key cell types in the brain, collaborate to mitigate proteotoxic stress linked to neurodegenerative disease? Both cell types collaborate to construct a complex network of trillions of synaptic connections in the brain which enable thought and behavior. Similar to neurons, the majority of astrocytes are post-mitotic and long-lived, requiring robust quality control pathways to maintain homeostasis and regulate proteome and organelle integrity. In fact, the accumulation of damaged organelles and misfolded protein is a defining feature of many neurodegenerative diseases (e.g. PD). Two key pathways that regulate the proteome are autophagy and endocytic trafficking, which converge on lysosomes to degrade cargos. During autophagy, cytoplasmic components are enveloped into autophagosomes which fuse with lysosomes to enable cargo degradation by resident hydrolases. During endocytosis, material from the extracellular space is taken into the cell via endosomes which are routed to lysosomes. Changes in these pathways cause neurodegenerative disorders. Little is known, however, about how these pathways are regulated in the context of neurons, let alone astrocytes. Many studies mapping these pathways have been performed in yeast and smaller less-polarized mammalian cells, which lack the complexity of neurons. Moreover, many paradigms established in non-neural cells do not translate to neurons. Thus, it is critical to study these processes in neural cells. Further, since activating autophagy can mitigate neurodegeneration, these quality control pathways are a therapeutic target for neurodegenerative diseases. Thus, it is critical to define the mechanisms by which quality control is regulated in neurons and astrocytes.

In this proposal, we will elucidate how autophagy and endocytic trafficking are regulated in neurons and astrocytes in the context of PD-linked proteotoxic stress. To study cell-type-specific pathways, the Maday lab established a robust system to co-culture neurons and astrocytes (Fig. 2A). Monocultured astrocytes are polygonal, but upon receiving neuronal cues, undergo a dramatic maturation. Astrocytes co-cultured with neurons exhibit mature, highly arborized morphologies and acquire signatures reminiscent of astrocytes in vivo. Thus, our system recapitulates aspects of astrocyte development and is a tractable system to define cellular mechanisms with high spatiotemporal resolution. Using this system, we have established fundamental differences in how neurons and astrocytes carry out quality control under basal conditions and in response to metabolic stress (Sidibe et al., in preparation). Here, we aim to extend these findings to models of proteotoxic stress. Thus, we will challenge neurons and astrocytes with α-syn PFFs associated with PD. Based on our preliminary data, we propose that neurons and astrocytes have fundamentally distinct pathways for quality control to facilitate cell-type-specific functions and responses to proteotoxic stress. To test this hypothesis, we will use cutting-edge live-cell imaging and quantitative cell biology to pursue two Aims (Fig. 1):

Aim 1: Define cell-type-specific pathways for quality control in neurons versus astrocytes in response to proteotoxic stress associated with neurodegenerative disease. Little is known about how quality control pathways are regulated in response to proteotoxic stress in neurons. Our knowledge of these processes in astrocytes, key regulators of neuronal homeostasis, is even more sparse. In this aim, we will examine the effect of proteotoxic stress on autophagy and endocytic trafficking within neurons and astrocytes. Information from this aim will help define cell-type-specific roles in neurodegeneration.

Aim 2: Define how neurons and astrocytes collaborate to mitigate proteotoxic stress associated with neurodegeneration. In this aim, we will leverage our co-culture system that recapitulates neuron-astrocyte
interactions observed in vivo to investigate intercellular pathways between neurons and astrocytes that may mitigate proteotoxic stress. This aim will explore roles for neuron-astrocyte coupling in managing proteotoxic stress and neurodegeneration.

**APPROACH.** Aim 1: Define cell-type-specific pathways for quality control in neurons versus astrocytes in response to proteotoxic stress associated with neurodegenerative disease. We will induce proteotoxic stress with exogenous PFFs of human α-syn, using both wild type (WT) and the pathogenic A53T variant. Elevated expression of WT α-syn and A53T α-syn cause PD. To determine cell-type-specific effects of α-syn PFFs on autophagy and endocytic trafficking, we will add α-syn PFFs to co-cultured primary mouse hippocampal neurons and astrocytes. The Maday lab has extensive experience in mapping the autophagy and endolysosomal pathways from initiation to degradation. Thus, we will measure the effects of α-syn PFFs on the formation, density, dynamics and distribution, maturation, flux, and degradative function of organelles in these pathways using live-cell imaging combined with quantitative immunofluorescence. We have developed a procedure to separate co-cultured neurons from astrocytes using fluorescence-activated cell sorting; cell populations will be lysed and analyzed by biochemical approaches for molecular markers of each pathway. We will also add fluorescently-labeled PFFs of α-syn to track their itinerary and final destination. We will assess whether PFFs effectively reach a degradative compartment in neurons or astrocytes using live-cell probes of proteolytic activity combined with pharmacological inhibition of lysosomal function and assess effects on PFF clearance. Experiments will be performed as a function of time (up to two weeks) to track the dynamics of this process in neurons and astrocytes. It is established that exogenous PFFs hijack the endogenous α-syn to generate more fibrils (distinguished by phosphoryl forms of α-syn at serine 129). We have successfully added exogenous PFFs to co-cultures and observed uptake in neurons and astrocytes; seeding of endogenous α-syn in neurons is demonstrated by increased levels of phospho-α-syn (Fig. 2B). The exact process by which this amplification occurs, however, is not understood. We will define the mechanism by which fluorescently-labeled PFFs escape organelles to hijack endogenous α-syn, and the autophagic response to the escaped population. A careful analysis of the trafficking itinerary of α-syn PFFs has not been performed. Thus, we will map how PFFs are processed in neurons and astrocytes.

**Aim 2: Define how neurons and astrocytes collaborate to mitigate proteotoxic stress associated with neurodegeneration.** In this aim, we will define how interactions with astrocytes impact proteotoxic stress in neurons. We will selectively apply proteotoxic stress to only neurons with the use of compartmentalized microfluidic chambers, a technology deployed in the Maday lab (Fig. 2C). In this system, neurons are plated in the proximal chamber; only axons extend through narrow microgrooves to reach a distal chamber where α-syn PFFs will be added. In our preliminary data, we find that a percentage of PFFs get endocytosed in the axon (colocalization with endocytic tracer BSA) and are transported to the soma (Fig. 2C'). We will then measure the degree of seeding of pathogenic α-syn in neurons ± astrocytes in the proximal chamber. Thus, only neurons are directly exposed to the proteotoxic stress, and we will define whether astrocytes accelerate or decelerate the processing of PFFs and progression of α-syn pathology in neurons as in Aim 1. We will also examine alterations in astrocytes ± proteotoxic stress in neurons. Following acute stress, astrocytes may be neuroprotective. We will explore this possibility by examining whether (1) neuronally-derived α-syn is transferred to astrocytes for clearance, and (2) astrocytes elevate neuroprotective markers (e.g. NF-kB C-rel subunit, antioxidant pathway members: NRF2, GSH, SOD1). Following prolonged stress, astrocytes may switch to a neuroinflammatory state, as measured by immunostain for NF-kB p65 subunit, ROS. This aim will define the role for neuron-astrocyte coupling in responding to proteotoxic stress in neurons.

**IMPACT.** This study will investigate how quality control pathways are regulated within and between neurons and astrocytes in response to proteotoxic stress. We will define how neurons and astrocytes process proteotoxins associated with PD, both individually and collaboratively. Knowledge from this study will help define cell-type-specific roles in neurodegeneration and new pathways for therapeutic intervention.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Maday, Sandra

eRA COMMONS USER NAME (credential, e.g., agency login): SMADAY

POSITION TITLE: Assistant Professor of Neuroscience

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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A. Personal Statement

I am an Assistant Professor of Neuroscience at the Perelman School of Medicine at the University of Pennsylvania. Trained as a cell biologist, I work at the interface between the fields of cell biology and neuroscience to study the connections between fundamental cellular pathways and neuronal function and disease. The goal of my independent research program is to determine the mechanisms, roles, and regulation of autophagy in neurons and astrocytes, and how these processes are altered in neurodegenerative disease. My educational training combined with my experiences and publication record make me well qualified to be a Sponsor for this NRSA fellowship application. I received my Ph.D. from Yale University School of Medicine, working in the laboratory of Dr. Ira Mellman, a member of the National Academy of Sciences. In Dr. Mellman’s laboratory, I received a rigorous and extensive training in cell biology in the field of intracellular trafficking. I further developed these skills in cell biology and diversified my methodology and expertise to areas of neuroscience during my postdoctoral training in Dr. Erika Holzbaur’s laboratory at the University of Pennsylvania. During my postdoctoral research, I led the studies that uncovered novel findings about the spatiotemporal regulation of autophagy in neurons. My research established a new paradigm for the mechanisms of autophagy in primary neurons, a paradigm distinct from observations in smaller, less polarized cells. My work was recognized with a prestigious NIH Pathway to Independence (K99/R00) Award from the NINDS. In my independent research laboratory, I have extended these studies to investigate how these pathways for neuronal autophagy respond to cues from the surrounding microenvironment. My lab has identified how several key factors that impact neuronal viability and function (synaptic activity, neurotrophins, and astrocytes) regulate neuronal autophagy, in a compartment-specific manner (e.g. axon versus dendrites versus soma) (Journal of Cell Biology, 220: e202002084; Journal of Neuroscience, 42: 8524-8541; Journal of Biological Chemistry, 298: 102673). Moreover, we have elucidated several cell type-specific pathways for autophagy in neurons versus astrocytes, highlighting the differential regulation of quality control pathways in key cell types of the brain (Autophagy, 16:1651-1667; Autophagy, 19: 570-596). In addition, my lab has published a methods article in Methods in Molecular Biology, and several invited reviews in the Journal of Neuroscience, The Journal of Cell Biology, Current Biology, Current Opinion in Neurobiology, Developmental Neurobiology, Brain Research, Trends in Neurosciences, and Autophagy Reports. I have received funding from The McCabe Fund Fellow Award (UPenn), Alzheimer’s Disease Core Center Pilot Award (UPenn), and an Institutional Intellectual and Developmental Disabilities Research Center New Program Development Award (CHOP/UPenn), and the NINDS. I am an Associate Editor at Autophagy, Section Editor for Neuroscience at Autophagy Reports, and an Academic Editor at PLOS One. I have been selected to give talks at the Society for Neuroscience annual meetings (2016 and 2018), Molecular & Cellular Cognition Society Symposium (2022), American Society for Cell Biology annual meetings (2017, 2019, and 2022), French Society for Cell Biology
(2023), Biophysical Society Conference (2023), a workshop on neurodegeneration hosted by the Chan Zuckerberg Initiative (2017), a Gordon Research Conference on neurotrophins (2019), and EMBO and Keystone conferences on autophagy (2022 and 2023). Through these experiences, I am establishing myself as a leader in the field of neuronal and glial autophagy and I am well qualified to execute the proposed studies.

Ongoing projects that I would like to highlight include:
R01 NS110716. Maday (PI). 05/15/2020-03/31/2025
Defining the roles and regulation of neuronal autophagy

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present  Section Editor for Neuroscience, Autophagy Reports
2021  Ad hoc reviewer, NIMH Board of Scientific Counselors Review of NIMH Intramural Research Programs
2020  Ad hoc reviewer, R01 Special Emphasis Panel, ZRG1 MDCN-Q (03), Member Conflict: Cellular and Molecular Mechanisms of Neurodegeneration
2020  Ad hoc reviewer, NINDS Innovation Grants to Nurture Initial Translational Efforts Program, Neurological Sciences and Disorders B Study Section
2019-present  Associate editor, Autophagy
2019-present  Academic editor, PLOS ONE
2016-present  Assistant Professor, Department of Neuroscience, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
2013-present  Member, Society for Neuroscience
2008-2015  Postdoctoral Researcher, Department of Physiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
2007  Postdoctoral Researcher, Department of Cell Biology, Yale University School of Medicine, New Haven, CT
2002-present  Member, American Society for Cell Biology
1998-present  Member, Sigma Xi Scientific Research Society
1998-2007  Graduate student, Department of Cell Biology, Yale University School of Medicine, New Haven, CT

Honors

2023  Invited Talk, Biophysical Society Conf. on “Membrane Fusion and Budding”, Estes Park, CO
2023  Discussion Leader, Gordon Research Conference on “Neurotrophic Mechanisms in Health and Disease”, Newport, RI
2023  Invited Talk, Keystone Meeting on “Autophagy and Neurodegeneration: Mechanisms to Therapies”, Snowbird, UT
2023  Invited Talk, French Society for Cell Biology Meeting on “Cell Biology of Neurons & Beyond”, Institut Curie, Paris, France
2022  Conference Organizer and Speaker, Annual Society for Cell Biology, Special Interest Subgroup on “Mechanisms of autophagic and endolysosomal trafficking in neuronal function and neurodegeneration”, Washington, DC
2022  Invited Talk, Molecular & Cellular Cognition Society Symposium, San Diego, CA
2022  Invited Talk and Discussion Leader, EMBO Conference on “Brain Autophagy in Health and Disease”, Sant Feliu de Guixols, Spain
2019  Invited Talk, American Society for Cell Biology Annual Meeting, Washington, DC
2019  Invited Talk, Gordon Research Conference on “Neurotrophic Mechanisms in Health and Disease”, Newport, RI
2018  Intellectual and Developmental Disabilities Research Center, New Program Development Award, CHOP and UPenn
2018  Alzheimer’s Disease Core Center Pilot Award, UPenn
2018  Invited Talk, Society for Neuroscience Annual Meeting, San Diego, CA
2017  Invited Talk, American Society for Cell Biology Annual Meeting, Philadelphia, PA
1. Defined aspects of neuronal biology that regulate neuronal autophagy in a compartment-specific manner.

My lab investigates how key factors that impact neuronal viability and function regulate neuronal autophagy. Our current work focuses on how compartment-specific pathways for neuronal autophagy (e.g. axonal versus dendritic) respond to synaptic activity. Loss of autophagy in the hippocampus causes deficits in learning and memory, suggesting critical roles for autophagy at neuronal synapses. Little is known, however, about the molecular underpinnings of autophagy at synapses. We found that synaptic activity controls the motility and function of autophagic vacuoles (AVs) in dendrites. Synaptic activity acts locally to arrest AVs near synapses, and stimulates their maturation into degradative organelles. Strikingly, these activity-dependent effects on AVs are specific to dendrites and do not occur in axons. Our work defines how the activity state of the neuron dynamically regulates autophagy, and highlights the compartment-specific nature of intracellular trafficking pathways for degradation in neurons. This process may locally regulate the synaptic proteome by balancing degradation with protein synthesis to impact synaptic function and plasticity. Our most recent study investigates how the axonal pathway for autophagy is altered in models of Parkinson’s Disease. I served as senior investigator in all of these reports. Manuscripts in preparation and under review are investigating how other cues from the surrounding microenvironment (e.g. neurotrophins and astrocytes) impact neuronal autophagy.


2. Defined cell type-specific pathways for autophagy-lysosomal degradation in neurons versus astrocytes.

Neurons and astrocytes each have unique demands on their proteomes. Both cell types collaborate to construct a complex network of trillions of synaptic connections in the brain. Moreover, similar to neurons, the majority of astrocytes are also post-mitotic and long-lived, requiring robust quality control pathways. But how autophagy is regulated in neurons and astrocytes to facilitate cell-type specific functions and responses to cellular stress (e.g. metabolic, proteotoxic, and oxidative stress) is unknown. In Kulkarni et al. (2019), we found that autophagy is strongly activated in astrocytes in response to metabolic stress induced by nutrient deprivation or pharmacological inhibition of mTOR. Both paradigms of metabolic stress inhibit mTOR, but the molecular mechanisms activating autophagy are distinct. In contrast to astrocytes, neurons have a more muted induction of autophagy in response to metabolic stress. Thus, we find that neurons and astrocytes differentially regulate autophagy in response to metabolic stress, revealing striking differences in how autophagy is managed between different cell types in the brain. Our study by Yuan et al. (2022)
investigates the connection between autophagy and another quality control pathway, the ubiquitin-proteasome system (UPS), in astrocytes and neurons. Prior studies in non-neural models report a compensatory relationship whereby inhibition of the UPS stimulates autophagy. To our surprise, inhibition of the proteasome did not robustly upregulate autophagy in astrocytes or neurons. In fact, the effects on autophagy are modest particularly in comparison to paradigms of metabolic stress. Rather, we find that UPS inhibition in astrocytes induces formation of ubiquitin-positive aggregates that harbor the selective autophagy adaptor, p62, but these structures were not productive substrates for autophagy. We observed a significant increase in lysosomal degradation in astrocytes in response to UPS inhibition, but this stimulation was not sufficient to reduce p62 levels. Lastly, UPS inhibition was more toxic in neurons than astrocytes, suggesting a cell type-specific vulnerability to proteotoxic stress. Our study provides critical insights into how astrocytes and neurons regulate quality control pathways to manage proteotoxic stress associated with aging and neurodegenerative disease. Publications from my independent research group include 2 primary research articles and a review article. I am also co-author on a review article invited by the Society of Neuroscience from our Minisymposium at the annual meeting.

3. Defined the pathway for axonal autophagy in neurons. My postdoctoral and K99 research investigated the spatiotemporal mechanisms and dynamics of autophagy in primary neurons. Autophagy is a critical degradative pathway in neurons; defects in autophagy have been linked to the progression of neurodegenerative disease. However, very little is known about the basic cellular mechanisms driving autophagy in neurons. Using live-cell imaging, I established that autophagy in neurons is a constitutive and highly compartmentalized process. Axonal autophagosomes originate predominantly in the distal end of the axon and then undergo robust retrograde transport toward the soma. Upon entry into the soma, autophagosomes are confined within the somatodendritic region. This compartmentalization likely facilitates maturation into autolysosomes by promoting fusion with resident lysosomes concentrated in the soma, and may ensure efficient recycling of biosynthetic building blocks to primary sites of protein synthesis. Thus, this retrograde pathway for axonal autophagy overrides the spatial barriers presented by the extended distance of the axon to deliver cargo from distant regions of the axon to the soma for degradation. Surprisingly, canonical autophagy inducers such as starvation or mTOR-inhibition that robustly activate autophagy in other cell types (e.g. hepatocytes and HeLa cells), do not robustly upregulate autophagy in neurons in monoculture. Thus, my research established a new paradigm for the mechanisms of autophagy in primary neurons, and revealed that several canonical paradigms established in non-neuronal cells do not necessarily translate to neurons. I led the projects performed in these studies.

4. Defined mechanisms of axonal transport initiation in neurons. To maintain function and homeostasis, neurons face the challenge of transporting organelles and RNA/protein complexes across the extended distance of the axon. While it is well characterized that transport along the axon is driven by the microtubule-based molecular motors dynein and kinesin, mechanisms coordinating these events are only beginning to emerge. In a collaborative effort, we examined how cargoes in the distal axon begin their
journey toward the soma and have found that transport initiation in the distal axon is mediated by the ordered assembly of proteins binding to the plus-end of microtubules. This work provides insights into the mechanisms underlying transport initiation in the distal axon, meters away from sites of action for these organelles. This body of work also includes review articles documenting the current understanding of axonal transport in health and disease.


5. Elucidated basolateral sorting pathways that maintain epithelial polarity. The unifying goal of my research career has been to understand trafficking pathways operating in polarized cells. My graduate research focused on the long-standing question of how epithelial cells generate and maintain a polarized membrane architecture with distinct apical and basolateral domains. To study this problem, I combined advanced confocal microscopy techniques with classical pulse-chase biochemical assays. My research elucidated a role for PDZ-mediated interactions in the sorting of basolateral membrane proteins along the biosynthetic pathway. Classically, PDZ-mediated interactions were thought to retain membrane proteins at the plasma membrane. However, I uncovered a novel function for these interactions early in the secretory pathway. A second aspect of my work was focused on understanding how the epithelial-specific clathrin adaptor complex AP-1B specifically recognizes and sorts cargo destined for the basolateral membrane. In this endeavor, I identified a specific class of sorting signals decoded by AP-1B required for receptor targeting to the basolateral membrane. Collectively, my graduate work deciphered molecular mechanisms that sort membrane proteins to the basolateral surface of polarized epithelial cells. I led this series of studies and collaborated with a team of investigators.


*These authors contributed equally to this paper.


Complete List of Published Work in MyBibliography:
NAME: Luk, Kelvin C.

eRA COMMONS USER NAME (credential, e.g., agency login): KELVINCL

POSITION TITLE: Research Associate Professor of Pathology and Laboratory Medicine

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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<td>MSTR</td>
<td>05/2013</td>
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A. Personal Statement

The goal of my research is to understand how proteins such as alpha-synuclein (aSyn) form the distinctive pathologies found in Parkinson’s disease (PD) and related neurodegenerative conditions such as dementia with Lewy bodies, multiple system atrophy and Alzheimer’s disease, and to decipher their roles in contributing to these incurable disorders. My passion for a mechanistic understanding of the formation and deconstruction of neuronal circuitry grew during my graduate training in experimental pathology and developmental neuroscience at the Montreal Neurological Institute where I examined the role of amino-acid neurotransmitters in forebrain neurogenesis and the biology of mammalian dopaminergic systems. I further expanded my scientific repertoire through postdoctoral and translational research training fellowships at the University of Pennsylvania, developing expertise in histopathology, quantitative microscopy, protein biochemistry, cell biology, and small animal techniques. During this time, I focused on the role of protein-misfolding in the neurodegenerative process.

My research program has since focused on defining the mechanisms by which aSyn misfolds and then act as self-propagating pathologic agents that spread between cells of the central and peripheral nervous systems. My laboratory’s work applies novel in vitro, cell-based, and in vivo models we have developed to specifically address fundamental questions regarding the pathogenesis of synucleinopathies at the molecular-, cellular- and meso-scales. We are now complementing this work with efforts to elucidate the biology of aSyn under both physiological and disease conditions, with a particular focus on the interaction between aSyn with genetic, regional and external environmental factors. We are also leveraging our aSyn knowledgebase through organic and collaborative research to understand factors that trigger synucleinopathy and influence its progression.

I am PI or Co-Investigator on multiple NIH- and foundation-funded grants on neurodegenerative disorders and have experience in administering and participating in large collaborative efforts. The impact of my research is reflected by my recent publications, external collaborations, and the widespread adaptation of the tools generated by our group. Through my work, I have mentored undergraduate, pre-doctoral, and postdoctoral
trainees, helping them develop robust and responsible research practices, a passion for translational research, and exposing them to cutting-edge experimental approaches for better understanding neurodegeneration. These skillsets have helped them to successfully transition to the next stage of their scientific careers.

Highlighted ongoing or recently completed projects:

2R01NS088322 (Luk) 02/01/2021 – 12/31/2025  
Propagation of Lewy pathology in Parkinson’s disease and related disorders

1U19AG062418 (Lee; Luk Project II PI) 09/01/2019 – 08/31/2024  
Alpha-synuclein strains in Alzheimer’s disease and related dementias

NIH, 1U19 NS110456 (Mach; Luk Co-I) 06/01/2019 – 05/30/2024  
Center without Walls for Imaging Proteinopathies with PET (CW2IP2)

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 – Present  Research Associate Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine
2022 – Present  Member, Scientific Advisory Board, Multiple System Atrophy Coalition
2017 – Present  Ad hoc reviewer, NIH study section: CMND (since 2017), ZRG1-F03A1 (2022), ZRG1-OBT-Y (2022)
2017 – Present  Grant Reviewer, Austrian Science Fund (FWF), German Research Foundation (DFG), Parkinson’s Foundation
2015 – Present  Editorial Board, Neurobiology of Disease
2015 – Present  Reviewer, CORE, Fonds National de la Recherche Luxembourg, MRC, Parkinson’s UK, Hong Kong GRC
2012 – 2020  Research Assistant Professor, University of Pennsylvania Perelman School of Medicine
2010 – 2012  Research Associate, University of Pennsylvania Perelman School of Medicine
2010 – 2010  Senior Research Investigator, University of Pennsylvania Perelman School of Medicine
2000 – Present  Member, Society for Neuroscience

Honors

2010 – 2012  Research Fellowship, Institute for Translational Medicine and Therapeutics, University of Pennsylvania
2002  Teuber-Neysmith Research Award, Montreal Neurological Institute
2000 – 2003  Doctoral Research Award, Canadian Institutes for Health Research

C. Contributions to Science

1. Understanding how CNS structures form during development not only informs us of their function but also provides clues to their dysfunction and degeneration in aging and disease. My graduate work under the supervision of Abbas Sadikot and John Richardson at McGill/Montreal Neurological Institute examined factors that influence the proliferation and survival of neuronal progenitors in the mammalian basal forebrain. This work demonstrated that amino acid neurotransmitter signaling is critical to striatal and cortical development. These data help explain the devastating effects of alcohol exposure during gestation and indicates caution in using benzodiazeprenes and other psychoactive drugs during pregnancy.


2. Our collaborative work with Jacques Drouin’s group on Pitx3 was the first demonstration that this transcription factor plays a critical role in the maintenance and survival of midbrain dopaminergic neurons during early development. Subsequently, we validated Pitx3 as a marker for selectively vulnerable substantia nigra neurons in human PD and animal models, contributing to the discovery of their dependence on retinoid signaling for survival.


3. During postdoctoral training at the University of Pennsylvania with Virginia Lee, I demonstrated that misfolded aSyn has prion-like properties and that the amyloid configuration of this protein is sufficient to nucleate the formation of Lewy pathology in a variety of cell types. Since establishing my own research laboratory, I have extended this paradigm to in vivo models, showing that aSyn is transmissible between neurons and propagates within neuroanatomical connectomes. These seeding models represented the first successful attempts to simultaneously recapitulate the core elements of human synucleinopathies, namely aSyn pathology that closely recapitulates the features of authentic human Lewy inclusions, motor phenotypes, as well as chronic disease progression. These findings have helped bridge the mechanistic gap between clinical, genetic, and experimental observations and have already made a significant impact in this field as evidenced by the widespread adoption of these tools across the research community.


4. My lab has applied our novel synucleinopathy models towards developing and evaluating novel therapeutic strategies (e.g., immunotherapy, antisense therapy) for treating PD and other synucleinopathies. I am also part of efforts to disseminate the aSyn-related models and reagents to broader research community and to facilitate their usage.


Complete List of Published Work in MyBibliography (82 total):

H-index: 41, Citations: 11,752 as of 1/23/2023
BUDGET

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BUDGET JUSTIFICATION

Erin Smith, Graduate Student in the Maday lab. Funds are requested to support Erin’s salary. Erin will help plan, execute, and analyze experiments proposed in this project plan. Erin will also help write manuscripts generated from this project and present results at scientific meetings.

Consumables (Maday lab). Funds are requested for cell culture, experiment reagents, and microfluidic chambers. These procedures will be performed in Dr. Maday’s lab.

Consumables (Luk lab). Funds are requested for protein purification and fibril assembly that will be performed in Dr. Luk’s lab.