The Cell Biology of Neurodegeneration and Repair

November 30 | Location: Virtual

Tuesday, November 30, 2021
10:00 AM – 5:00 PM ET
Virtual
We thank ASCB President Ruth Lehmann for forming this Doorstep Meeting on *The Cell Biology of Neurodegeneration and Repair*, and for appointing its two organizers: **Erika Holzbaur, University of Pennsylvania Perelman School of Medicine** and **Andrea Stavoe, University of Texas Health McGovern Medical School**. Both are experts in this field and we appreciate their insights during the planning process.

Thanks to everyone for making this meeting happen!

**2021 Doorstep Meeting Program Chairs**

![Erika Holzbaur](image1.png)  
**Erika Holzbaur**  
*William Maul Measey Professor of Physiology*  
*University of Pennsylvania Perelman School of Medicine*

![Andrea Stavoe](image2.png)  
**Andrea Stavoe**  
*Assistant Professor, Neurobiology and Anatomy*  
*University of Texas Health McGovern Medical School*

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SCHEDULE

The Cell Biology of Neurodegeneration and Repair
Neuronal Homeostasis, Neurodegeneration, and Neuroregeneration

10:00 am ET  Meeting Room Opens
Attendees arrive, find their seats, meet and network with other attendees.
Attendees may turn ON camera and microphone when networking.

10:30 am ET  Welcome Remarks by Program Chairs
Erika Holzbaur, University of Pennsylvania Perelman School of Medicine
Andrea Stavoe, University of Texas Health McGovern Medical School

Attendees please turn OFF camera and microphone during presentations.

10:35 am ET  Super Resolution Imaging of Actin-dependent Vesicle Transport in the Squid Giant Axon
George Langford, Syracuse University

Video Enhanced Contrast-DIC (VEC-DIC) microscopy was one of the first super resolution imaging techniques used to detect structures in living cells smaller than the limit of resolution of the light microscope. We used this technique to discover the actin-dependent component of vesicle transport in the squid giant axon. Newer techniques continue to push the boundary of detection by breaking the diffraction barrier and thereby improve imaging of dynamic structures in living cells. One such technique is TIRF-SIM, a technique that has the temporal and spatial resolution plus gentle enough to acquire images of dynamic structures in living cells without significant photodamage. We used TIRF-SIM to follow the movement of submicroscopic membrane projections (microvilli) on surfaces of pancreatic beta cells. These membrane projections share similarities with dendritic spines of nerve cells and TIRF-SIM promises to be another way to determine the dynamic changes of the actin cytoskeleton in spines in real time.

10:55 am ET  Novel Pathways of Intracellular Lipid Traffic and Neurodegenerative Diseases
Pietro De Camilli, Yale University School of Medicine, Howard Hughes Medical Institute, and Kavli Institute for Neuroscience

Membrane lipids traffic from one compartment to another within cells as part of the membranes of vesicular carriers. However, this mode of lipid traffic is complemented by the action of lipid transport proteins that often act at membrane contact sites. Typically,
l lipid transport by these proteins is achieved by lipid binding modules that shuttle back and forth between the participating membranes. However, recently, studies of VPS13 family proteins (which also comprise the autophagy factor ATG2) have revealed a new mechanism of lipid transfer mediated by rod-like proteins that bridge two adjacent bilayers and harbor a hydrophobic groove that runs along their entire length. Most interestingly, loss of function mutations of members of this protein family result in neurodegenerative or neurodevelopmental diseases, including Parkinson’s disease (VPS13C) and a Huntington-like syndrome called chorea acanthocytosis (VPS13A). The talk will provide an overview of the known properties of mammalian VPS13 proteins and of potential mechanisms through which their mutations result in neurodegeneration (Leonzino M, Reinisch KM and De Camilli P. 2021. Insights into VPS13 properties and function reveal a new mechanism of eukaryotic lipid transport. PMID: 34216812)

11:25 am ET  Microtubule Retrograde Flow Retains Neuronal Polarization in a Fluctuating State
Frank Bradke, German Center for Neurodegenerative Diseases  30 minutes

In developing vertebrate neurons, a neurite is formed by more than a hundred microtubules. While individual microtubules are dynamic, the microtubule array has been regarded as stationary. Using live cell imaging in combination with photoconversion techniques and pharmacological manipulations, we uncovered that the microtubule array flows retrogradely within neurites to the soma. This microtubule retrograde flow drives cycles of microtubule density, a hallmark of the fluctuating state before axon formation. Shortly after axon formation, microtubule retrograde flow slows down in the axon, which stabilizes microtubule density cycles and thereby functions as a molecular wedge to enable axon extension. We propose microtubule retrograde flow and its specific slowdown in the axon to be the long-sought mechanism to single one neurite out to drive neuronal polarization.

11:55 am ET  Break  10 minutes

12:05 pm ET  Short Talks (Session 1)  60 minutes
10 6-minute presentations
Nuclear accumulation of CHMP7 initiates nuclear pore complex injury in familial and sporadic ALS
Alyssa Coyne, Johns Hopkins University School of Medicine

Alyssa N. Coyne, Victoria Baskerville, Benjamin L. Zaepfel, Dennis W. Dickson, Frank Rigo, Frank Bennett, C. Patrick Lusk, Jeffrey D. Rothstein

Nuclear pore complex (NPC) injury has recently emerged as an early and significant contributor to familial and sporadic Amyotrophic Lateral Sclerosis (ALS) disease pathogenesis. However, the molecular events leading to this pathological phenomenon characterized by the reduction of specific nucleoporins (Nups) from the NPC remains largely unknown. This is due in part to a lack of knowledge regarding the biological pathways and proteins underlying NPC homeostasis specifically in human neurons. Using induced pluripotent stem cell (iPSC) derived neurons (iPSNs) and postmortem human CNS tissues, we have recently uncovered that aberrant nuclear accumulation of the ESCRT-III protein CHMP7 initiates NPC injury in familial and sporadic ALS neurons. Critically, knockdown of CHMP7 alleviates disease associated Nup alterations, deficits in Ran GTPase localization, defects in TDP-43 associated mRNA expression, and impaired neuronal survival in response to glutamate stress. Using cutting edge genome wide Crispr screening, mass spectrometry, biochemistry, and confocal and super resolution microscopy technologies, we are investigating the molecular mechanisms by which 1. CHMP7 is recruited to the nuclear envelope and/or nucleoplasm in human neurons in health and disease, 2. CHMP7 aberrantly accumulates within human ALS neuronal nuclei, and 3. CHMP7 initiates Nup removal and degradation from the NPC in human neurons in health and disease. In yeast and non-neuronal mammalian cells, nuclear relocalization of CHMP7 has been shown to recruit the ESCRT-III proteins CHMP4B, CHMP2B, and VPS4 to facilitate NPC and nuclear envelope (NE) repair and homeostasis. Intriguingly, neither CHMP4B nor CHMP2B pathology is observed in familial and sporadic ALS neurons. In contrast, VPS4 expression is significantly increased in a CHMP7 dependent manner in ALS neuronal nuclei prior to the emergence of nuclear pore injury. However, unlike CHMP7 knockdown, impaired VPS4 function does not mitigate NPC injury and instead results in the emergence of intranuclear POM121 “degradation intermediates”. Collectively, these data support a role for altered CHMP7 mediated Nup homeostasis as a prominent initiating pathomechanism for familial and sporadic ALS and highlights the potential for CHMP7 as a therapeutic target. Moreover, this work sheds light on the cell biological mechanisms that regulate CHMP7 localization and activity in human neurons in health and disease.

Elucidating the Cellular Functions of Timm50, a Mitochondrial Transport Protein, in Neurons and Astrocytes
Eyal Paz, Tel Aviv University

Paz E.1 2, Gottfried I.1, Azem A.1 2, Ashery U.1 2
1 School of Neurobiology, Biochemistry and Biophysics, Life Sciences Faculty, Tel Aviv University 2 Sagol School of Neuroscience, Tel Aviv University

Mitochondria are essential, double membrane-bound organelles found in almost all eukaryotic cells. In humans, the mitochondrial proteome consists of about 1400
different proteins; the majority of which are encoded by the nuclear genome, synthesized in the cytosol and must be transferred into the mitochondrion. Several complexes mediate the trafficking and sorting of imported precursor proteins into the different mitochondrial compartments. One of particular interest is the TIM23 complex, which mediates the import of all matrix proteins as well as some inner membrane and inter membrane space proteins. Timm50 is an essential member of the TIM23 complex and is the first TIM23 subunit that recognizes and interacts with precursor proteins as they emerge into the inter membrane space. After recognition, Timm50 handles the precursor protein to the channel's core. Essentially, hundreds of proteins rely on Timm50's proper function in order to reach their destination. Therefore, defects in the Timm50 protein subunit, are expected to lead to severe phenotypes, and indeed, Timm50 was recently linked to an epileptic encephalopathy disease.

Children carrying different mutations in the Timm50 protein presented severe intellectual disability accompanied by epilepsy, optic atrophy, persistent 3-MGA-uria and other prognoses. Previous studies include basic research done with patient’s fibroblasts. However, it is apparent that the common ground between almost all the patient’s phenotypes is neurological, which agrees with the notion that the brain is highly enriched with mitochondria and uses 15-20% of the body’s total oxygen and energy. Nevertheless, its roles in neurons were never investigated. Hence, we aimed to study the neuronal functions of Timm50 and the effects of its mutant forms on mouse primary neuronal cultures.

In our research, we applied knockdown techniques to manipulate the expression levels of Timm50 and examined the changes it caused to several key mitochondrial and neurological features. Using cortical neuronal culture, we show that Timm50 knockdown leads to specific destabilization of the TIM23 core import complex. This in turn causes a reduction in the levels of several oxidative phosphorylation complexes and has a deteriorating effect on the mitochondrial membrane potential, which leads to problems with oxygen consumption and energy production. Additionally, we show that Timm50 knockdown has a negative impact on mitochondrial mobility along neurites. Our approach allows us to examine the neuronal defects caused by Timm50 malfunction in a controlled, neurobiological system, in hopes of understanding the molecular basis of the disease phenotypes.

12:17pm ET  Ribosome collisions fuel a vicious cycle of neurotoxicity in Huntington’s Disease
Ranen Aviner, Stanford University

Ranen Aviner, Ting-Ting Lee, Vincent B. Masto, Dan Gestaut, Kathy H. Li, Raul Andino and Judith Frydman

Huntington’s disease (HD) is caused by expansion of a CAG trinucleotide repeat in the Huntingtin (Htt) gene, encoding an aggregation-prone polyglutamine (polyQ) tract. Still, it remains unclear whether aggregation is the main driver of neurotoxicity. We find that CAG expansions alter Htt translation, causing an elongation rate conflict when ribosomes rapidly decoding the polyQ encounter a downstream slowly-decoded polyproline tract. This leads to ribosome collisions that activate ribotoxic stress signaling, triggering ubiquitination of ribosomal proteins and phosphorylation of
translation initiation factor eIF2a. Because translation of Htt is inhibited by an upstream open reading frame (uORF), stress-induced eIF2a phosphorylation increases uORF skipping and therefore synthesis and aggregation of mutant Htt, further amplifying the proteotoxic stress. With age, mutant Htt protein sequesters elongation factor eIF5A, needed to prevent and resolve collisions and a central regulator of the Integrated Stress Response (ISR). eIF5A depletion exacerbates ribosome collisions across a large proportion of the translatome and causes co-translational proteostasis defects, including impaired ribosome and proteasome assembly, disrupted myelin biogenesis and altered polyamine metabolism. Loss of eIF5A also abrogates the induction of protective ISR responses, rendering HD striatal neurons hypersensitive to acute stress. Thus, aberrant translation elongation on CAG expansions is a key contributor to cellular collapse in HD and a possible therapeutic target.

12:23pm ET ER stress-induced JNK promotes stress granule formation via epigenetic modifications in C9orf72 mediated ALS/FTD
Sahana Gopalakrishna, Mayo Clinic

Sahana TG, Ke Zhang,*
Mayo Clinic, Department of Neuroscience, Jacksonville, FL 32224 USA

Amyotrophic Lateral Sclerosis is a neurodegenerative disease affecting upper and lower motor neurons. A GGGGCC hexanucleotide repeat expansion (HRE) in the gene C9ORF72 is the most common genetic cause of ALS. Interestingly this repeat expansion is also a genetic factor for Frontotemporal Dementia (FTD), one of the most common dementia (collectively referred to as c9ALS/FTD). This repeat expansion generates dipeptide protein repeats (DPRs) via noncanonical translation, resulting in five different DPR species. Among these species, the arginine-rich DPRs, poly(glycine-arginine, or GR), and poly(proline-arginine, or PR) are especially toxic and believed to play a critical role in c9ALS/FTD pathogenesis. However, how poly(GR) and poly(PR) causes neurodegeneration is incompletely understood.

In an RNAi screen in a Drosophila model of c9ALS/FTD, we identified loss of bsk, the fly homolog of c-Jun N-terminal kinase (JNK) to suppress neurodegeneration. JNK is a member of the mitogen-activated protein kinase pathway (MAPK). We found that the Bsk/JNK activity is upregulated in fly or cell models of c9ALS/FTD, which is caused by ER-stress-induced activation of IRE1/TRAF2. Furthermore, JNK hyperactivation transactivates G3BP1, a key stress granule (SG) assembly factor. SGs are RNA-protein condensates formed in eukaryotic cells upon stress. In c9ALS/FTD, the condensates contain several RNA binding proteins namely TDP-43, FUS, hnRNP which can potentially form solid aggregates which is the pathological hallmark of ALS/FTD. Our results show that JNK promotes G3BP1 expression via epigenetic modulation of Histone protein 3 (H3). Importantly, IRE1 or JNK inhibitors suppress H3 phosphorylation, G3BP1 protein levels, SG assembly, and survival defects in cells expressing poly(GR) or poly(PR). Hence, our data connected ER stress, JNK, epigenetic regulation, and SG assembly in a unified pathway contributing to neurodegeneration.
**Presynaptic autophagy is coupled to the synaptic vesicle cycle via ATG-9**
*Sisi Yang, Yale University*

**Sisi Yang**, Daehun Park, Laura Manning, Sarah E. Hill, Mian Cao, Zhao Xuan, Ian Gonzalez, Yongming Dong, Benjamin Clark, Elias M. Wisdom, Lin Shao, Ifechukwu Okeke, Agustin Almoril-Porras, Jihong Bai, Pietro De Camilli and Daniel A. Colón-Ramos

Autophagy is a cellular degradation pathway essential for neuronal health and function. Autophagosome biogenesis occurs at synapses, is locally regulated and increases in response to neuronal activity. The mechanisms that couple autophagosome biogenesis to synaptic activity remain unknown. In this study we determine that trafficking of ATG-9, the only transmembrane protein in the core autophagy pathway, links the synaptic vesicle cycle with autophagy. ATG-9 positive vesicles in C. elegans are generated from the trans-Golgi network via AP3-dependent budding, and delivered to presynaptic sites. At presynaptic sites, ATG-9 undergoes exo-endocytosis in an activity-dependent manner. Mutations that disrupt endocytosis, including a lesion in synaptojanin 1 associated with Parkinson’s disease, result in abnormal ATG-9 accumulation at clathrin-rich synaptic foci, in defects in activity-dependent presynaptic autophagy, and in aging-dependent defects in neurotransmission and locomotory behavior. Our findings uncover regulated key steps of ATG-9 trafficking at presynaptic sites, and provide evidence that ATG-9 exo-endocytosis couples autophagosome biogenesis at presynaptic sites with the activity-dependent synaptic vesicle cycle.

**Modulating Histone Modifications in ALS/FTD: New Avenues for Suppressing Toxicity of Neurodegenerative Disease Proteins**
*Mariana Torrente, Brooklyn College/City University of New York*

Seth A. Bennett, Samantha N. Cobos, Elizaveta Son, Michel Fallah, George Angelakakis, Melagras Mirzakandova, Navin Rana, Muna Hugais and Mariana P. Torrente.

Amyotrophic lateral sclerosis (ALS) is a fatal and incurable neurodegenerative disease that affects cells in the brain and the spinal cord. Frontotemporal dementia (FTD) is another disorder involving progressive neuronal loss in the frontal and temporal lobes of the brain. ALS and FTD form a neurodegenerative continuum and share pathological and genetic features. ALS/FTD has been linked to mutations in many genes including FUS, TDP-43 and C9orf72. Interestingly, the protein products of these genes accumulate in inclusions within affected neurons.

Eukaryotic DNA is packaged into chromatin, a highly organized protein-DNA complex. Changes in the structure of chromatin are sufficient to cause heritable phenotypic changes termed epigenetic. Epigenetic mechanisms include the methylation of DNA and the covalent post-translational modification of histone proteins. We have discovered distinct histone modification profiles associated with FUS, TDP-43 and C9orf72 proteinopathies in yeast and human cell models. Furthermore, we demonstrate that interfering with histone modification changes can counter the repercussions of protein aggregation on cell survival. Our data raises the novel hypothesis that the toxic effect of protein aggregation in neurodegeneration is related to its association with altered histone marks. Altogether, our findings highlight novel
Epigenetic mechanisms at play in ALS/FTD. Epigenetic processes are highly accessible targets for pharmaceutical treatments and thus they can lead to novel, alternative approaches in the treatment of ALS/FTD and other neurodegenerative diseases.

**12:41pm ET**

**SHIP164 is a Chorein Motif Containing Lipid Transport Protein that Controls Membrane Dynamics and Traffic at the Endosome-Golgi Interface**

*Michael Hanna, Yale University*

1Departments of Neuroscience and 2Cell Biology, 3Howard Hughes Medical Institute, 4Program in Cellular Neuroscience, Neurodegeneration and Repair, 5Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, CT, 6Aligning Science Across Parkinson’s (ASAP) Collaborative Research Network, Chevy Chase, MD.

Recent studies have shown that proteins with an N-terminal chorein motif are lipid transport proteins and further suggested that they mediate lipid transfer between closely apposed membranes by a novel bridge-like mechanism. Within these proteins, the chorein motif represents the beginning of a rod-like structure that harbors a hydrophobic groove running along its entire length. Lipids are thought to transfer between bilayers by sliding along this groove (PMID: 34216812). VPS13 and ATG2 are founding members of this family. Another protein with a predicted N-terminal chorein motif is SHIP164 (UHRF1BP1L), previously identified as a Syntaxin 6-binding protein (PMID: 20163565) and as a Parkinson’s Disease (PD) candidate gene (PMID: 28137300). Here, we first explored whether the similarity of SHIP164 to VPS13 and ATG2 extends beyond the chorein domain and determined by cryo-EM that SHIP164, like these two proteins, has an elongated hollow rod-like structure. We also found that SHIP164 harbors glycerolipids in an aqueous environment and transports them between membrane bilayers in a liposome-based assay. We further investigated the localization and physiological function of SHIP164 in mammalian cells. We found that endogenous SHIP164 is localized to cation-independent mannose-6-phosphate receptor (MPR)-positive vesicular structures at the cell periphery and that its over-expression induces the abnormal formation of dynamic clusters of small 50-70nm vesicles enriched in these receptors and anchored to endosomes. Further, SHIP164 interacts with proteins implicated retrograde microtubule-based transport from endosomes to the Golgi complex: the dynein/dynactin accessory factor LC8 and dynein interactor Rab45/RASEF. Accordingly, in SHIP164 knockout (KO) RPE-1 cells, the traffic of MPR and Sortilin positive vesicles to the Golgi complex is partially impaired. An additional defect observed in SHIP164 KO cells is the absence of the largest endosomes positive for PI3P and EEA1. In view of the lipid harboring properties of SHIP164 it is tempting to speculate that the latter phenotype may be explained by its lipid transport properties that, as in the case of VPS13 and ATG2, may allow membrane expansion. Direct evidence for such a model is missing. However, we found that SHIP164 positive vesicles are also positive for ATG9, the autophagy factor recently found to function as a scramblase in partnership with ATG2 on autophagosome membranes. An attractive possibility is that SHIP164 may participate in the regulation of endocytic flow by acting in partnership with ATG9 in the control of phospholipids/protein ratio on the membranes of endocytic vesicles.
ER network stability promotes organized microtubule disassembly during Compartmentalized Cell Elimination

Piya Ghose, The University of Texas at Arlington

Karen Juanez, Rashna Sharmin and Piya Ghose, The University of Texas at Arlington

Programmed cell death is a critically important event for normal development and homeostasis. Morphologically complex cells are characterized by elaborate processes, such as axons and dendrites in neurons. While complex cells are very common, their programmed elimination is poorly understood, as is their elimination under pathological conditions or following injury. Microtubule (MT) disassembly is associated with region-specific elimination, also known as pruning, of morphologically complex neurons, but the exact nature of this relationship is unknown. We discovered a ‘tripartite’ killing program that eliminates the morphologically complex tail-spike cell (TSC) and the sex-specific CEM neurons during C. elegans embryonic development. This program, called Compartmentalized Cell Elimination (CCE), is characterized by three cell regions dying in three disparate ways. Of particular note, the single process/dendrite of these cells displays two very different elimination morphologies in its two segments. The proximal segment fragments in a manner strikingly reminiscent of developmental pruning or injury-induced Wallerian degeneration of axons; whereas the distal segment retracts, much like axons do following nutrient deprivation.

Here we report that MTs have stereotyped dynamics throughout the development and death of the TSC. Through forward genetic screens, we found that genes promoting endoplasmic reticulum (ER) network stability, atnl-1/atlastin and Inp-1/lunapark, which encode the homologs of human Atlastin GTPase and Lunapark, promote process dismantling during CCE. We find that atnl-1/atlastin and Inp-1/lunapark promote the function of the conserved MT-severing ATPase SPAS-1/Spastin in facilitating CCE. Human Atlastin, Lunapark and Spastin are all associated with neurodegenerative conditions. We propose that the stable ER network and ER network stability proteins anchor SPAS-1/Spastin to allow for precisely targeted and organized MT disassembly, which leads to the highly defined demise of the TSC process during CCE. Our findings shed new light on the localized elimination of complex cells and provide a mechanism for how MTs are linked to pruning and neurodegeneration through an unexpected connection with the ER.

Activation of the CaMKII-Sarm1-ASK1 MAP kinase pathway protects against axon degeneration caused by loss of mitochondria

Chen Ding, Yale University

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Mitochondrial defects are tightly linked to axon degeneration, yet cellular mechanisms that can modify mitochondria-triggered degeneration remain poorly understood. In C. elegans ric-7 mutants, PVQ axons lack mitochondria completely, and as a consequence, PVQ axons degenerate spontaneously with age. Using an unbiased
In Vitro Reconstituted Stress Granule-Like Condensates are Nucleation Sites for Aggregation of Misfolded Proteins

Andrii Kopach, International Institute of Molecular and Cell Biology in Warsaw

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Stress granules are hypothetical sites for onset of amyotrophic lateral sclerosis (ALS) (1, 2). Previous studies provide evidence for transition of stress granule proteins from liquid- to a solid-like state (3-7), which is often associated with sequestration of misfolded proteins, such as mutant versions of superoxide dismutase 1 (SOD1), into stress granules (8). But how do liquid-like stress granules solidify upon the enrichment with misfolded proteins? Here, we show that model misfolded protein Ubc9ts selectively enriches stress granule-like condensates, which can be artificially formed in a test tube via phase separation of key stress granule protein Ras GT Pase-activating protein-binding protein 1 (G3BP1). Our biophysical experiments using fluorescence recovery after photobleaching (FRAP) and fluorescence correlation spectroscopy (FCS) show that Ubc9ts becomes immobile upon sequestration into the condensates. We further demonstrate using optical tweezers that G3BP1 condensates lose ability to fuse immediately after addition of Ubc9ts to the in vitro system. We propose that misfolding of cytoplasmic proteins drives formation of molecular interactions with key stress granule components, thereby inducing misfolded protein enrichment into stress...
granules followed by their localized aggregation (9). These findings are in line with previous studies and highlight that stress granules are promising targets for novel ALS therapies.

References
Mitochondria-lysosomes crosstalk alterations and neurodegeneration: Charcot-Marie-Tooth type 2B as the paradigm of nervous peripheral damage

Flora Guerra, University of Salento

Guerra Flora, Romano Roberta, Manganelli Fiore, Nolano Maria, Santoro Lucio, Chengbiao Wu, Bucci Cecilia

Charcot-Marie-Tooth type 2B (CMT2B) is a rare inherited disorder affecting the peripheral nervous system caused by 5 missense mutations in the RAB7A gene, which encodes a GTPase of the RAB family. RAB7A has multiple pivotal roles in cellular physiology, controlling transport to late endocytic compartments and regulating late endocytic organelle biogenesis, positioning, and functions, influencing trafficking and degradation of signaling receptors. The biochemical and functional properties of the CMT2B-causing RAB7 mutant proteins have been previously investigated, but the exact mechanism by which mutated RAB7, albeit ubiquitous, causes dysfunction in peripheral neurons is still not clear.

Previously, we have demonstrated that mutation of RAB7 determines higher lysosomal degradative activity and compromission of autophagic flux in CMT2B patient’s fibroblasts. Moreover, we also found alterations in lipid metabolism and impairment of lipid droplets breakdown. Emerging evidence suggest a key role of the crosstalk between mitochondria and lysosomes in cellular physiology and its dysregulation in neurodegenerative disease as mitochondrial impairment can influence lysosomal function and viceversa. Notably, recent data have elucidated several new roles of RAB7 in many mitochondrial processes, such as mitophagy, fusion and fission, mitochondrial protein translation, and mitochondrial-derived vesicle formation. Moreover, RAB7 is responsible of the regulation of untethering of mitochondria-lysosome contact sites influencing duration, number, and frequency of them. In light of this premise, it is reasonable to suppose that Rab7 might represent the mediator of inter-organelle communication and its dysfunction might affect their interplay inducing massive alterations in peripheral neurons. For these reasons, we have investigated mitochondrial dynamics and mitochondrial biogenesis in CMT2B patient’s fibroblasts and in HeLa cells transfected with a CMT2B RAB7 mutant. Interestingly, we found significant mitochondrial fragmentation in human patient fibroblasts with alterations in mitochondrial morphology and networking. Moreover, analysis of mitochondrial biogenesis showed a decrease of many regulators of process and also a reduction of expression of mitochondrial respiration complex subunits. Furthermore, modulation of RAB7 can significantly influence mitochondrial biogenesis. Thus, CMT2B-causing RAB7A mutations determine altered mitochondrial dynamics and biogenesis metabolism that, considering the role of mitochondria in neurons and in skeletal muscle, could be a major cause of neurodegeneration.

Phase Separation at the Synapse: Material Properties and Functional Implications

Dragomir Milovanic, German Center for Neurodegenerative Diseases (DZNE)

Hoffmann Christian, Sansevino Roberto, Trnka Franziska, Wang Han, Rankovic Branislava, Milovanovic Dragomir
Compelling evidence suggests that liquid-liquid phase separation (LLPS) is emerging as a major mechanism for the organization of macromolecules, particularly proteins with intrinsically disordered regions, in compartments non-limited by a membrane or a scaffold. In the last several years, a surge of studies shows that spatial and temporal organization of many structures in neurons is formed via LLPS, such as SV clusters, stress granules, active zones, post-synaptic densities (both excitatory and inhibitory). The lack of regulation of LLPS in neurons leads to protein and organelle aggregation, which are the hallmark of many neurodegenerative diseases. We employ reconstitution assays, spectrometry, live-cell imaging, optogenetics, and single-particle tracking to scrutinize the phase separation at synapses. During this talk, we will discuss three specific aspects. First, how synaptic vesicle condensates can act as molecular beacons to dynamically recruit disordered proteins such as alpha-synuclein. Second, we will share our progress in employing new approaches to characterize the material properties of synaptic vesicle/alpha-synuclein condensates. Finally, we will present our most recent data showing that the aberrant phase separation leads to lysosome sequestering and acidification, suggesting that lysosomes can actively triage aggregates from condensates. Together, our results outline the molecular mechanisms and functional consequences for keeping organelles and proteins soluble in the crowded environment of the nerve terminal.

2:27 pm ET  Kinesin-13 regulates developmental pruning of dendrites in the PVD neurons of Caenorhabditis elegans

Swagata Dey, National Brain Research Centre, Manesar, India

Swagata Dey (DBT/Wellcome Trust India Alliance Early Career Fellow, National Brain Research Centre, Manesar, India)
Nitish Kumar (Present affiliations: Pennsylvania State University, PA, USA)
Anindya Ghosh-Roy (National Brain Research Centre, Manesar, India)

Dendritic arbors are characteristic features of the neurons correlated to their function. Growth and pruning of dendritic branches have been correlated to consolidation or refinement of the neural circuit during development but also in neurodegenerative conditions. The cytoskeletal basis of dendrite remodeling events concerning physiological or pathological cues is yet to be fully characterized.

Using PVD neurons in C. elegans, we are investigating how the regulation of microtubule cytoskeleton architecture influences the dendritic pruning during development. PVD neurons have an extensive and stereotyped dendritic arbor with a distinct cytoskeletal organization as per the hierarchy in the arbor. Live imaging reveals that, unlike conventional degeneration-like pruning, these dendrites show recurrent phases of growth and shrinkage at each hierarchical level during the Larva-3 to Larva-4 stage of development.

Disruption of microtubule dynamics by genetic perturbation of KLP-7, a microtubule depolymerizing enzyme of the Kinesin-13 family, leads to an increased number of quaternary (highest order) branches in these neurons. Furthermore, live imaging of these branches showed that the dynamic events were significantly reduced in the klp-7 mutant. Although the relative orientation or dynamics of microtubules in the primary
dendrites did not change due to loss of klp-7 function, a significant number of dynamic microtubules were mislocalized to the secondary dendritic branches as observed by the dynamics of EBP-2::GFP. Relative enrichment of KLP-7 at the incipient branch points is indicative of its role in branch retraction and limiting microtubule ingress to higher-order branches.

These observations highlight the role of Kinesin-13 as one of the key regulators of microtubule organization and dendritic retraction during developmental pruning. Further experiments are in progress to understand the collaboration of KLP-7 with other cytoskeletal regulators in physiological and pathological dendritic remodeling.

2:33 pm ET  The Troyer syndrome protein spartin mediates selective autophagy of lipid droplets  
Jeeyun Chung, Harvard University

Jeeyun Chung1,2, Joongkyu Park4, Zon Weng Lai1,2,3, Talley J. Lambert1, Ruth C. Richards1,2, Robert V. Fares Jr.1,2,5,* , Tobias C. Walther1,2,3,5,6,*

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Lipid droplets (LDs) are crucial organelles for energy storage and lipid homeostasis. Autophagy of LDs is an important pathway for their catabolism, but the molecular mechanisms mediating targeting of LDs for degradation by selective autophagy (lipophagy) are unknown. Here we identify spartin as a receptor localizing to LDs and interacting with core autophagy machinery, and we show that spartin is required to deliver LDs to lysosomes for triglyceride (TG) mobilization. Mutations in SPART (encoding spartin) lead to Troyer syndrome, a form of hereditary spastic paraplegia. We find that interfering with spartin function leads to LD and TG accumulation in motor cortex neurons of mice. Our findings thus identify spartin as a lipophagy receptor and suggest that impaired LD turnover may contribute to Troyer syndrome development.

2:39 pm ET  Spastic paraplegia protein ortholog, reticulon-like 1, governs presynaptic ER organization and Ca2+ dynamics  
Rebecca Smith, University of Cambridge

Smith RC1, Pe´rez-Moreno JJ1, Oliva MK1, O’Kane CJ1
1: Department of Genetics, University of Cambridge, UK

The endoplasmic reticulum (ER) is a dynamic, continuous organelle with a complex network of tubules. In neurons, ER is pervasive through dendrites, soma, axons, and terminal boutons. Its shape and continuity are influenced by ER-shaping proteins,
mutations in which can cause axon degeneration in the Hereditary Spastic Paraplegias (HSPs). While HSPs are thought of as axon degeneration diseases, the susceptibility of distal axons suggests a “dying back” pathology, in which presynaptic terminals could also be affected. To test how ER organisation could affect presynaptic function, we investigated how loss of Rtnl1, a Drosophila ortholog of the human HSP gene RTN2 (SPG12), which encodes an ER-shaping protein, affected ER organization and the function of motor neuron terminals. Loss of Rtnl1 depleted ER membrane at synapses and diminished ER-plasma membrane contacts. However, ER loss appeared to mainly affect narrow tubular ER, but not cisternae, suggesting little change in Ca2+ storage capacity. Nevertheless, we observed major reductions in neurotransmission, as well as in activity-evoked Ca2+ fluxes in the cytosol, ER, and mitochondria. Our results illuminate the importance of localized ER tubule organization in regulating presynaptic organelle physiology, and implicate altered presynaptic physiology as a potential factor in the pathological changes found in HSPs.

**2:45 pm ET**  
**DLK regulates mitochondrial fission by phosphorylating DRP1 after axonal injury**  
**Jorge Gomez Deza, National Institutes of Health**

**Jorge Gomez-Deza PhD, Matthew Nebiyou, Claire E. Le Pichon PhD.**

Dual leucine zipper kinase (DLK) is a stress-sensing protein that is activated in neurodegenerative conditions and can promote axonal death or regeneration depending on exact conditions. Using immunolabeling and live imaging in human iPSC-derived neurons, we have identified that a subset of DLK puncta localize to axonal mitochondria. To investigate the role of DLK relating to mitochondria we performed laser axotomies combined with live imaging. Immediately after axotomy, mitochondria shrink and undergo fission in a DRP1-dependent manner. Further investigation revealed that DLK localizes to the mitochondrial fission site after axotomy. Moreover, pharmacologic, or genetic inhibition of DLK does not prevent the axotomy-induced mitochondrial shrinkage but does inhibit the mitochondrial fission. Our results show that, after axotomy, there is an increase in DRP1 phosphorylation in a DLK-dependent manner and that DLK directly phosphorylates DRP1 using an in vitro phosphorylation assay. Additionally, both DLK and DRP1 knockdown prevents axotomy-induced axonal degeneration. Taken together our results identify DLK as a novel regulator of mitochondrial fission after injury by directly phosphorylating DRP1. Moreover, it highlights the importance targeting mitochondrial fission in order to prevent axonal degeneration in human neurons.

**2:51 pm ET**  
**ApoE targets astrocyte cytoplasmic lipid droplets to modulate phosphatidylcholine metabolism and droplet size**  
**Ian Windham, University of North Carolina at Chapel Hill**

**Ian A. Windham, E. Diane Wallace, Colby Wagner, and Sarah Cohen**

APOE is the strongest genetic risk factor for late-onset Alzheimer’s Disease (AD). Individuals with one or two copies of the APOE4 variant are at an increased risk of developing AD compared to those homozygous for the APOE3 variant. In the central nervous system, Apolipoprotein E (ApoE) is expressed primarily by astrocytes.
Astrocytes secrete ApoE-containing lipoproteins which supply neurons with lipids to maintain their plasma membranes and synapses. However, the trafficking and function of ApoE within astrocytes is not well understood, nor is the mechanism by which the E4 variant predisposes individuals to AD.

Surprisingly, we discovered that in response to hypoxia or lipid loading, ApoE diverts from the secretory pathway and instead targets cytoplasmic lipid droplets (LDs). This raises the possibility that ApoE plays previously unrecognized roles in cellular lipid metabolism by acting directly on LDs in astrocytes. Using immunogold electron microscopy and live-cell imaging, we found that ApoE targets the cytosolic face of the endoplasmic reticulum (ER) before translocating onto LDs via membrane bridges at ER-LD contact sites. Mutations of positively charged residues in the N-terminal lipoprotein receptor binding region, including the rare, protective Christchurch variant, exhibit increased trafficking to LDs. Lipidomics studies demonstrated that APOE knockdown reduces intracellular phosphatidylcholine (PC) levels after fatty acid loading. Knockdown cells also exhibit higher levels of PC species with unsaturated fatty acyl chains. PC has previously been shown to act as a surfactant on LDs, preventing their coalescence through Oswalt ripening. Consistent with this idea, knockdown of APOE causes fewer, larger LDs. Like APOE knockdown cells, we observed that APOE4 cells have fewer and larger LDs than ApoE3-expressing cells, indicating that ApoE4 has a loss-of-function or dominant-negative effect. Our data indicate that ApoE can localize to cytoplasmic LDs in astrocytes, where it regulates LD size and phosphatidylcholine metabolism. We hypothesize that cells with larger LDs caused by ApoE depletion or APOE4 are sensitized to lipid peroxidation or lipotoxicity, which could contribute to AD risk.

2:57 pm ET  Exploring The Role of the E3 Ubiquitin Ligase TRIM9 in Alzheimer’s Disease
Charise White, University of North Carolina at Chapel Hill

Charise White, Shalini Menon, Laura McCormick, Harrison Hockenberry, Stephanie L. Gupton

A sequela associated with many neurodegenerative diseases is the accumulation of protein aggregates in the brain. In Alzheimer’s disease (AD), one of the most abundant proteins in the aggregates is the microtubule associated protein tau (MAPT). As disease progresses, myriad responses aimed at eliminating protein accumulations and aggregations are triggered. The ubiquitination-proteosome system is an important mechanism for protein degradation. Tripartite motif protein 9 (TRIM9) is a brain-enriched E3 ubiquitin ligase, which our lab has demonstrated plays fundamental roles during developmental neuronal morphogenesis. Using biotin proximity ligation assays (BioID), we identified many candidate TRIM9 interacting partners in neurons, including MAPT. Gene ontology enrichment analysis of the putative TRIM9 interactome suggested that TRIM9 may be associated with AD. Several additional lines of evidence support the hypothesis that TRIM9 continues to play a critical role in the health and function of the aging neuron. First, TRIM9 enrichment in the nervous system persists in adulthood and is repressed in the brains of patients with Parkinson’s disease and dementia with Lewy bodies. Our work has shown that deletion of murine Trim9 results in dramatic cognitive impairment, specifically in spatial learning and memory. Our
collaborative work with the Jung lab demonstrated that Trim9-/− mice exhibit increased neuroinflammation, whereas increasing TRIM9 expression plays anti-inflammatory, neuroprotective roles following ischemic stroke. Finally, in collaboration with the Honnorat lab, we found that TRIM9 was a novel marker for paraneoplastic cerebellar degeneration. Here we provide additional evidence for TRIM9 function in the aging neuron. First, our preliminary data indicate that TRIM9 is strongly enriched in the postsynaptic density (PSD) of cortical neurons in the adult mouse, and that when TRIM9 is lost, the proteome of the PSD is significantly affected. Second, we find that loss or overexpression of TRIM9 alters the number and size of dendritic spines. To assess the role of TRIM9 in AD, we crossed Trim9-/− mice with PS19 tauopathy AD model mice. Six-month-old PS19 animals lacking Trim9 displayed increased levels of phosphorylated MAPT, another characteristic of AD, compared to Trim9+/+:PS19 mice. Further, we examined TRIM9 protein in brain tissue from late-stage AD patients and age-matched controls and found that TRIM9 was present in more of the age-matched controls, which suggests that TRIM9 expression may be correlated with better cognitive function later in life.

3:03 pm ET  TPPP Forms Liquid Condensates and Aggregates in Multiple System Atrophy

Shahrnaz Kemal, NIH

Shahrnaz Kemal, Hunter Richardson, Thomas MacAlear, Joseph Nowacki, Susanne Bechstedt, Meng-meng Fu

Multiple System Atrophy (MSA) is a neurodegenerative disorder characterized by cytoplasmic alpha-synuclein inclusions in oligodendrocytes. There are currently no therapies for MSA, which leads to death within an average of 9 years from symptom onset. There is a critical need to understand MSA disease etiology to identify viable targets for intervention.

Aggregates of several other proteins have been identified along with alpha-synuclein within oligodendroglial cytoplasmic inclusions in MSA, including tubulin polymerization promoting protein (TPPP). Though this initial observation was made two decades ago, very little is known about why TPPP aggregates in MSA. Our lab previously showed that TPPP is a microtubule nucleator that localizes to Golgi outposts, which are found along oligodendrocyte processes and within myelin sheaths at significant distances from the cell body. Tppp KO mice have shorter myelin sheaths and are hypomyelinated. We are now investigating the link between TPPP and MSA at the protein, cellular, and organismal level.

While purifying recombinant TPPP, we made the discovery that TPPP forms liquid condensates that are functional and robustly nucleate microtubules. TPPP shares many properties common to proteins that undergo liquid-liquid phase separation. First, TPPP contains a prominent N-terminal intrinsically disordered region. Second, TPPP droplets undergo fission and fusion. Third, recombinant TPPP droplets are dynamic in FRAP experiments. Further confirmation of these properties comes from cultured primary oligodendrocytes expressing GFP-TPPP, which forms droplet-like structures that exhibit fast FRAP recovery.
We examined brain samples from MSA patients and made several striking observations. MSA brains contain widespread perinuclear cytoplasmic TPPP inclusions in oligodendrocytes. We identify a discrete population of TPPP inclusions that are more diffuse, fibril-like, and far from the cell body; some of these fibrils colocalize with myelin markers. Contrary to prevailing hypotheses, our data suggests that aggregation may initiate at distal sites where TPPP is normally localized to perform microtubule nucleation and subsequently spreads to the perinuclear cytoplasm. Also, we observed many perinuclear TPPP inclusions that lack alpha-synuclein. TPPP aggregation may precede alpha-synuclein aggregation and be a driving force for what has historically been considered the pathological hallmark of MSA.

Together, our results showcase the duality of TPPP. Its normal liquid condensate properties allow it to exert precise control over oligodendrocyte cytoarchitecture, thus enabling myelin sheath formation. However, these properties simultaneously increase its propensity to aggregate and contribute to disease pathology in MSA.

3:09 pm ET  **Insulin signaling enhances the anterograde speed of Rab4-associated vesicles in the cholinergic neurons of Drosophila**

*Kamaldeep Singh, Tata Institute of Fundamental Research, Mumbai, India*

**Kamaldeep Singh**, Asmita Sarkar, and Krishanu Ray

Insulin signaling, which activates Rab4-associated vesicular transport in adipocytes, also regulates synaptic plasticity in the central nervous system (CNS). Increased Rab4 levels in the CNS are associated with synaptic atrophy and neurodegeneration in Drosophila and humans. In addition, patients with Type-II diabetes have a higher predisposition to develop Alzheimer's-like symptoms. We used time-lapse imaging in semi-intact preparations of Drosophila larvae to investigate the correlation between insulin signaling, Rab4-associated vesicular transport in axons, and synapse homeostasis in the larval brain. The results indicate that a) Insulin signaling via a specific phosphoinositide 3-kinase (PI3K) enhances the anterograde speed and flux of Rab4-associated vesicles in axons, and b) Increased Rab4 influx is adversely correlated with synapse density in the developing larval brain. Together, these observations delineate a potentially negative influence of localized insulin stimulation on synaptic stability in Drosophila CNS.
The abnormal accumulation of protein aggregates has long been recognized as a common theme in adult onset neurodegeneration, however to what extent these structures contribute to disease pathogenesis remains unclear. This has especially been the case, given that the segregation of aggregated proteins, from their often essential non-aggregated counterparts has been difficult. To address this question, we have focused on modulating the degradation pathway macroautophagy to turnover selectively aggregated proteins. In this presentation, we will discuss our most recent findings about how augmenting aggregate-clearance via autophagy may provide therapeutic benefit for a canonical protein aggregation disorder, Huntington’s disease.
After studying at the Freie Universität Berlin and University College London, Bradke carried out research at the European Molecular Biology Laboratory (EMBL) in Heidelberg as part of his doctoral thesis. As a postdoctoral researcher, he moved to the University of California in San Francisco and Stanford University in 2000. In 2003, he was appointed a group leader at the Max Planck Institute of Neurobiology in Martinsried. In 2011, he was awarded the IRP Schellenberg Prize, one of the most prestigious awards in the field of regeneration research. In the same year he became full professor at the University of Bonn, and was appointed head of the Axon Growth and Regeneration research group at the DZNE.

Bradke is an elected a member of the Leopoldina (the German National Academy of Sciences), the Academia Europaea, and the European Molecular Biology Organization (EMBO). In 2016, he was awarded the Leibniz Prize, which is the most important research award in Germany. In 2018, he received the Roger de Spoelberch Prize and in 2021 he was selected for the Carl Zeiss Lecture.

I have worked in the neurodegenerative field for the past 25 years with a specific interest in developing therapies for these devastating disorders. My Ph.D thesis focused on tau biology and Alzheimer’s Disease (AD). My post-doctoral fellowship focused on the development of a SOD1 mouse model of ALS and this model was the first to demonstrate that aggregation of SOD1 is a prominent feature and one potential mechanism in human disease. This has led to the development of multiple therapeutic strategies focused on protein aggregation and recently Orphazyme initiated a clinical trial of Arimoclomol based on this hypothesis. In addition my work demonstrated that mutant SOD1 leads to disease not as a result of loss of the normal protein function but due to a novel gain of toxicity. These studies formed the basis of the use of antisense technology to reduce the level of mutant SOD1 protein. Combining my pharmacology background and research in neurodegeneration I joined Bristol Myers Squibb as Research Scientist and Group
leader focusing on AD and Parkinson’s research. During this time I established a transgenic mouse and rat facility within the company, developed cell based assays for CNS drug discovery, developed a mouse model for AD that was used to identify lead molecules in the AD program and introduced stem cell technology in the department to develop novel glial and neuronal assays for high throughput screening. In addition, working with numerous departments my team built multi-disciplinary partnerships and I participated in the review of novel acquisitions within the company together with the head of neuroscience including a multiyear partnership with Lexicon Genetics.

At the ALS Association I established the first translational research program for ALS, Translational Research Advancing Therapies for ALS (TREAT ALS). Through partnerships between academia, government and industry and soliciting donor contributions for strategic programs I have established initiatives for drug development, clinical trials, biomarkers, assistive technology, precision medicine, large scale sequencing and analytics. Solicitations for proposals includes the development of requests for proposals, one on one engagement with partners and through crowd sourcing approaches. Identifying novel scientific opportunities, evaluating the science, working closely with the FDA (most recently in developing an FDA guidance document with the ALS community) advising on the appropriate experiments and identifying partners in the neurodegenerative space with the goal of developing new therapeutic approaches for disease has been a critical part of the last 18 years with The ALS Association and in my role on many non-profit advisory boards. One example of a significant success arising from The ALS Association research portfolio is the development of antisense technology for ALS which is now in clinical trials for ALS, Huntington’s Disease and AD and led to the FDA approval of the first treatment for Spinal Muscular Atrophy (SMA), a childhood motor neuron disorder. This discovery is a direct result of the establishment of academic and industry partnerships at The ALS Association. Building multi-disciplinary global teams to tackle these complex diseases is critical to success and the identification of new therapies for CNS disorders.
A native of Italy, De Camilli earned his M.D. degree from the University of Milano. He was a postdoctoral fellow with Paul Greengard in the Department of Pharmacology at Yale, and subsequently an assistant professor in the Yale Section of Cell Biology. Following a brief return to Italy, he moved back to Yale in 1988. From 1997 to 2000 he served as Chair of the Department of Cell Biology, in 2005 co-founded the Yale Program in Cellular Neuroscience, Neurodegeneration and Repair, and from 2015 to 2021 he served as Chair of the Department of Neuroscience. Since 2015 he is Director of the Kavli Institute for Neuroscience. He is a member of the National Academy of Sciences, the National Academy of Medicine and of the American Academy of Arts and Sciences.

The De Camilli lab is interested in the mechanisms underlying the dynamics of cell membranes with emphasis on the role of these mechanisms in neuronal physiology and synaptic transmission. His studies on synaptic vesicle dynamics have contributed to the general fields of exocytosis and endocytosis. His discovery and characterization of the role of phosphoinositide metabolism in the control of endocytosis have broad implications in the fields of phospholipid signaling and of membrane traffic. More recently he helped advance the field of organelles cross-talk at membrane contact sites. His studies have also contributed to the elucidation of pathogenetic mechanisms of human diseases, including, most recently, neurodegenerative diseases.
Chantell Evans is an Assistant Professor of Cell Biology at Duke University. She received her Ph.D. in Molecular and Cellular Pharmacology from the University of Wisconsin and was a Postdoctoral Fellow at the University of Pennsylvania. Her lab uses advanced microscopy and biochemical techniques to gain insight into the various mitochondrial quality control pathways in neurons and how mitochondrial regulation contributes to neurodegenerative diseases. She is particularly interested in the molecular mechanisms that regulate mitophagy in primary neurons. Chantell is a Duke Science and Technology Scholar and an inaugural recipient of the Hanna Gray Fellowship from the Howard Hughes Medical Institute.

Dr. Carlos (Charly) Guardia is an incoming Stadtman Tenure-Track Investigator at NIEHS, NIH. He was born, raised and trained as a chemist and structural biologist in Buenos Aires, Argentina. After getting his PhD, he joined Dr. Bonifacino’s lab (NICHD, NIH) to study lysosomal movement in cells, including neurons. He’s now mostly interested in autophagy and intracellular trafficking mechanisms in the placenta, using iPSCs-derived trophoblast cells and model organisms. He has been recently awarded a prestigious Distinguished Program Scholarship that recognizes his contributions to diversity and inclusion and will support his future efforts to train and retain a diverse workforce at NIH.
George M. Langford is Distinguished Professor of Neuroscience and Professor of Biology at Syracuse University and Dean Emeritus of the College of Arts and Sciences. As a cell biologist, he studies the role of the actin cytoskeleton and molecular motors in cells including neurons and pancreatic beta cells. He served as dean of the College of Natural Sciences and Mathematics at the University of Massachusetts-Amherst, the inaugural Ernest Everett Just Professor of Natural Sciences at Dartmouth College and professor of Physiology, the School of Medicine at the University of North Carolina Chapel Hill. In 2021 he was elected to the American Academy of Arts and Sciences. He was appointed in 1998 by President Clinton to the National Science Board and awarded an honorary Doctor of Humane Letter by Beloit College in 2001. He is a Fellow of the American Association for the Advancement of Science (AAAS; 2013) and a Fellow of the American Society for Cell Biology (ASCB; 2017). Professor Langford was the first recipient of the ASCB EE Just Lectureship Award. He served on the Science Education Advisory Board of the Howard Hughes Medical Institute (HHMI) and was former chair of the Board of Directors of the Burroughs Wellcome Fund. He is Program Director of the Syracuse University CHANcE Project funded by the HHMI Inclusive Excellence Initiative and Program Director of the ASCB PAIR-UP program funded by the Gordon and Betty Moore Foundation.

Lee Ligon is Associate Professor of Biological Sciences and Associate Dean for Academic Affairs for the School of Science at Rensselaer Polytechnic Institute. At Rensselaer she serves as the co-chair of the LGBTQ+ Task Force and the Coordinator of School of Science Diversity, Equity and Inclusion Initiatives. She also serves as co-Chair of the ASCB Public Information Committee which focuses on science communication and outreach and previously served as co-chair of the ASCB LGBTQ+ Task Force/Committee. She has a PhD in Neuroscience from the University of Virginia and did postdoctoral research at the University of Pennsylvania before starting her lab at Rensselaer studying the microtubule cytoskeleton and cell-cell adhesion.
Priyanka Narayan is a Stadtman Tenure Track Investigator at the National Institutes of Health in Bethesda, MD since April 2020. She performed her graduate degree at the University of Cambridge in biophysics as a Marshall Scholar and her postdoctoral work at the Whitehead Institute and MIT in cell biology, genetics, and neuroscience supported by a Helen Hay Whitney Fellowship and a K99. Her lab at the NIH studies the ways in which genetic and environmental factors alter cell biology to increase susceptibility or improve resilience to neurodegenerative diseases like Alzheimer’s disease. They use a combination of genetics, biochemistry, molecular biology, and human iPSC-derived neuronal and glial cell types to answer these questions.

Shalini joined the Michael J. Fox Foundation in January 2016. As Director, Research Programs, Shalini stays closely linked with the Parkinson’s research community to maintain a current view of the PD drug development landscape and ensure that MJFF research priorities reflect and best serve the ultimate needs of patients. This includes regularly meeting with academic and industry researchers at Foundation-hosted workshops and conferences as well as traveling to Parkinson’s/neuroscience congresses and symposia around the world.

Shalini heads the Foundation’s Discovery Research strategy to advance the understanding of genetic, environmental, and other risk factors that contribute to initiation and progression of PD pathophysiology, with a focus on target and pathway discovery and validation in support of therapeutic and biomarker development strategies. This includes overseeing the process of soliciting investigator proposals, peer review, awarding and contracting funds, troubleshooting and assessing projects as they go forward, and assessing the potential for supplemental or follow-on funding.

Shalini earned an undergraduate degree in Pharmaceutical Sciences from U.I.C.T, India and a PhD in Neuroscience from the Medical College of Georgia. Prior to joining the Foundation, Shalini trained as a postdoctoral research scientist at Columbia University where she worked on validating novel targets to treat Parkinson’s disease using a gene
therapy approach. With several years of research experience, she has developed a strong understanding of the dopaminergic system in the healthy brain and its dysfunction in patients with Parkinson’s disease.

Andrea attended Michigan State University for undergrad, earning degrees in Biochemistry/Molecular Biology/Biotechnology and French. She earned her PhD in Cell Biology at Yale University, studying the molecular mechanisms of presynaptic development in C. elegans with Daniel Colón-Ramos. Andrea conducted her postdoctoral research with Erika Holzbaur at the University of Pennsylvania as a F32 NRSA postdoctoral fellow before being awarded a K99/R00 from NINDS. The Stavoe lab opened in 2020 at the University of Texas Health Science Center at Houston (UTHealth) in the Department of Neurobiology and Anatomy. The Stavoe lab is investigating how neuronal autophagy changes and is regulated during aging and neurodegenerative disease, aiming to increase nervous system healthspan by identifying and understanding the molecular mechanisms that regulate this critical pathway.

Ai Yamamoto is an Associate Professor in the Departments of Neurology, and Pathology and Cell Biology at Columbia University. After graduating with a Bachelor’s degree in Material Science and Engineering from MIT, she received her Ph.D. with Dr. René Hen at Columbia University, and was a Helen Hay Whitney Postdoctoral Fellow with Dr. Jim Rothman at Memorial Sloan Kettering Cancer Center. The goal of her lab is to define how protein trafficking pathways can be modulated to impact neurodegeneration, by examining these question within the context of the adult brain. Her work in Huntington’s disease was recently recognized by the Hereditary Disease Foundation, as an awardee of the 2021 Leslie Gehry Brenner prize for Innovation in Science.