UCLA Intramural **Parkinson's Disease** Research Symposium

2020-2021
Multiday + Virtual zoom

Tuesday, July 7 @ 1:00 pm - Physiology, Circuits, and Behavior
Wednesday, July 8 @ 12:00 pm - Epidemiology, Toxicology, and Genetics
Friday, July 17 @ 12:00 pm - Molecular Neuroscience and Pharmacology

UCLA Intramural Parkinson's Disease Research Symposium

Tuesday, July 7 @ 1:00 pm | **Wednesday, July 8** @ 12:00 pm | **Friday, July 17** @ 12:00 pm

ZOOM: https://uclahs.fyi/pdsymposium

This link is for guests. Speakers will be provided unique links.

PHYSIOLOGY, CIRCUITS, BEHAVIOR
Tuesday, July 7, 2020 | 1:00 pm – 3:30 pm

1:00 p.m.	**Welcome**
1:05 p.m.	Michele A. Basso, PhD
1:20 p.m.	William Zeiger, MD, PhD
1:35 p.m.	Sotiris Masmanidis, PhD
1:50 p.m.	**Discussion/Break**
2:05 p.m.	Nigel Maidment, PhD
2:20 p.m.	David Krantz, MD and Felix Schweizer, PhD
2:35 p.m.	Nader Pouratian, MD, PhD
2:50 p.m.	Ausaf Bari, MD, PhD
3:05 p.m.	**Discussion/Break**

EPIDEMIOLOGY, TOXICOLOGY, GENETICS
Wednesday, July 8, 2020 | 12:00 pm – 2:30 pm

12:00 p.m.	**Welcome**
12:05 p.m.	Cynthia Kusters, MD, PhD
12:20 p.m.	Chao Peng, PhD
12:35 p.m.	Elizabeth Videlock, MD, PhD
12:50 p.m.	**Discussion/Break**
1:05 p.m.	Jeff Bronstein, MD, PhD
1:20 p.m.	Beate Ritz, MD, PhD
1:35 p.m.	Allan Wu, MD
1:50 p.m.	Kimberly Paul, PhD
2:05 p.m.	**Discussion/Break**

MOLECULAR NEUROSCIENCE, PHARMACOLOGY
Friday, July 17, 2020 | 12:00 pm – 2:30 pm

12:00 p.m.	**Welcome**
12:05 p.m.	Jose Rodriguez, PhD
12:20 p.m.	Gal Bitan, PhD
12:35 p.m.	Ming Guo, MD, PhD
12:50 p.m.	**Discussion/Break**
1:05 p.m.	Wael El-Nachef, MD, PhD
1:20 p.m.	Lin Jiang, PhD
1:35 p.m.	Varghese John, PhD
1:50 p.m.	Sally Frautschy, PhD
2:05 p.m.	**Discussion/Break**

ABSTRACTS & FACULTY BIOS

PHYSIOLOGY, CIRCUITS, and BEHAVIOR

Tuesday, July 7, 2020 | 1:00 pm – 3:30 pm

Cognition & Movement in PD – A Role for the Subcortical Circuits in Perceptual Decision Making

Michele A. Basso, PhD

Cognition and Movement in Parkinson's disease

In my laboratory, we are interested in understanding how decisions evolve in the brain, particularly when we are faced with ambiguous or unreliable sensory evidence to inform those decisions. In a situation with ambiguous information, a good strategy is to rely on past experiences or memories of similar situations to help guide those decisions. Indeed, healthy humans and monkeys will do exactly this. However, people with Parkinson's disease (PD) show impairments in the ability to use previously learned information to guide their decisions in conditions of sensory uncertainty. We performed a series of experiments involving computational modeling of data obtained from people with PD and manipulations of brain circuits in monkeys trained to perform decision-making tasks, and discovered that this novel memory based decision making impairment seen in people with PD may involve a subcortical area of the brain called the superior colliculus.

A Role for the Subcortical Circuits in Perceptual Decision Making

In my laboratory, we are interested in understanding how decisions evolve in the brain, particularly when we are faced with ambiguous or unreliable sensory evidence to inform those decisions. In a situation with ambiguous information, a good strategy is to rely on past experiences or memories of similar situations to help guide those decisions. Indeed, healthy humans and monkeys will do exactly this. In a simple experiment, healthy humans and monkeys observe a computer screen that has a visual stimulus on it and they must decide whether the visual stimulus is pointing to the left or to the right. This perceptual decision – is it left or right – is reported by the participant by making an eye movement to the left or the right, or by pressing a key on a computer keyboard. In some trials, we make the decision very difficult by making the perceptual discrimination – is it left or right – very hard to determine. In this situation, humans and monkeys guess, choosing left and right randomly on each trial. However, if we surreptitiously change how often the left or right stimulus appears, healthy people and monkeys will choose left or right more often but only on those trials in which the sensory evidence is ambiguous. Thus, people and monkeys incorporate their past experience and rely on it when sensory information is unclear – they show decision biases. We recently discovered that people with Parkinson's disease are impaired in this memory-based decision making. To unravel the neuronal circuits that underlie this cognitive impairment, we transiently and reversibly inactivated the midbrain superior colliculus (SC) to mimic the Parkinsonian state in monkeys while they performed the decision task. We found that inactivation of the SC produced profound decision biases in the absence of any biases in eye movements, indicating that the manipulation did not cause motor or attentional changes. Based on our results, we conclude decision making impairment seen in PD may stem for altered function of the subcortical circuit from the basal ganglia to the midbrain SC.

Michele A Basso, PhD

Michele A Basso, PhD is a Professor in the Department of Psychiatry and Biobehavioral Sciences at the Jane and Terry Semel Institute for Neuroscience and Human Behavior. Dr. Basso is the Director of the Joaquin Fuster Laboratory of Cognitive Neuroscience where she oversees a research portfolio that extends across model systems and is designed to unravel the neuronal circuits of decision-making in health and disease. Dr. Basso has a long-standing interest in movement disorders and diseases of the basal ganglia beginning with her work as a PhD student which unraveled the neuronal circuits of the blink reflex abnormalities seen in people with Parkinson's disease called the glabellar tap sign. She also worked on the development of a rodent model of a focal dystonia called blepharospasm. As a post-doctoral fellow at the National Institutes of Health, Basso focused on the basal ganglia – brainstem circuits and their role in cognitive processes, a line of research she continues today. Basso was a faculty member at the University of Wisconsin Madison until 2012 when she was recruited to join the faculty at UCLA.

Mechanisms of visual cortical circuit dysfunction mediated by α-synuclein

William Zeiger, MD, PhD

Parkinson disease (PD) and dementia with Lewy bodies (DLB) are progressive neurologic diseases marked by impairments in movement including stiffness, slowness, and tremor. In addition, there are frequently other symptoms, often including problems with thinking, memory, and particularly, how vision is perceived. It is thought that these diseases are caused by the abnormal accumulation of a protein in the brain called α-synuclein. However, we still do not understand exactly how α-synuclein leads to problems with the cells and circuitry of the visual system. We plan to use advanced microscopy techniques to directly record the activity of brain cells in the visual system of mice and test the effect of α-synuclein on the function of these cells over time. We hope that these studies will lead to a better understanding of how brain cells and circuits are affected in PD and DLB and may offer clues to new treatment options.

William Zeiger, MD, PhD

Dr. William Zeiger is currently a fellow in the Department of Neurology at UCLA. He obtained his M.D.,Ph.D. from the University of Chicago. During his Ph.D. with Dr. Gopal Thinakaran, he studied calcium homeostasis in the context of the cellular stress response and the processing of amyloid precursor protein (APP). Dr. Zeiger completed a residency in neurology at Johns Hopkins Hospital and UCLA. He currently works 20% time as a clinical fellow in movement disorders and 80% time as a research fellow in the laboratory of Dr. Carlos Portera-Cailliau. His current studies utilize two-photon in vivo imaging, circuit mapping, and animal behavior tasks to investigate the mechanisms of functional circuit remapping after stroke in mice. In the future, Dr. Zeiger plans to transition to a position as an independent investigator and has a strong interest in using similar techniques to investigate the mechanisms of circuit dysfunction and synuclein pathology in Parkinson disease.

Tools for recording aberrant network-level brain activity in mouse models of Parkinson's disease

Sotiris C. Masmanidis, PhD

Dr. Masmanidis' talk will focus on approaches for studying how brain activity goes awry in mouse models of Parkinson's disease. Mice represent a more genetically tractable organism than humans or other mammals, but at the same time they contain most of the same brain areas implicated in human Parkinson's disease. In order to better understand brain circuit dysfunction, a key requirement is the ability to measure activity across circuits involved in motor control. To address this challenge, we have developed the silicon microprobe, a device containing arrays of miniaturized electrodes that enable measurements from large numbers of brain cells and regions. I will discuss how these tools, together with other approaches, have potentially transformative applications for elucidating the role of specific circuits in controlling movement in models of Parkinson's disease.

Sotiris C. Masmanidis, PhD

Sotiris Masmanidis is an Associate Professor in the Department of Neurobiology at UCLA. His group studies neural circuits underlying movement initiation and reward-guided learning in mice, by combining electrophysiological and optogenetic methods to record and manipulate brain activity. Dr. Masmanidis has pioneered the development of low cost, open source, silicon-based microelectrode arrays, which allow for simultaneous measurement of spiking activity from tens to hundreds of neurons in behaving mice. He has applied these tools to study motor and learning-related neural dynamics in the striatum, a nucleus in the basal ganglia with strong involvement in movement disorders including Parkinson's disease (PD).

In one published study, his group discovered that a class of striatal interneuron can boost behavioral performance early in Pavlovian learning, by amplifying neural output. These findings may have important implications for PD, in which striatal interneuron connectivity is known to be disrupted. In another study, his group used temporally precise optogenetic manipulations during a Pavlovian conditioning task to find that midbrain dopaminergic neurons – the cells which are degenerated in PD – are primarily involved in regulating associative learning, and that they have a comparatively smaller role in generating online movements. He is interested in extending studies of dopaminergic neuron function to animal models of PD.

Dr. Masmanidis is also committed to tool sharing and collaboration and has provided his silicon probes to around 40 other research labs. Finally, he is actively involved in enhancing training in computational methods for studying brain function and is co-chair of a graduate elective course entitled *Introduction to Signal Processing for Neuroscientists*.

Probing dopamine neurotransmission and neuroprotective strategies in alpha-synuclein and LRRK2 models of Parkinson's disease

Nigel Maidment, PhD

Reproducing, in animals, genetic mutations that cause inheritable forms of PD provides models with which to study pathways of degeneration that may be similar to those of the more common forms of the disease, and to test potential new therapies to halt disease progression. My laboratory has used such animal models to study early changes in the function of dopamine-containing neurons, degeneration of which is responsible for many of the movement symptoms of the disease. The goal is to identify changes that occur in such neurons before the neurons die, with the goal of finding ways of stopping the progression to neuronal death. We have used these models to test gene therapies and drug interventions. One promising approach we have found is to increase the potential of the neurons to package dopamine. Another avenue we are exploring is the use of drugs to block an enzyme known to be more active in one of the genetic forms of the disease, and another is to genetically express a protein that helps guide another key protein, whose over-abundance is associated with PD, into compartments within neurons where it is destroyed.

Nigel Maidment, PhD

My laboratory uses pharmacology, analytical neurochemistry, behavior, and genetic tools to study dopamine and peptide transmission in models of Parkinson's disease and addiction. We have studied both neurotoxin- and genetics-based models of Parkinson's disease in flies, mice and rats. More recent collaborative studies with Michele Basso at UCLA and with Clive Svendsen at Cedars-Sinai have extended our work into monkey and human models, respectively. The idea that disruption of dopamine homeostasis and packaging may be a factor in PD has been entertained for some time. The discovery of genes associated with familial PD allowed us to probe this in relevant animal models. In highly collaborative studies, we found elevated extracellular dopamine that preceded degeneration in two such models – parkin knockout and alpha-synuclein over-expressing mice. When combined with evidence from several other groups of deficits in evoked DA release, these data supported a deficit in vesicular packaging. In further studies we found that environmental toxicants associated with increased risk for PD also disrupt DA homeostasis. Following up on a series of studies with David Krantz in flies, we hypothesized that over-expressing VMAT may provide neuroprotection, and collected evidence in support of this idea using a lentivirus-mediated alpha-synuclein (aSyn) rat model of PD. In further collaboration with the Krantz lab, we identified drugs capable of facilitating VMAT function as potential therapeutic agents. More recent work has used LRRK2 mutant rats to further probe pre-degenerative changes in dopamine transmission using fast-scan cyclic voltammetry and has supported the potential therapeutic promise of LRKK2 inhibitors. Other recent investigations have focused on the neuroprotective potential of a unique secretory chaperone protein – proSAAS – using alpha-synuclein pre-formed fibril and overexpression approaches in vivo and in cellular models.

Identification of a new pathway by which neuronal excitability might increase the risk of PD

David E. Krantz, MD, PhD
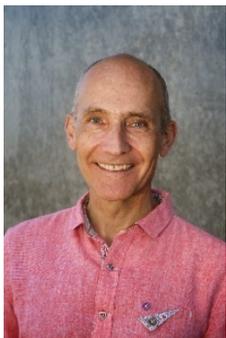## Felix Schweizer, PhD

Farm workers exposed to very high concentrations of some pesticides have a higher risk of getting Parkinson's disease (PD). By contrast, the concentrations we might be exposed to at the supermarket are far too low to have any effect on the incidence of PD in the general population. Nonetheless, understanding the pathways by which pesticides increase the risk of PD in farm workers will provide important clues about the way in which more standard cases of PD develop. We are investigating the pathways by which pesticides might alter the function of brain cells in a laboratory model. In doing so, we may have stumbled upon an important, general risk factor for PD that was not previously suspected.

David E. Krantz, MD, PhD

David Krantz is a Professor in Residence in the Department of Psychiatry and Biobehavioral Sciences at the David Geffen School of Medicine at UCLA. He was an undergraduate at Brown University, then combined research and clinical training as an MD/PhD student at UCLA.

After further clinical training as a psychiatry resident at UCLA, he moved to UCSF to study the regulation neurotransmitter transporters as a post-doctoral fellow. Since joining the UCLA faculty, his laboratory has used the model genetic organism Drosophila to study how neurotransmitter transporters influence synaptic transmission and behavior, and the mechanisms by which changes in dopamine homeostasis and environmental toxicants may increase the risk of PD.

Felix E. Schweizer, PhD

Felix was born in Basel, Switzerland and conducted his graduate research in the laboratory of Prof. Max M. Burger under the direction of Dr. Theo Schafer. He received his PhD degree in biochemistry summa cum laude from the University of Basel in 1989. From 1990 to 1994, he was a post-doctoral fellow in the Department of Molecular and Cellular Physiology at Stanford University in the laboratory of Prof. Richard W. Tsien. From 1994 to 1998, he was postdoctoral fellow in the Department of Neurobiology at Duke University in the laboratory of Professor George J. Augustine. Dr. Schweizer joined the Department of Neurobiology in the David Geffen School of Medicine at UCLA in 1998 as Assistant Professor and was promoted to Full Professor in 2010. Dr. Schweizer's research interests concern the molecular mechanisms by which neurons communicate, the regulation of communication by neurons and how alterations in neuronal communication might contribute to neuronal diseases. The Schweizer laboratory uses electrophysiological and optical tools to investigate the dynamic molecular mechanisms underlying the regulation of neurotransmitter release. We are particularly interested in the role of protein ubiquitination in regulating neuronal excitability and synaptic transmission. In collaboration with Dr. James Wohlschlegel, we used multiplexed SILAC and identified synaptic proteins that are dynamically regulated. More recently, in collaboration with Dr. David Krantz, we are using pesticides linked to neuro-degenerative disorders as unbiased tools identify novel pathways that might be involved in early signs of degeneration. In addition, we are characterizing transmission at the first synapse of the vestibular system, i.e. between utricular sensory hair cells and primary afferent neurons. In collaboration with Dr. Larry Hoffman we are finding that changing the gravitational load alters synaptic structures. We are now using serial EM and EM tomography in addition to physiology and cell biology to define in more detail the transfer function between head-movement input and afferent nerve-firing output.

Deep Brain Stimulation – Building a roadmap of brain networks to understand and treat Parkinson's

Nader Pouratian, MD, PhD

Parkinson disease is most often considered to be due to degeneration of deep brain structures, in particular the substantia nigra and basal ganglia. Still, it is not clear how disease in these deep parts of the brain affect how the brain controls movement and results in the symptoms of Parkinson disease. We hypothesize that, like many other neurological and psychiatric diseases, the symptoms of Parkinson disease result from abnormal communication across different parts of the brain. Specifically, like the heart develops arrhythmias, we hypothesize that the motor circuits in the brain become oversyncrhonized resulting in symptoms of PD. We use unique opportunities offered by neurosurgical procedures to record from multiple areas of the brain in patients with PD to evaluate how different parts of the brain are affected and communicate with one another. Our work has identified 'hypersynchrony' of brain oscillations in the motor cortex and that the motor cortex is also 'hypersynchronized' with deep brain structures, particularly the basal ganglia. We show that these abnormal oscillations underlie specific symptoms of PD, like impairments with initiating movements. We further show that these oscillations and 'hypersynchrony' are suppressed by therapeutic brain stimulation (and not by non-therapeutic stimulation). We are now investigating whether medications and brain stimulation work though similar mechanisms. These brain signals serve as important biomarkers that can be monitored for therapy development and monitoring. Limitations of our approach include the inability to record from all areas of interest in the brain of patients with PD, so we are exploring opportunities to extend human studies to animal models. We anticipate that a similar model can be used to investigate and develop therapies for other diseases, like depression and chronic pain.
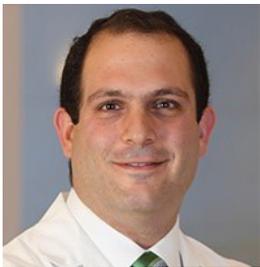
Nader Pouratian, MD, PhD

Dr. Pouratian is a Professor of Neurosurgery and Radiation Oncology and affiliated faculty in Bioengineering and Neuroscience. He has broad yet in depth training in both functional and restorative neurosurgery as well as brain mapping. He sees neurosurgery as a window of an opportunity to learn about the human brain, to understand how diseases affect the brain, and how to develop novel therapies to treat a wide spectrum of diseases. This work is particularly exciting in that brain function seems to influence nearly every system and part of the body. He uses a vast array of techniques with complex analyses to understand brain-behavior and brain-disease relationships, including functional and connectivity-vased MRI, optical imaging, evoked potentials, electrocortical stimulation mapping, electrocorticography, local field potentials, and single unit recording.

He has published extensively in the field of human brain mapping. As a neurosurgeon, neuroscientist, and bioengineer, he has the unique perspective and training to integrate these fields and take advantages of the unparalleled opportunities presented by neurosurgery to study human brain function and design novel neurotechnologies. His current focus is understanding the network basis of disease and designing novel network-based neuromodulatory therapies to address neurological and psychiatric disease. Current areas of focus include Parkinson disease, depression, chronic pain, and blindness. Dr. Pouratian received both his MD and PhD from UCLA School of Medicine. He completed his residency in surgery and neurosurgery at the University of Virginia Medical Center.

The Role of Norepinephrine in Parkinson's Disease

Ausaf A. Bari, MD, PhD

While the last several decades have focused on the role of dopamine in Parkinson's disease (PD), there is growing body of scientific work that is showing that norepinephrine (NE) may play a significant role in PD. For example, while significant insights and therapeutics have been targeted towards the motor symptoms of PD, few therapies have been successful at treating the mood and cognitive changes seen in these patients. In this project, we aim to use a specialized MRI technique to visualize the NE connections in the brain. Our present results show that the part of the brain that produces NE, the locus coeruleus (LC) has distinct connections with other mood and cognitive brain areas and is correlated with measures of emotion. In the next phase of this study, we plan to extend this methodology to understand how NE affects mood and cognition in patients with PD.

Ausaf A. Bari, MD, PhD

Dr. Bari specializes in the neurosurgical repair and restoration of brain and nerve function. Following his neurosurgery residency training at UCLA, Dr. Bari was awarded the prestigious William P. Van Wagenen Fellowship to train at the world-renowned functional neurosurgery program at the University of Toronto. He has extensive clinical and research experience in the use of deep brain stimulation (DBS) in the treatment of both movement and neuropsychiatric disorders. Dr. Bari's clinical practice includes DBS surgery for Parkinson's disease (PD), tremor, dystonia, depression and OCD. In addition, Dr. Bari performs epilepsy surgery, neurosurgical procedures for pain and peripheral nerve surgery.

Dr. Bari's research uses an interdisciplinary approach to study the neurobiology of PD. His laboratory combines neuroimaging techniques with direct human electrophysiology to better understand the brain circuits underlying the mood, cognitive and motor circuits involved in PD. Ongoing projects related to PD include the use of tractography to delineate subcortical circuits, recovery of neuronal cells during DBS surgery for genomic and proteomic analyses, and electrophysiological studies on impulsivity in patients with existing DBS electrodes.

As part of his fellowship training, Dr. Bari studied the relationship between the motor and reward systems of the brain and the use of deep brain stimulation to modify and enhance them. A native of California, Dr. Bari completed his neurosurgery residency training at UCLA after receiving his MD and PhD degrees from Boston University. He completed his undergraduate training at UC Berkeley in the field of neurobiology.

ABSTRACTS & FACULTY BIOS

EPIDEMIOLOGY, TOXICOLOGY, and GENETICS

Wednesday, July 8, 2020 | 12:00 pm – 2:30 pm

Genetic risk scores and Parkinson's disease
Cynthia DJ Kusters, MD, PhD

Hallucinations are a common symptom among Parkinson's disease (PD) patients. We examined if genetic risk for Alzheimer's disease (AD), schizophrenia (SZ), and PD has an influence on the occurrence of hallucinations in PD. We created four scores, called polygenic risk scores (PRS), that are associated with the individual genetic risk for AD, SZ, PD and height, respectively. Hallucinations after five years disease duration in two studies (ParkWEST, Norway, and PEG, USA) provided us with information from 399 PD patients. A higher prevalence of hallucinations was observed among those subjects that had a higher genetic risk score for AD. This effect was mainly driven by *APOE*, a well-known AD gene. These results suggest that hallucinations among PD patients are related to the genetic risk for AD. This could suggest that the process for developing AD and hallucination in PD are overlapping.

Cynthia DJ Kusters, MD, PhD

Dr. Kusters primary focus and clinical experience is anchored in the examination of underlying mechanisms of complex neurological diseases. She is currently a first-year Ruth Kirchstein postdoctoral fellow, in the Department of Genetics at the David Geffen School of Medicine at UCLA, under guidance of Dr. Steve Horvath.

During her dissertation, she worked and studied with Drs. Beate Ritz and Janet Sinsheimer. She is an active member of the UCLA-based Parkinson's Environment and Genetics (PEG). During her dissertation, she identified environmental and genetic risk factors that influence PD treatment complications; non-motor symptoms and; PD susceptibility. Before embarking on her PhD, she was a medical resident in pediatrics and clinical genetics in university hospitals in the Netherlands. During her residencies, Dr. Kusters conducted research on the associations and risk factors of neurodevelopmental delays in preterm infants. This included a collaboration with Dr. Olaf Dammann at Tufts Medical Center, where she studied the association and interaction between two common neurological complications, intraventricular hemorrhage and periventricular leukomalacia, in very young preterm infants.

During her post-doctoral training, Dr. Kusters' research focused on the role of sex steroids on aging, and aging-related diseases, such as Parkinson's disease, Alzheimer's disease, and cognitive decline. For this, she will utilize a multi-omics approach, using whole-genome wide genetics, epigenetics and metabolomics data to estimate hormone exposure.

Transmission and conformational diversity of pathological alpha-synuclein
Chao Peng, PhD

Accumulation of misfolded α-synuclein (α-syn) is a key pathological feature of Parkinson's disease (PD). During the past decades, transmission of pathological α-syn in the central nervous system is thought to be a key mechanism underlying the progression of PD. Our lab focuses on illustrating the molecular machinery responsible for the transmission of pathological α-syn as well as the genetic and environmental risk factors that could modulate this transmission process. On the other hand, pathological α-syn is not unique for PD, but exists in a group of neurodegenerative diseases collectively known as α-synucleinopathies, which also includes dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and Alzheimer's disease (AD) patients with Lewy body co-pathology. We found that misfolded α-synuclein from different diseases have distinct conformation and biological activities. Pathological α-synuclein from MSA patients forms a more compact structure is about 1000-fold more efficient to induce α-synuclein pathological than those from PD/D, DLB and AD, which likely contribute to the clinical and pathological diversity of these diseases. Furthermore, we demonstrated that different intracellular environment (neurons versus oligodendrocytes) lead to the generation of different pathological α-synuclein conformations, which provide critical insights into the origin of disease diversity.

Chao Peng, PhD

Chao Peng, Ph.D., is currently an assistant professor in the department of neurology at UCLA. Dr. Peng obtained a B.S. degree with honor in life science from Wuhan University. He then obtained a Ph.D. degree in developmental biology from Fudan University. There he developed new genetic tools to perform somatic mutation screens in mice and explored role of late endocytosis system on neuron survival, migration and dendrite development. Then, Dr. Peng joined Virginia Lee's lab as postdoc and expanded his research from basic neuroscience to neurodegenerative disease. Dr. Peng's research concentrating on understanding the molecular mechanisms of α-synuclein related neurodegenerative diseases including Parkinson's Disease with the goal to develop new diagnostic methods and therapies for these diseases. At UCLA, Dr. Peng's lab will focus on two main directions: 1) The transmission of pathological α-synuclein in the central nervous system. 2) The conformational diversity of pathological α-synuclein. 3) The interaction of pathological α-synuclein with other pathological proteins.

Altered gene expression in the colon of young mice overexpressing alpha-synuclein

Elizabeth Jane Videlock, MD, PhD

One purpose of the colon is to maintain a barrier intestinal contents and the blood stream. Both weakened barrier ("leaky gut") and the inflammation which results, have been seen in some PD patients. There is no reliable biomarker for PD in the blood. This may be due to the fact that the underlying cause for PD may is different in different people. We believe that all of the different causes can result in "leaky gut" and inflammation, which can cause an inflammation in the brain through the gut-brain axis. The overall goal of our research is to understand what changes in the gut in PD that makes it "leaky" and inflamed. If "leaky gut" and gut inflammation are a common pathway in PD, we may be able to diagnose and treat PD through identifying and correcting these changes in the gut. It is much easier and safer to collect tissue from and treat inflammation in the gut compared to the brain. Today's presentation highlights early changes in the gut-brain axis in a mouse model of PD and describes additional ways that our group is addressing the gut-brain axis in PD.

Elizabeth Jane Videlock, MD, PhD

Dr. Videlock completed her undergraduate studies at Yale and medical school at UCLA. She trained in Internal medicine at Beth Israel Deaconess Medical Center in Boston, and Gastroenterology at UCLA. She earned her PhD in the Department of Molecular, Cellular, and Integrative Physiology at UCLA in the laboratory of Dr. Charalabos "Harry" Pothoulakis with co-mentorship from Dr. Lin Chang, and her research focused on translational and cell culture approaches to peripheral molecular changes in irritable bowel syndrome. She currently studies the role of gastrointestinal inflammation, "leaky gut" and the gut-brain-immune axis in PD using clinical samples, rodent disease models, and isolated cells from PD models. Her primary hypothesis is that early inflammation in PD makes the gut barrier more permeable, which leads to neuroinflammation in the brain. Her clinical interests include disorders of the brain-gut axis, such as irritable bowel syndrome, as well as chronic constipation and defecatory disorders. Dr. Videlock receives mentorship from Ming Guo and Jeff Bronstein. Her work presented today is a collaborative project with Dr. Varghese John. She is also collaborating with Dr. Ming Guo to study the effect of PINK/Parkin mutations, which cause early onset PD, on the gut barrier. Their hypothesis is that oxidative stress caused by these mutations cause "leaky gut" and gut inflammation.

Studying Environmental Risk Factors in PD using Zebrafish

Jeff Bronstein, MD, PhD

My lab studies the causes of Parkinson's disease and the development of new therapies. More specifically, we study how the environment increases risk of developing Parkinson's disease using genetically modified zebrafish and cell cultures in collaboration with an epidemiologist. Using these tools, we determine the molecular mechanisms by which toxins and genetic alterations lead to neuronal injury and death. Pesticides have been a focus of our lab but recently, we have been studying how air pollution increases the risk of developing Parkinson's and Alzheimer's diseases.

Jeff Bronstein, MD, PhD
Professor, UCLA Department of Neurology
Fred Silton Family Chair in Movement Disorders
Director of Movement Disorders

Jeff Bronstein received his bachelor's degree from the University of California, Berkeley and M.D. and Ph.D. from UCLA as a recipient of the Medical Scientist Training Program Award. He completed a residency in Neurology and fellowship training in Movement Disorders at UCLA and at Queens Square in London. Dr. Bronstein also completed a postdoctoral fellowship in molecular biology before being appointed Director of the Movement Disorders Program at UCLA in 1996. Professor of Neurology in 2006, and Professor of Molecular Toxicology in 2007. He directs a basic science laboratory investigating the causes of PD (environmental and genetic) using cell and zebrafish models as well as population-based studies. His clinical interests include the medical and surgical management of Parkinson's disease (PD), Wilson's disease and other movement disorders. Dr. Bronstein active research program includes clinical trials to develop new therapies.

Risk factor and predictors of progression in Parkinson's disease: a population-based study of patients living in Central California

Beate Ritz, MD, PhD

Very few population-based studies of Parkinson's disease (PD) exist and even fewer studied PD progression. Over the past two decades, we have been conducting a population-based case control study of new-onset Parkinson's disease (PEG) in Central California and collected motor and non-motor progression data from ~550 PD patients for nearly a decade after disease onset. We will present an overview over the results from the PEG progression study, specifically present on pesticide gene-environment associations and the importance of the use of 'omics' and genetic markers as potential predictors of progression. Finally, we will provide an overview over lifestyle factors that were found to influence motor or cognitive progression such as physical activity, smoking, alcohol and coffee drinking and, also, the contributions of stress inducing life events on depression onset after PD diagnosis. We hope that our PEG study results and resources will stimulate new collaborations with scientists at UCLA.

Beate Ritz, MD, PhD

Beate Ritz, MD, PhD, is a Professor of Epidemiology, Environmental Health, and Neurology at the UCLA School of Public Health and School of Medicine. For a decade, she co-directed the NIEHS-funded Center for Gene-Environment (GxE) in Parkinson's disease (PD) at UCLA targeting occupational and environmental toxins such as pesticides in relation to neurodegenerative disorders, mainly Parkinson's disease and Alzheimer. She collaborates with neuroscientists, human geneticists, and clinicians at UCLA. She is the PI of two large population-based case control studies of PD in Denmark (PASIDA study with 3600 participants) and in California's central valley the long-running Parkinson, Environment and Genes (PEG) study that started collecting data from 1,870 PD patients and controls in 2000. For PEG, Dr. Ritz' team has also collected and stored bio-samples (blood, serum, plasma, saliva, urine, fecal matter) and recorded longitudinal motor and non-motor progression in the PD patients over a decade of follow-up. Her lab has available an array of genetic, genomics, epigenetic, metabolomics, questionnaire and clinical phenotyping and progression data for PEG study participants enrolled between 2001 and 2018 and continues to engage in progressive updates of patient status. In 2008, she received a research Award from the American Parkinson's Disease Association and in the past decade she served on several NAS-IOM committees such as the 'Gulf War Illnesses', 'Health Effects of Veterans from Herbicide Exposures in Vietnam', and 'Incorporating 21st Century Science into Risk-Based Evaluations' committees. In 2017, she was elected President of the International Society for Environmental Epidemiology, and she made the Thompson-Reuters most highly cited authors list in 2019.

The California Parkinson's Disease Registry and Learning Healthcare Systems

Allan D. Wu, MD

The California Parkinson's Disease Registry (CPDR) is a novel, mandatory statewide population-based registry that will be used to assess the incidence and prevalence of Parkinson's disease. Since 2018, the CPDR requires all California clinicians to report patients diagnosed with Parkinson's disease (PD) to the California Department of Public Health. To facilitate reporting, an electronic health record-based algorithm was developed to automatically report required data to CPDR without affecting clinical workflows. Recent work suggests that significant limitations in the EHR algorithm in that patients with definite PD are identified with a moderate positive predictive value of 79% and a very low specificity for date of diagnosis (20% correct within a year). At a recent workshop at UCLA, stakeholders discussed how the infrastructure present in the CPDR could be leveraged to not only address epidemiology, but also improve patient care, assuring healthcare quality and safety, and facilitate research. We will discuss steps involved toward the development of a learning healthcare system (LHS) where clinical care provides data which can be turned into knowledge to drive clinical decision support, quality improvement, and research. Steps toward a LHS focused on PD, supported by robust Health Information Technologies (HIT) and electronic health record (EHR) designs, has the potential to creatively address the healthcare demands of an increasing population of patients affected by PD.

Allan Wu, MD

Allan Wu is Professor of Neurology in the Movement Disorders Division and a Physician Informaticist at UCLA. Besides teaching fellows and seeing patients affected by Parkinson's disease, as a Physician Informaticist, Dr. Wu works on institution-wide electronic health record (EHR) projects that improve patient care, physician efficiency, clinical workflows, and care team communications. Dr. Wu is a member of the Adult Neuroscience Specialty Steering Board, a group of volunteer neurologists across the country, who meet monthly with Epic (UCLA's EHR vendor) to advise on standardizing EHR content for neurologists. Dr. Wu serves on the American Academy of Neurology (AAN) Practice Management and Technology Subcommittee and is an AAN representative to the American College of Physicians High Value Care Coordination Workgroup. Dr. Wu is also active with the California Regional Users Group (RUG), a group of informaticists and medical center leaders representing Epic-using institutions in California working on EHR interoperability standards.

DNA methylation aging and Parkinson's disease in the PEG study

Kimberly C. Paul, PhD

"Epigenetic clocks" are DNA methylation biomarkers that can accurately predict age and be used to describe biologic aging. We have previously shown in the PEG Parkinson's disease (PD) study that epigenetic age acceleration, faster biologic than chronologic aging, is associated with PD. Here, we aim to investigate whether epigenetic age acceleration is associated with motor symptoms among PD patients. This study used data from 552 PD patients, 336 of whom were followed to assess disease progression. We found that accelerated biologic aging was associated with having already progressed to ≥ Hoehn Yahr stage 3 at baseline, and a higher risk of progressing to ≥ Hoehn Yahr stage 3 faster over follow-up. When looking at components of the biologic aging clock, epigenetic signatures for different disease-related proteins were also associated with faster motor symptom development. Our results suggest that faster biologic aging measured at baseline is associated with faster motor symptom decline among PD patients, and epigenetic clocks and protein surrogates may inform blood-based markers in PD.

Kimberly C. Paul, PhD

Dr. Paul is an environmental and aging epidemiologist, whose research lies at the intersection of genetic, molecular, and environmental epidemiology, integrating toxicant exposure and molecular information in disease modeling. Her research aims to use modern, "omic" technologies to define the neurodegenerative disease process and elucidate risk at a biologic level, integrating a systems biology approach. From defining biologic profiles of susceptibility and exposures prior to disease, to profiles reflecting the phenotype as disease develops. She is currently a postdoctoral scholar in the Department of Epidemiology, Fielding School of Public Health. And was recently awarded the 2018 UCLA Chancellor's Award for Postdoctoral Research, for her work in public health and Parkinson's disease.

She currently employs several large-scale population-based cohorts to examine neurodegenerative consequences resulting from long-term low-level exposure to environmental toxicants and endocrine disrupting compounds among older adults, considering how metabolic dysfunction mediates this risk. Her most influential works include a series of reports that link organophosphate pesticides with neurotoxic pathways and neurodegeneration in a population-based setting. She has also studied the genetic and molecular components of sporadic Parkinson's disease and dementia in Parkinson's. During her postdoctoral research career at UCLA, Dr. Paul has received several competitive research awards and produced numerous influential publications in high-impact journals which have contributed to public policy and pollutant regulation reports.

ABSTRACTS & FACULTY BIOS

MOLECULAR NEUROSCIENCE & PHARMACOLOGY

Friday, July 17, 2020 | 12:00 pm – 2:30 pm

Probing the origin and spread of synuclein amyloids through structure-activity relationships

Jose Rodriguez, PhD

Parkinson's is a devastating neurodegenerative disease associated with the aggregation of the α-synuclein protein throughout the nervous system. Heroic structural efforts have succeeded in revealing molecular views of disease-related α-synuclein aggregates, giving us a glimpse of their dense fibrillar assemblies. Meanwhile, atomic resolution structures of short synuclein segments have taught us about the atomic interactions that facilitate the formation of these aggregates. We are now investigating the set of molecular events that can give rise to the fibrils that promulgate disease by developing and employing new methods in cryoEM that capture important but fleeting structures. These structures are expected to help guide the design of compounds that prevent or stagnate the growth of α-synuclein aggregates, bringing us closer to a Parkinson's therapy. Our investigation of amyloids capable of seeding synuclein fibril formation will teach us about the origins of synuclein aggregates and offer avenues for early detection and prevention of disease.

Jose Rodriguez, PhD

Jose Rodriguez earned a bachelor's degree in Biophysics from the University of California, Los Angeles (UCLA) followed by a Ph.D. in Molecular Biology from the same institution. He then stayed at UCLA, pursuing postdoctoral studies in Biological Chemistry under the direction of David Eisenberg. In the Eisenberg laboratory, I investigated the structures of amyloid forming proteins in their aggregated state by crystallographic means. During the course of those studies, a primary line of research involved the investigation of structures for toxic segments of α-synuclein, the basis for Parkinson's disease. With experience in the use and application of high-end instruments including X-ray and electron sources, I helped advance the a new cryoEM technique known as electron micro-diffraction (MicroED) to investigate synuclein structures. Using this technique, I determined an atomic structure of the toxic core of alpha-synuclein fibrils, the cause of Parkinson's disease - the first new structure determined by MicroED. Completing my postdoctoral training, I initiated a structural biology group at UCLA to understand fundamental aspects of molecular shape and function and its role in disease. This includes the development of new treatments to combat devastating and incurable diseases, and the development of new tools and approaches that advance our knowledge of biomolecules. In collaboration with other structural biology groups across UCLA, my group is now investigating the molecular events that give rise to synuclein fibrils and promulgate disease. In doing so, we hope to curb the growth of α-synuclein aggregates, bringing us closer to a Parkinson's therapy. Our investigation of amyloids capable of seeding synuclein fibril formation will teach us about the origins of synuclein aggregates and offer avenues for early detection and prevention of disease.

α-Synuclein in CNS derived exosomes distinguishes Parkinson's disease from multiple system atrophy

Gal Bitan, PhD

Diagnosis of parkinsonian diseases is difficult because the symptoms of the different diseases overlap substantially, especially at early stages. Misdiagnosis rates are high, causing distress to patients and their families and hampering clinical trials because of the difficulty to recruit the appropriate patients who may benefit from experimental therapy. CNS-derived exosomes isolated from serum or plasma provide a unique insight into biochemical processes in the brain, which otherwise require a more invasive analysis of cerebrospinal fluid (CSF). Moreover, CNS-derived exosomes allow analysis of biomarkers from different cell types, which is an important advantage compared to CSF biomarker analysis. We used this strategy to compare among healthy controls, patients with Parkinson's disease (PD), and patients with multiple system atrophy (MSA) in two separate cohorts and have found that analysis of α-synuclein in neuronal and oligodendroglial exosomes can distinguish among these groups with high sensitivity and specificity. In particular, the ratio between the α-synuclein concentrations in oligodendroglial and neuronal exosomes is a useful biomarker for separating PD from MSA. This strategy may become a useful diagnostic tool for clinicians and patients in the near future.

Gal Bitan, PhD

Gal Bitan earned his PhD in organic chemistry from the Hebrew University of Jerusalem, Israel. Dr. Bitan's graduate work on unnatural amino acids and non-conventional peptide cyclization methodologies led him to postdoctoral studies on the structural biology of ligand-receptor systems including integrins and G protein-coupled receptors at Clark University, Worcester, MA and Beth Israel-Deaconess Medical Center/Harvard Medical School, Boston, MA. Dr. Bitan then moved on to tackle the problem of protein misfolding and aggregation, which is involved in over 30 devastating diseases, such as Alzheimer's disease, Parkinson's disease, prion diseases (e.g., Mad Cow disease), amyotrophic lateral sclerosis (Lou Gherig's disease), and type II diabetes. Working at Brigham and Women's Hospital/Harvard Medical School, Boston, MA, Dr. Bitan has made fundamental contributions to the study of early events in the pathologic cascades that cause Alzheimer's disease. In Alzheimer's disease, the amyloid ß-protein (Aß) self-associates to form a variety of oligomeric and polymeric structures with potent neurotoxic activities. In particular, Aß oligomers have been implicated as the probable cause of Alzheimer's disease. Dr. Bitan introduced the use of novel photochemical protein cross-linking techniques for investigation of Aß assembly and discovered one of the earliest oligomers in the assembly cascade, the paranucleus. In 2004, Dr. Bitan joined UCLA where he is currently a Professor of Neurology. His research program is focused on translational science geared at developing novel, mechanism-based diagnostic and therapeutic tools for neurodegenerative diseases, including Alzheimer's disease and other tauopathies, Parkinson's disease, multiple system atrophy, and amyotrophic lateral sclerosis.

Making Mitochondria Great Again
Ming Guo, MD, PhD

Our lab is interested in finding the root cause of Parkinson's disease (PD) and cures for this disorder. Mutations in PINK1 and Parkin lead to inherited forms of PD. We were the first the show that these two genes work together to maintain health mitochondrial quality to ward of PD. Over the years, we have made several additional key findings seeking to revert the disease pathology in animal models and human patient cells.
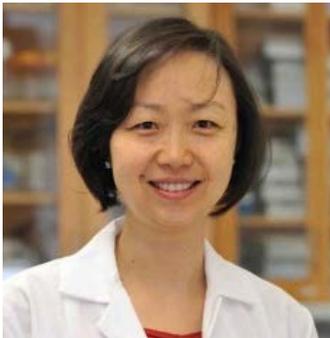
Ming Guo, MD, PhD

Professor, UCLA Department of Neurology
P. Gene & Elaine Smith Chair in Alzheimer's Disease Research

Dr. Guo is the P. Gene and Elaine Smith Chair in Alzheimer's Disease Research, and a Professor of Neurology and Pharmacology at UCLA David Geffen School of Medicine. As a board-certified neurologist, Dr. Guo sees patients with neurological disorders, with an emphasis on neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's (AD). She draws referrals from California and nearby states, as well as China, Taiwan, India, Hong Kong, and Southeast Asia. She also runs a basic and translational research laboratory aiming to understand the cause of the diseases and to find cures for these currently incurable disorders. Her lab was the first worldwide to discover that two PD genes function together to control mitochondrial quality and health. Her landmark work has shown that defects in mitochondrial function are an important cause of PD. This work, along with her subsequent observations in the field have far-reaching implications for finding therapies for aging-related diseases, including PD, AD, cancer, diabetes, heart disease, and muscle frailty. She is a sought-after speaker, both nationally and internationally.

Dr. Guo has received numerous awards at the national level, including the Alfred P. Sloan Foundation Fellowship; the Brain Disorders Award from the McKnight Foundation (given to 3 percent of the applicants); the Klingenstein-Simons Fellowship Award; the Robert H. Ebert Clinical Scholar award (given to one awardee each year); the American Neurological Association (ANA) Derek Denny Brown Neurological Scholar Award (given to one or two awardees each year); and the National Institutes of Health Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) award. Dr. Guo is actively involved in the medical and scientific communities. She served as Chair of the Board of Scientific Counselors at the National Institute of Neurological Disorders and Stroke (NINDS), on the Scientific Program Advisory Committee for the ANA, and the Program Committee for the Society for Neuroscience. She currently serves on the Scientific Advisory Committee for the A.P. Giannini Foundation, and on the Selection Committee for the Neuroscience of Memory and Cognitive Disorders Awards at the McKnight Neuroscience Foundation. She serves on the Editorial Board of Aging Cell. At UCLA, Dr. Guo was the Associate Director for the UCLA-Caltech Medical Scientist Training Program, and is the co-founding Chair of the UCLA Women in Science and Doctors of Medicine (WiSDoM) group. She is an elected member of the ANA and the American Society for Clinical Investigation.

Dr. Guo received her M.D. degree from Fudan University in Shanghai, China, then completed her neurology residency at UCLA, followed by fellowship training in neurodegenerative diseases at UCLA.

The "Second Brain" and Parkinson's Disease
Wael El-Nachef, MD, PhD

Most patients with Parkinson's disease (PD) experience symptoms of abnormal gastrointestinal (GI) motility, which can slow movements in all parts of the GI tract. Our understanding of how PD affects the nervous system of the GI tract is limited, including whether cells of the intestine's nervous system are lost to the disease process. Part of the problem in assessing this question is our inability to reliably count the nerve cells in the intestine in humans and other animals due to their size. Our work has focused on a zebrafish model of PD, and we are able to count all the nerve cells of the entire intestine using an advanced 3-dimensional microscope. This allows us to compare the cell counts between animals that express the PD-causing protein and those that do not. Determining whether PD causes a loss of intestinal nerve cells will be fundamental to our understanding as to why PD patients have slowed GI movement and will assist us in treating patients in our pilot clinic for PD patients with GI symptoms.

Wael El-Nachef, MD, PhD

Dr. Wael El-Nachef completed his undergraduate studies at UC Berkeley and medical school at Northwestern University. He trained in Internal Medicine at Harbor-UCLA and Gastroenterology at UCLA. He additionally completed a research fellowship at Children's Hospital Los Angeles (funded by the California Institute for Regenerative Medicine) where he explored tissue engineering solutions for enteric neuropathies, and obtained a PhD from UCLA in the Department of Molecular, Cellular, and Integrative Physiology while studying enteric neurogenesis and regeneration in the laboratory of his mentor, Dr. Marianne Bronner, at Caltech. His research interests include enteric neuronal regeneration, pharmacologic approaches to promote enteric neurogenesis after injury, and enteric neuronal degeneration in conditions such as Parkinson's disease (PD). His primary hypothesis is that the pathology of PD initially manifests in intestinal neurons and then spreads to the central nervous system. His clinical interests are focused on gastrointestinal motility including esophageal dysmotility disorders, gastroparesis, small intestine bacterial overgrowth, and slow transit constipation.

Exploring the structure and pathogenic action of alpha-synuclein fibrils in Parkinson's disease (PD)

Lin Jiang, PhD

Like other amyloid proteins, the intrinsically disordered protein α-synuclein forms polymorphic fibrils. Different α-synuclein fibrils have been associated with a group of neurodegenerative disorders, termed synucleinopathies, including Parkinson's disease. However, little is known about how these polymorphic fibrils differ in atomic structure and biological activity, creating a hurdle in targeting α-synuclein aggregation and seeding for drug development. My lab aims to use cutting-edge cryo-Electron Microscopy (cryo-EM) technologies, combined with other structural methods, to explore the conformational space of α-synuclein fibril polymorphs, and determine atomic structures of recombinant wild-type, disease-related mutants, and brain-derived α-synuclein fibrils. We demonstrated the feasibility of this integrative method using recently determined cryo-EM structures of two α-synuclein fibril polymorphs with resolutions of 3.7 Å, recently published in Nature Communication (Li et al., Nature Communication 2018). Built on these successes, our cryo-EM study started to explore the conformational space of other α-synuclein fibrils to elucidate the structural elements underlying fibril polymorphism. Our EM study of disease mutant α-synuclein fibrils (H50Q and E46K), together with the biological experiments of two fibril preparations, has laid the groundwork to correlate structural differences to the biological activity changes in seeding and toxicity (Boyer et al, Nat Struct Mol Biol 2019 and Boyer et al, PNAS 2020). Moreover, our research efforts on cryo-EM structure of α-synuclein fibrils have allowed us to further explore the molecular action of structure and biological activity of α-synuclein in Parkinson's disease. In collaboration with Dr. Varghese John's lab at UCLA Neurology, we have discovered two α-synuclein fibril preparations with distinct in vitro seeding patterns and different in vivo seeded spreading in mouse brains, associated with motor behavior changes. We are also working with Dr. Chao Peng in the same department and Dr. Virginia Lee's laboratory at University of Pennsylvania to seek to determine the structures of brain-derived α-synuclein fibrils using cryo-EM, in order to understand the pathological relevance of the existing recombinant fibril structures. The biological activity experiments of these α-synuclein fibrils, together with their atomic structures, will enable structure-activity relationship studies for future drug development to precisely target α-synuclein aggregation and seeding.

Lin Jiang, PhD

Lin Jiang completed his undergraduate studies at Peking University, Beijing, followed by a Ph.D. is biochemistry and postdoctoral fellowship from the University of Washington. He is an assistant professor of Neurology at UCLA and has spent his career pursuing computational structural biology to understand and solve biological and biomedical problems. The goal of his research, and the focus of his laboratory, is to identify suitable therapeutic targets for designing new drugs to treat Neurodegenerative Diseases, including Parkinson's Disease. To accomplish this, we will integrate structural, computational, and cellular approaches to elucidate the underlying mechanisms of how protein aggregation lead to disease.

Neutral sphingomyelinase 2 as a novel target for Parkinson's Disease therapeutics development

Varghese John, PhD

Parkinson's disease (PD) is a debilitating progressive neurodegenerative disorder that leads to motor symptoms and cognitive decline. On the molecular level the disease is characterized by the accumulation of insoluble inclusions composed from aggregated protein alpha-synuclein (αSyn) in the brain. Some of those aggregates, called seeds, can be transferred from affected brain cells to naïve cells and lead to propagation of the pathology across brain regions. Small membranous vesicles, exosomes, are one of the ways the seeds can be transferred between cells. Inhibition of enzyme neutral sphingomyelinase 2 (nSMase2) may suppress release of a subpopulation of exosomes carrying αSyn seeds and reduce its propagation. We are developing a novel series of nSMase2 and dual nSmase2/ acetylcholine esterase inhibitors to evaluate their disease-modifying potential using cellular and mouse models of PD.

Neutral sphingomyelinase 2 (nSMase2) is highly expressed in the brain, with the highest level of expression in the striatum. The enzyme catalyzes sphingomyelin hydrolysis to ceramide and phosphorylcholine and controls ceramide-dependent production of exosomes - a subset of extracellular vesicles (EVs) of endocytic origin. Multiple lines of evidence suggest a significant role for exosome/EV-mediated transfer of pathological α-synuclein (αSyn) species in the spread of pathology within the brain in Parkinson's disease (PD). EV-encapsulated αSyn aggregates have been isolated from CSF and brain tissue of PD and Lewy Body Dementia (LBD) patients, as well as from culture medium of PD cellular models. These EVs can be taken up by healthy cells and can propagate αSyn pathology both *in vitro* and in animal models.

We investigated the role of the nSMase2-dependent pathway of exosome biogenesis in αSyn propagation using *in* vitro models and Thy1- αSyn mouse model of PD. Pro-inflammatory cytokines IL1 and TNF are elevated in PD brain and are known to increase nSMase2 activity. Our data shows that IL1 i.c.v. injection significantly increased concentrations of CD-63 positive EVs in the exosome-enriched fraction isolated from Thy1- αSyn mouse brains which is in good correlation with a significant increase in concentration of small EVs (50-200nm) measured using tunable resistive pulse sensing. Pretreatment with a known nSMase2 inhibitor cambinol suppressed IL1 induced EV release. Interestingly, five-week treatment of Thy1-αSyn mice with cambinol (100 mg/Kg/day) led to a significant reduction of the area occupied by PK-resistant αSyn aggregates in the dorsal medial region of the substantia nigra and to improvement of motor dysfunction based on Thy1- αSyn /cambinol group performance in the pole test.

Based on our *in vivo* findings with cambinol we are evaluating a novel series of dual nSMase2/AChE inhibitors and testing them in PD models to evaluate their suppression of proteopathic seed propagation.

Varghese John, PhD

The Drug Discovery Lab (DDL) in the UCLA Department of Neurology and is led by Varghese John who is a member of the Mary S. Easton Center for Alzheimer's Disease Research and the Brain Research Institute at UCLA. Varghese is a medicinal chemist with over 20 years of experience leading small-molecule CNS drug discovery projects in the pharmaceutical industry. The DDL is involved in number of discovery collaborations to identify preclinical candidates for Alzheimer's disease (AD), Parkinson's disease and other CNS disorders. Currently one of the candidates, DDL-110, is moving toward clinical testing in AD patients. The DDL is involved in identifying novel compounds that are dual neutral sphingomyelinase-2 and Acetylcholine esterase (nSMase2/AChE) inhibitors for evaluation in the Thy-1 Syn mouse model to determine their effect on the progressive spread of Syn pathology in this model. The DDL collaborates with several UCLA labs focusing on medicinal chemistry campaigns for hit- to-lead optimization and identification of lead candidates.

Potential of aSyn-fibril-structure-based peptide inhibitor liganded to nanoparticles (LMNPs) as a MRI-based Biomarker and therapy for Parkinson's Disease (PD)

Sally Frautschy, PhD

Parkinson's Disease is characterized by the presence of intraneuronal inclusions of the protein a-synuclein (aSyn) which propagates interneuronally. Strong genetic, clinical and preclinical evidence support endosomal-lysosomal (endo-lyso) dysfunction as a major contributor to Parkinson's (PD) pathogenesis, causing reduced aSyn clearance. The Eisenberg lab has designed peptide inhibitors that target the pathogenic structure (Sangwan et al. 2020). Here, we explore the utility of these inhibitors liganded to 10 nm magnetic nanoparticles (LMNPs) as contrast agents for MRI imaging of aSyn pathology as well for therapy. Dextran coated superparamagnetic NPs are taken up by and naturally activate the endo-lyso system and autophagosomes, which make them particularly useful for targeting this system. Liganding these particles to the aSyn fibril inhibitor to produce LMNPs is used to increase selectivity for PD aSyn Lewy pathology. Since un-degradable synuclein aggregates further damage the endo-lyso system and impede lysosomal biogenesis, LMNPs may not only improve aSyn clearance, but also restore endo-lyso and autophagic functions, including mitophagy.

Methods. We used M83 a-Syn transgenic mice inoculated at 2 months of age with a-Syn fibrils via intracerebral injections into the right somatosensory cortex and striatum. At 4 months of age, LMNPs are injected into the tail vein.

Results. Our data demonstrate the following: After injection of LMNPs into the tail vein of M83 seeded mice, the particles are visualized in the brain using MRI imaging. Data demonstrate penetration and widespread distribution in the brain by 1.5 hr; while at 24 hr, the particles are concentrated in ventricles and areas rich in a-Syn burden, with asymmetry being most prominent in the thalamus, ipsilateral and posterior to injection. By 48 hrs, the particles are cleared except for some retention in the cerebellum and brain stem. Post-mortem a-Syn pathology was examined at various time points after LMNPs injection, and brain regions showed a time dependent reduction in cell body and neuritic pathology at 12 and 24 hr with a shift from neurite to microglial-like aSyn staining in some regions. Induction of autophagic markers was observed in most regions including substantia nigra. Colocalization of a-Syn with increased LC3b was observed in the motor cortex.

Conclusions. In summary, tracking PD aSyn aggregate deposition using MRI with LMNPs as a contrast agent may be a useful diagnostic tool as well as an important outcome in clinical trials. It is also possible that these particles have therapeutic utility in rapidly clearing a-Syn aggregates via activation of the endosomal lysosomal system and effective autophagic clearance. We are currently attempting to validate and expand on these exciting findings.

Sally Frautschy, PhD

Dr. Frautschy is a Professor in Residence of Neurology at the David Geffen School of Medicine at UCLA. She focused her graduate & initial post-graduate work on understanding the adverse effects of chronic stress on physiology, intrigued by the work of Hans Selye who in 1956 coined a word "stress" from physics to use to describe the physiological/chemical response to an emotional reaction. Dr. Frautschy worked under experts in the field of 'stress', completing her MS under the late Gary Moberg at UC Davis and PhD under Professor Robert Liptrap, DVM, PhD at Univ. of Guelph, Ontario Canada. After completing her PhD, Dr. Frautschy trained with neuroendocrinogist Dipak Sarkar (UCSD; Rutgers). During her second post doc with Dr. Andrew Baird & directorship of Roger Guillemin (a nobel laureate who did his post doc under Hans Selye), Sally worked on brain injury induction of neurotrophic factors where she bega her collaboration with Dr. Cole. In collaboration with Dr. Cole, she decided to evaluate the brain's response to human amyloid, and was the first to describe the inflammatory response. Since then, her priority has been to develop practical and effective approaches, particularly nutritional, for stopping this tragic disease, which in part, evolves from a personal experience with head injury.