

2023 AKN Annual Research Symposium

July 28 – 29
Salk Institute, La Jolla, CA



Association of
Korean
Neuroscientists

4th AKN Annual Research Symposium

Main Organizers

Dr. Yongsoo Kim (yuk17@psu.edu), Penn State University, symposium co-organizer
Dr. Han Sung (sunghan@salk.edu), Salk Institute, symposium co-organizer
Dr. Yoon-Seong Kim (yk525@rwjms.rutgers.edu), Rutgers University, AKN president

Symposium venue

Salk Institute for Biological Studies

Address: 10010 N Torrey Pines Rd, La Jolla, CA 92037

The main meeting area is located in the building 2 (1st floor). Please register here.

Day1 dinner and Day 2 lunch will be served in the building 3 (5th floor).

Coffee and Day 2 breakfast will be served in the building 2 (1st floor).



Please call (or Text) main organizers if you have trouble finding the symposium location.

Dr. Yongsoo Kim at 631-827-4328

Dr. Sung Han at 206-393-8019

Symposium Agenda

Day 1 (Jul/28, Friday)

- 5pm – 5:30pm: Registration
- Opening remark and introducing Plenary speaker by Yongsoo Kim
- 5:30pm – 6:30 pm: Plenary lecture by **Dr. Byungkook Lim** (UCSD),
Title: The Neural Basis of Early Life Stress-induced Behavioral Adaptation
- 6:30pm – 9pm: Dinner with networking activity, moderated by **Dr. Daewoo Lee** (Ohio State)

Day 2 (Jul/29, Saturday)

- 8am – 9am: Light breakfast
- 9am - 10am: Keynote speaker by the Tong H. Joh Research Innovation Awardee
Introduction by AKN president
Speaker introduction by Nam Chul Kim
Dr. Hyunglok Chung, Houston Methodist Research Institute

Title: Rare to Common Diseases: Role of Lipid Metabolism in Neuroinflammation
- 10am - 10:20am: Tong Award runner-up talk
Youngju Jo (Deisseroth lab), Stanford University

Title: Measuring, modeling, and controlling cell-type-specific and brain-wide neural dynamics
- 10:20am - 10:35am: *Coffee break*
- 10:35am - 11:55am: Short talk 1 (12min talk + 3min Q&A)
Drs. Jun-Hyeong Cho (UC Riverside)

Title: Neuronal and synaptic correlates of emotional memories in the prefrontal cortex, hippocampus and amygdala

Sung Soo Kim (UC Santa Barbara)

Title: Neural network dynamics underlying visual processing during navigation

Ryan Cho (Princeton)

Title: Choice information is preferentially routed across layers in the anterior cingulate cortex during decision-making

Euiseok Kim (UC Santa Cruz)

Title: Long-range circuit motifs and their development in the mouse cortex

Yongsoo Kim (Penn State)

Title: Developmental common coordinate frameworks for quantitative cell type mapping in developing mouse brains
- 12pm - 1pm: *Lunch break*
- 1pm - 2:40pm: Short talk 2 (12min talk + 3min Q&A),
Drs. Jae Kyung Lee (U. Georgia)

Title: Understanding the role of innate immune cells in Synucleinopathies

Daewoo Lee (Ohio State)

Title: Activity-dependent release of human alpha-synuclein in Lewy body disease

Yoon-Seong Kim (Rutgers U.)

Title: Aging, a major risk factor for Parkinson's Disease: Single-Cell Multiomic Approach of Human Midbrain

Hyun Kyoung Lee (Baylor)

Title: White Matter Matters: The Role of Glia in White Matter Degeneration

Nam Chul Kim (U. Minnesota)

Title: Mitochondrial liquid-liquid phase separation in neurodegeneration

Sung Han (Salk Institute)

Title: Novel genetically encoded tools for imaging or silencing neuropeptide release from presynaptic terminals in vivo

- *2:40pm - 3pm: Coffee break*
- 3pm - 4pm: Subgroup discussion,
 - Group1 (systems neuroscience): Sungsoo Kim, Byungkook Lim, Ryan Cho, + α
 - Group2 (neurodegeneration): Hyun Kyoung Lee, Nam Chul Kim, Yoon-Seong Kim, + α
 - Group3 (novel methods): Yongsoo Kim, Sung Han, Euseok Kim, + α
- 4pm - 5pm: Career development, panel discussion with senior investigators, Grant application tips/tricks, Open Q&A, Panelists: **Drs. Hyunglok Chung, Byungkook Lim, and Jae Kyung Lee**
- 5pm and onward: Formal dinner, networking activities, and departure.



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Dr. Yoon-Seong Kim

Professor

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A. Research Interests

1. The Gut-Brain Axis in Parkinson's disease (PD): focusing on the role of NADPH oxidases (NOXs)-mediated oxidative stress and Synucleinopathy. In addition to mitochondria, we have identified NADPH oxidase 1 (NOX1) as a molecular source of ROS which is responsible for dopaminergic neuronal death. NOX1 is highly expressed in the intestinal epithelium, from where recent accumulating evidence suggests that α -SYN aggregates progressively propagate to the brain parenchyma. Using Nox1 null mice, we are investigating gut microbiome-Nox1 activation- α -SYN pathogenesis axis in PD.

2. Contribution of transcriptional mutagenesis of oxidative DNA lesions to generating new mutant α -SYN species and aggregation. We have recently discovered that 8-oxo-dG, the most frequent oxidative DNA lesion, can generate mutant α -SYN species by the intriguing mechanism called transcriptional mutagenesis. These mutant α -SYN mRNA species were more frequently observed in the *substantia nigra* of PD patients compared to normal subjects. We are investigating how these mutant species contribute to the alpha-synucleinopathy.

3. Pum2-mediated translational regulation of alpha-synuclein mRNA on the outer surface of mitochondria. Interplay between mitochondria and α -SYN has been widely documented yet without clear molecular mechanism. We have found that α -SYN mRNA is localized to the outer surface of mitochondria and its translation is initiated upon stimuli causing mitochondrial ROS. We have identified that Pum2, a translational repressor, binds to the 3'UTR of α -SYN mRNA and it is released upon mitochondrial ROS, allowing translational initiation of α -SYN near mitochondria. We are investigating the role of translational control of α -SYN near mitochondria.

4. Aging, Oligodendrocytes, and Microglia in PD: perspective from single-nucleus Multiomic analysis. Aging is a major risk factor contributing to PD pathogenesis. Recently we analyzed the midbrain of young, aged, and PD postmortem samples using the combined snRNA-seq and snATAC-seq and found that oligodendrocytes and microglia change during aging and further contribute to PD pathogenesis. Peak-gene association analysis reveals the cell-type-specific contribution regarding which PD-associated SNPs may play roles in the pathogenesis.

B. Major techniques established in the lab

1. Multiomic analysis using single nuclei RNA-seq and snATAC-seq of postmortem brain. We established this technique to investigate cell-type-specific transcriptomic and epigenomic profiles of single nuclei obtained from postmortem brain samples.

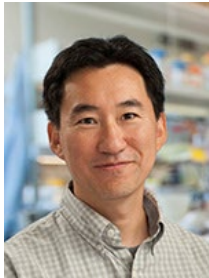
2. The CRISPR/dCas9-Suntag based target-specific epigenetic modifiers. We recently established ten epigenetic modifying enzymes that modulate major histone marks including H3K4me3, H3K27me3, H3K9ac, H3K27ac and DNA methylation using CRISPR/dCas9-Suntag system. This epigenetic tool kit allows target-specific modulations of each genomic loci. In conjunction with sgRNA library spreading over the entire genome, this innovative technique can be applied to the identification of specific genes whose epigenetic modulations are critical for various disease conditions.

3. Single-molecule fluorescence in situ hybridization (smFISH, RNAscope) with human brain clearing technique.

To overcome strong auto-fluorescence from human brain tissue, especially dopaminergic neurons due to neuromelanin, we have established the technique to clear proteins/lipids after RNA-anchoring/gel embedding, enabling clear visualization of a single RNA. Together with the expansion microscope technique, subcellular localization of single RNA molecule can be visualized.



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A. Research Interest

The main objective of research in my laboratory is to understand the neural circuit-mechanisms underlying neuropsychiatric diseases including drug addiction, feeding disorder, depressive disorder, social impairment and movement disorder. Given the circuit and synaptic complexity of the brain, the characterization of specific neural circuitry responsible for behavioral changes has been challenging. To address the anatomical and functional properties of neural circuitry involved in these mental disorders, our laboratory applies and develops a variety of molecular strategies (ex. virus-mediated tracing and gene expression, transgenic mice expressing marker proteins in specific population of neurons) together with electrophysiological approaches. Furthermore, we applied cell-type specific or input-specific optogenetic manipulation and imaging techniques during a battery of behavioral tasks in animal models for mental disorders and neurodegenerative disorders. We are training graduate students and postdoc from other labs for all the techniques and strategies developed and adapted in our labs. We also have several collaborations using cutting-edge viral strategies and in vivo behavioral monitoring methods.

B. Research Projects and established techniques

The Projection Specific Roles of Distinct Reward Circuitries in Controlling Reward/Aversion and in Drug Addiction Utilizing expertise in molecular biology, virology, in vivo imaging, and electrophysiology, In recent work, we found that the distinct outputs of reward circuitry are involved in different stages of drug addiction. The examination of circuit specific roles of mesolimbic circuitry in reward and aversion and its changes induced by drug administration will provide a framework for understanding the circuit basis of adaptive and pathological motivated behaviors.

The Distinct Neural Circuits Underlying Separate Stress-induced Behaviors Using newly developed viral tools in my own lab, we dissected nucleus accumbens (NAc) and ventral pallidum (VP) circuitry in cell-type and projection specific manner. Recently, we identify two discrete circuits of parvalbumin-positive (PV) neurons in the VP projecting to either the lateral habenula or ventral tegmental area contributing to depression. The manipulation of each population mediates either social withdrawal or behavioral despair, but not both. We propose that distinct components of the VP PV circuit can subserved related, yet separate depressive-like phenotypes in mice which could ultimately provide a platform for symptom-specific treatments of depression. Furthermore, we found that lateral septum (LS) is another important nodal points for social dysfunction induced by early life stress. Understanding the common pathways involved in the response to stress will be very important to develop novel therapeutic targets for depressive behaviors.

Distinct Basal Ganglia Circuitry Associated with Different Parkinsonian Behaviors Using extensive anatomical analysis as well as cell-type and projection specific neural activity recording and manipulation. Recently, we identified distinct Globus pallidus external (GPe) circuitry mediating deficits in cognitive function and motor functions separately in dopamine-depleted animals. We also collaborated with Dr. Hongwei Dong (UCLA) to anatomically map cortico-basal ganglia-thalamic network.

C. Techniques of Interest

Two-photon microscopic imaging, Neuropixel multi-unit recording, viral-mediated circuit tracing, drug self-administration, 3D motion capturing



Association of Korean Neuroscientists



Dr. Sung Soo Kim

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A. Research Interests

Entering a room that we've never been inside before, we usually get our bearings within a few moments. In those moments, mammals like us are thought to create and update abstract internal representations of our surroundings. We are thought to then use these representations along with a sense of the current behavioral context to determine what actions to take next. Our lab is interested in understanding the brain-wide, multi-sensory information processing and integration that underlies this ability. To elucidate how the brain enables navigational decisions, we use a powerful genetic model organism, *Drosophila melanogaster*, which needs to solve some of the same navigational problems. Recent discoveries of compass-like neural representations in their brains suggest that they may even use some of the same tricks, which gives us the opportunity to understand these neural computations at the level of well-defined circuits, neurons and synapses. We combine a wide range of techniques including two-photon calcium imaging and electrophysiology in head-fixed behaving flies, cell-type specific optogenetic perturbation, electron-microscopy (EM) based neural circuit reconstruction, quantitative behavioral analysis of freely behaving flies and computational modeling of networks, to establish causal links from the neural circuit dynamics to cognitive behavior.

B. Techniques

Two-photon imaging: We combine virtual reality and physiology. A tethered fly is allowed to walk on a ball or fly, while its behavior is monitored. We measure the rotation of the ball, or measure the difference between fly's left and right wingbeat amplitudes and use this motor information to let the fly control the rotational velocity of the visual environment. We call this a closed-loop experiment because we close the loop from the fly's motor output to the visual scene that the fly experiences. We express the genetically encoded calcium indicator, GCaMP, in a genetically identified set of neurons to monitor calcium activity using a two-photon laser scanning microscope.

Optogenetics: We express a channelrhodopsin variant and a calcium indicator in a genetically identified set of neurons. Only a small subset of neurons is stimulated while the activity of the entire population is recorded. To do this, we developed a technique allowing simultaneous imaging and stimulation.

Computational modeling: A fundamental understanding of computational principles underlying complex neural dynamics does not come just from phenomenology, but from quantitative formulation. We develop dynamical models of the fly's navigational system and test their predictions using physiological tools such as two-photon imaging and optogenetics.



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Dr. Jun-Hyeong Cho

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A. Research Interests

My lab is interested in the neural mechanisms of learning and memory. We use a combined approach of electrophysiology, activity-dependent neuronal labeling, optogenetics, chemogenetics, virus tracing, and in vivo calcium imaging in rodent models of fear conditioning.

B. Research Projects and established techniques

The acquisition and consolidation of contextual memories

We investigate how contextual fear memory is encoded and consolidated at the synaptic level in a network of memory engram neurons in the amygdala, hippocampus, and neocortex.

Established techniques:

Electrophysiology in brain slices: whole-cell patch-clamp recording

Behavioral analysis: contextual and auditory fear conditioning

Activity-dependent neuronal labeling

Optogenetics and chemogenetics

Virus tracing: anterograde, retrograde, and trans-synaptic

In vivo calcium imaging with miniaturized microscope and two photon microscope

C. Techniques of interest

Computational neuroscience for analyzing neuronal population activity



Association of Korean Neuroscientists



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A. Research Interest

My lab currently focuses on understanding the role of innate immune cells in the progression of Lewy body disorders including Parkinson's disease (PD). We utilize a combination of *in vivo* and *in vitro* models of synucleinopathies to uncover the interaction between innate immune cells and abnormal protein aggregates. The long-term goal is to explain how the immune system influences PD-associated brain changes, which may represent a novel mechanism and an avenue for treating neurodegenerative diseases.

B. Research Project and established techniques

We utilize a combination of *in vivo* and *in vitro* models of synucleinopathies to uncover the interaction between innate immune cells and abnormal protein aggregates. We have established the mouse model of Lewy body diseases that exhibits many clinically relevant hallmarks of PD including dopaminergic cell loss, behavior deficits, and synucleinopathies. By utilizing this mouse model, we conducted a complete characterization of immune cell composition during a prodromal stage of the disease to determine whether CNS-initiated α -synucleinopathies alter immune cell profiles in the CNS and the periphery.

Innate immune lymphocyte in Lewy body diseases. My lab investigate the role of natural killer (NK) cells in the context of Parkinson's disease (PD). For that, I have established the relevant *in vivo* animal model, preformed fibril (PFF) alpha-synuclein (α -syn)-induced PD mice, which exhibit many clinically relevant hallmarks of PD including dopaminergic cell loss, behavior deficits, and synucleinopathies. By utilizing this model, I propose to investigate whether NK cells are neuroprotective or neurotoxic in PD. Both *in vitro* studies demonstrated that human NK cells efficiently clear extracellular α -syn and the systemic depletion of NK cells resulted in the exacerbated disease phenotypes in synucleinopathies *in vivo* (Earls et al, PNAS 2020). Based on these data, I hypothesized that NK cells play a neuroprotective role against synuclein pathology and neurodegeneration. Currently, we investigate the precise mechanism(s) by which NK cells reduce α -synuclein burden, modulate inflammation, and exert neuroprotection.

Modulating Microglia in Lewy body diseases. Our research program is to determine the extent to which microglia contributes the onset and/or progression of neurodegenerative diseases. Age-related changes in inflammation and metabolism in peripheral tissues and the brain have been implicated as risk factors for neurodegenerative diseases. However, the detailed mechanisms of how age-related inflammation and associated-metabolic changes affect the onset and/or progression of neurodegeneration have not been elucidated. Previously, I have identified a novel regulator of microglia activation and neuroinflammation, Regulator of G-protein Signaling (RGS) 10, and its neuroprotective effect on the nigrostriatal pathway. We generate microglia-targeting nanotherapeutics carrying RGS10 plasmid and AAV-mediated RGS10 gene delivery to attenuate pathology utilizing PFF α -syn-induced mouse model of Lewy body disorders. Our goal is by enriching RGS10 in microglia, we restores microglia homeostasis, enhances amyloid fibril clearance, therefore exerts neuroprotection for amyloid fibril-induced neuronal death as a potential therapeutics.

C. Techniques of Interest

Single cell analysis, Proteomics, Metabolomics



Association of Korean Neuroscientists



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A. Research Focus: *Developmental gliogenesis and associated disorders; white matter injuries (PVL, HIE, MS), brain cancer (GBM), ischemic stroke, vascular dementia, neuropsychiatric diseases.*

In my laboratory, we plan to take an interdisciplinary approach to the study of neural development and eventually, neurological and neurodegenerative diseases. Glia play diverse roles in the functioning CNS and, consequently, are associated with numerous neurological disorders and malignancies. In spite of their vital role in CNS physiology and pathology, the molecular mechanisms that control their development and diversity remain poorly defined; accordingly, how these processes contribute to CNS pathology also remains undefined. Therefore, our studies focus on the identification of novel molecular signaling and regulatory pathway in glial cell development using chick and mouse model systems and biochemical techniques combined with an array of complex CNS injury in vivo models. These studies will provide the foundation upon which we will translate developmentally relevant findings to demyelinating diseases, neurodegenerative disorders, and vascular-associated diseases in an effort to develop therapeutic interventions.

B. Research Projects and established techniques

Myelin development and regeneration (white matter injury). Myelin sheaths are essential for the nervous system, playing major roles in electrical conduction, metabolic support, and cognitive and motor function. Myelin disorders affect millions globally and have devastating effects, in part due to failure in myelin regeneration. Injured white matter is populated by "stalled" oligodendrocyte precursor cells (OPCs) that demonstrate exaggerated Wnt signaling and consequently impaired regenerative myelination, suggesting that manipulation of Wnt signaling could provide a means to restore myelinating OLs. Our research focuses on the mechanisms associated with Wnt signaling in OL lineage development and regeneration, and pinpoint potential targetable pathways for white matter disorder (Tools can be found at: PMID: 25754822, PMID: 32792353, PMID: 35101966, PMID: 37084732, bioRxiv 2023.04.11.536369).

Astrocyte development and reactivity (ischemic stroke). Astrocytes are dynamic cells that play important roles in CNS development, homeostasis, and injury response. Astrocytes closely interact with neurons and blood vessels via synapse and endfeet respectively, which is critical for sculpting synaptic transmission, neural circuits, and cerebrovascular networks in the central nervous system. Emerging evidence suggests astrocytes play a pivotal role in BBB reconstruction, but the exact mechanisms remain poorly defined. Our research focuses on key mechanistic pathways by which astrocytes govern blood-brain barrier recovery after ischemic stroke. We hope our research can lead to discovery of novel glia-specific therapeutic approaches, such as astrocytic metabolism-cytokine coupling, to stimulate brain repair after stroke injury (Tools can be found at: PMID: 34633730, PMID: 31498149, bioRxiv 2023.04.03.535167)

Brain cancer, glioblastoma. Malignant glioma is a devastating type of brain cancer characterized by an exceedingly poor prognosis. Even with seven decades of increasing knowledge about glioma origins, survival rates for patients suffering from malignant glioma have only seen marginal improvement. The challenges in treating glioma stem, in part, from the tumor's metabolic adaptations, pH imbalances, and immunosuppression within its microenvironment. Nonetheless, we have not yet fully unraveled the mechanisms involved in glioma development or their potential significance in treatment strategies. Our research is dedicated to exploring the mechanisms at play between glioma and the tumor microenvironment, with a goal to identify novel, actionable pathways for therapeutic intervention. (Tools can be found at: PMID: 29053101 PMID: 28166219, PMID: 28892058)

C. Techniques of interest

In vivo 2P/3P imaging, Computational analysis, Human MRI, pH sensors, Vascular imaging



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A. Research Interests

The mammalian cortex is composed of numerous functionally specialized areas. Interactions between these areas, mediated by widespread yet precise cell type specific circuits, are central to the neural computations that generate perception, cognition, and behavior, and make us who we are. Since circuit-level understanding of this brain-wide neural network will elucidate fundamentals of the human mind and behavior, my laboratory focuses on understanding the organizational logic of long-distance cortical circuits and the molecular mechanisms of their development using mouse visual cortex as a model. In the mature brain, what are the connectivity and functional bases of neural circuits at the cellular level? Using novel trans-synaptic tracers and in vivo imaging, we are investigating the identities of brain-wide input and output neurons and their functional contributions to information processing. In the developing brain, what are the mechanisms that match gene expression to neuronal connectivity? It is unknown how a population of neural progenitors in a single cortical area develops into diverse subtypes each projecting to particular brain areas and receiving specific brain-wide inputs. We are examining how genetic programs and neuronal activity interact to construct connectivity.

B. Research Projects and established techniques

Developmental Mechanisms of Fine-scale Cortico-cortical Circuit Formation: The long-term goal of my research program is to gain mechanistic insights into cortical circuit assembly at the single cell level in an effort to understand underpinnings of neurodevelopmental disorders and develop new therapies. In doing so, we will be able to identify molecular and genetic mechanisms that link gene expression and neural activity to neuronal connectivity. The objective of this project is to identify mechanisms by which long-range cortico-cortical neuronal connectivity is established in the mammalian cortex using the mouse visual system as a model.

Developing Novel Trans-Synaptic Viral Vectors for Orthogonal or Rapid Circuit Tracing: To determine the anatomical basis of complex neural behavior, it is critical to have the ability to trace more than one circuit simultaneously in the same animal. That's because complex animal behaviors or neural computation should be understood through the interaction of more than one circuit – cooperative, antagonistic, or else. In addition, it is necessary to rapidly capture the connectivity information in the dynamically changing brains during development and learning. We are developing novel trans-synaptic viral tracer systems for more comprehensive analysis of neural connectivity in more than one circuit and in more diverse context such as the developing brain where distinct synaptic networks emerge and neural plasticity such as learning across many model species.

C. Techniques of interest

Viral genetic neural circuit tracing, genomic sequencing, neurodevelopment, neuroanatomy



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A. Research Interest

Our main research goal is to understand molecular and cellular mechanisms underlying neurodegenerative diseases (NDs). In particular, we are interested in prion-like propagation of pathogenic proteins such as α -Synuclein (α -Syn) and microtubule associated protein tau (MAPT). Recently, it has been shown that key pathogenic proteins (e.g., human tau, α -Syn,) in NDs spread via the cell-to-cell propagation but underlying mechanisms are not well understood.

B. Research Projects and Established Techniques

Cell-to-cell propagation of α -Syn: Abundant neuronal protein α -Syn is a pathogenic protein to form abnormal protein aggregates, called Lewy body (LB) and causes several NDs including Parkinson's disease and LB dementia (LBD). Prion-like spreading of α -Syn is an exciting new discovery in the progression of NDs. However, there are critical gaps in our understanding of α -Syn spreading. We study how α -Syn is released, taken up, and thus spreads between neurons. We are particularly interested in α -Syn released by neuronal activity since well-known PD risk factors such as traumatic brain injury (TBI) and sleep deprivation increase neuronal activity and levels of extracellular α -Syn. In addition, hyperexcitability and seizures are known to be associated with pathological progression of LBD. Our goal is to study how neuronal subtypes, α -Syn mutants, and functional/molecular factors affect pathological transmission of α -Syn.

Mechanisms underlying activity-dependent human tau release: Studies have shown that a prion-like mechanism involving the transfer of hyper-phosphorylated tau between synaptically connected neurons underlies the spread of tau pathology throughout the brain. Interestingly, neuronal excitability increases during the early stages of Alzheimer's disease and tau release can be enhanced by the excitability. A better understanding of activity-dependent tau release is a key to uncover mechanisms underlying cell-to-cell propagation of tau. It still remains to explore the role of phosphorylation in activity-dependent tau release. In addition, proteins interacting with tau have yet to be identified for their role in mediating activity-dependent tau release.

We have developed a tractable and highly reproducible method of studying activity-dependent α -Syn and tau release in *Drosophila* primary neuronal culture & neuromuscular junction, and a human neuroprogenitor cell line (ReNcell), which form the experimental framework of our research. Optogenetic method has been also used to induce activity-dependent α -Syn and tau release.

Established techniques : Electrophysiology (patch clamp, amperometry), Primary neuronal culture, Human neuroprogenitor cell line (ReNCell), Cellular imaging/analysis, Western blot, ELISA, Confocal microscopy, Optogenetics & chemogenetics, *Drosophila* genetics (mutant & transgenic approaches), Behavioral assays (learning & locomotion)

C. Techniques of Interest: Protein Interactome, NGS/RNA-Seq, Imaging



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A. Research Interests

Our main research interest focuses on understanding anatomical and functional organizational principle of different cell types in the brain in order to support normal cognitive function and its changes in brain disorders such as autism and Alzheimer's disease. The unique challenge to understand governing principles of the mammalian brain is that microscopic structures (e.g., cell bodies, axon) interact each other in macroscopic network (e.g., whole brain) to generate behavior. To overcome the challenge, we have been developing high-resolution 3D brain mapping methods to image and quantify fluorescently labeled neuronal and non-neuronal cell types as well as cerebrovasculature in the entire mouse brain, and their changes across the lifetime. To complement our anatomical mapping, we utilize many systems neuroscience tools (e.g., *in vivo* neural activity recording) to gain functional significance of specific cell types in a given circuit. Our current projects include oxytocin system mapping in the context of social behavior, neurovascular mapping linked with aging, and creating new digital 3D atlases of developing mouse brains. Leveraging our novel approaches, we strive to understand cell type specific organization of the nervous system to support cognitive functions.

B. Research Projects and established techniques

Neural circuit organization of the oxytocin system: We are investigating detailed input and output anatomical organization of oxytocin (OT) neurons in the hypothalamus and functional roles of OT receptor (OTR) in the dorsal endopiriform cortex (EPd). We established OT wiring diagram provides quantitative anatomical insights of distinct behavioral functions of OT signaling in the brain (Son et al., 2022, *JNeurosci*). In parallel, my lab is currently testing a hypothesis that OTR signaling in this novel brain region serves as a part of salient circuit using *in vivo* recording (Miniscope), electrophysiology, and single cell transcriptome.

Cerebrovasculature Mapping: The brain contains intricate web of cerebrovasculature including microvessels that supplies energy and clear metabolic waste to support neuronal activity. Neurovascular dysfunction has been implicated in numerous cognitive disorders (e.g., stroke, Alzheimer's disease). To examine complete angioarchitecture in the mouse brain, we developed high resolution 3D imaging and computational analysis modules to detect, trace, and quantify detailed parameter on vasculature geometry (Wu et al., 2022, *Cell Reports*). We are currently working to examine cerebrovasculature and related cell type changes in normally aged mouse brain and mouse models of neurodegenerative disorders (e.g., ApoE KO with high fat diet, cerebrovascular amyloid angiopathy)

3D digital atlases and cell type mapping in developing mouse brains: Brain atlases are essential spatial framework to examine anatomical context. Yet, commonly used atlases rely on different anatomical delineations and nomenclature, creating confusion among neuroscientists. To overcome these issues, we imported the Franklin-Paxinos (FP) labels into the Allen CCF to merge the labels in the single atlas framework and added detailed segmentations the dorsal striatum (Chon et al., 2019, *Nature Communications*). We are currently working to create multi-modal developmental CCFs as integrative atlasing framework in seven key embryonic and postnatal ages with genoarchitecture based 3D labels.

C. Techniques of interest

High resolution 3D mapping, computational analysis, Brain cell type, angioarchitecture, brain atlasing, spatial transcriptome, *in vivo* recording



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A. Research Interests

Our long-term focus is to explore the role of lipids in non-neuronal cells and their contribution to neurodegeneration, with a particular emphasis on neuroinflammation. Currently, we are investigating the importance of preserving sphingolipids balance within the nervous system, a key element in preventing neurodegeneration and synaptic dysfunction. Our recent studies on *Drosophila* have revealed the combined effect of increased levels of Ceramides and sphingosine-1-phosphate (S1P) in glia and hemocytes (fly immune cells). These increased levels trigger the activation of the NF- κ B pathway within the nervous system, an event that precedes cell death. We are keen to further explore these lipids within glia and hemocytes, hoping to uncover the molecular mechanisms behind various neurodegenerative diseases. Using flies for initial variant assessments, we aim to uncover lipid metabolic genes not yet associated with human disease. Our methods encompass several fly-based strategies to evaluate variant function and gain a deeper understanding of these genes, including humanization strategies facilitated by CRISPR-Cas9. High-priority genes without existing mouse models will be targeted for mouse knockout generation and phenotyping, and human cells will be used to confirm findings when possible and appropriate.

B. Research Projects and established techniques

Investigate the cell-autonomous roles of S1P in glia. High S1P production by glial cells robustly activates NF- κ B pathway signaling. However, the precise mechanism by which S1P activates NF- κ B and the full repertoire of S1P-mediated signaling in glia remain unclear. We will employ single-cell sequencing (scRNA-seq) in flies expressing variable levels of S1P to comprehensively characterize the signaling events downstream of S1P, including NF- κ B, in fly brains. Furthermore, we will validate these signaling events in *in vitro* model systems and in human postmortem material.

Drosophila Functional core for human disease studies.

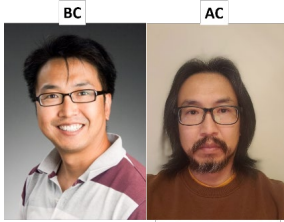
Flies are an ideal system for initial variant assessment, given that the enrichment of conserved-disease genes is about 80%, and studies using fruit flies have successfully identified new human disease genes. Many patients with rare diseases have been undiagnosed for many years. This 'diagnostic odyssey' severely impacts the lives and quality of life of patients and their family members and is costly for our society. Collaborating with clinical geneticists, we facilitate disease diagnosis by performing functional studies of candidate genetic variants identified through whole-exome and whole-genome sequencing techniques. We further dissect the underlying disease mechanisms and explore the therapeutic options via FDA-approved drug screening. We use multiple strategies in flies to assess variant function and a deeper mechanistic understanding of these genes. These include humanization strategies by replacement of the fly gene by human reference or variant cDNA facilitated by CRISPR-Cas9.

C. Techniques of interest

CRISPR-Cas9, scSeq, Lipidomics, electroretinogram, WGS/WES, Transgenesis



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A. Research Interests

Many mutations in a variety of genes have been identified as the cause of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and multisystem proteinopathy (MSP). Genes that cause these diseases can be divided into four broad categories: RNA homeostasis, protein homeostasis, cytoskeletal dynamics, and mitochondria. The most interesting question, therefore, is how functionally different gene groups can cause clinically indistinguishable diseases. Perhaps the simplest explanation is that all disease-inducing genes share a final effector or affect the common cell pathway to cause disease. Another possibility is that gene groups are closely linked and affect each other. So the end result is always similar, no matter which gene has a mutation. It is not clear what is actually true. To answer the question and develop treatment strategies, we must understand how mutant genes in each group cause disease and what is common to that mechanism. Therefore, our research is devoted to developing disease models based on genetic mutations that cause human diseases, and understanding basic molecular pathology using these models. The final goal is discovering druggable targets and developing therapeutic strategies in this process. Currently, we focus on mutant CHCHD10 and liquid-liquid phase separation.

B. Research Projects and established techniques

Mutant CHCHD10-induced tissue degeneration: CHCHD10 is a small mitochondrial protein encoded in the nuclear genome. When CHCHD10 is mutated, patients can have various tissue degeneration linked to amyotrophic lateral sclerosis, frontotemporal dementia, and mitochondrial myopathy. We are investigating how mutant CHCHD10 becomes toxic to cells using various models and techniques, including Drosophila genetics, human cells, proteome/interactome, whole brain single-cell RNAseq, and CRISPR/Cas9.

Liquid-liquid phase separation in tissue degeneration: Liquid-liquid phase separation has been suggested as a fundamental principle to organize biomolecular condensates in cells. We are investigating the role of LLPS in tissue degeneration and how it can be modulated therapeutically, especially in the context of mitochondrial biology. We are developing model systems to artificially modulate LLPS optogenetically or chemogenetically in Drosophila and human cells.

Drosophila models for human protein variants: Splicing processes are affected in many diseases, and the resulting protein variants can have dramatically different functions in disease pathogenesis. We are using Drosophila as an *in vivo* system to verify the functional difference of human protein splicing variants.

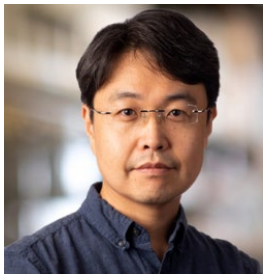
Fly-High: Insects do not have obvious orthologs for human opioid receptors. What if we introduce human opioid receptors into flies?

C. Techniques of interest

Single cell techniques, Drosophila Genetics, Spatiotemporal modulation of proteins, advanced microscopy, advanced genome editing.



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A. Research Interests

As a part of the Clayton Foundation Laboratory for Peptide Biology, my group is interested in neural circuit-based mechanisms of neuropeptides and their receptor actions in a range of physiological and emotional processes in the brain, such as pain, fear, anxiety, reward, and others. Neuropeptidergic system plays critical roles in vital brain functions, such as arousal, sleep/wake, reproduction, feeding, reward, learning/memory, and threat perception. Furthermore, dysregulation of neuropeptides has been closely associated with many neurological and neuropsychological disorders. Thus, elucidating the mechanism by which neuropeptidergic systems act in brain circuits is critical for understanding brain function and associated disorders. During the last 6 years at Salk, my group has primarily focused two topics: Innate threat perception and Opioid-induced physiological & behavioral abnormalities.

B. Research Projects and established techniques

Neuropeptide systems that mediate panic or fear: We reported that two neuropeptidergic circuits in the pontine parabrachial nucleus define fear and panic-like behaviors, PACAP neurons in the PBdl mediating CO₂-induced panic-like behaviors, and CGRP neurons in the PBel mediating innate fear from all sensory modalities, suggesting that the parabrachial neuropeptidergic circuits play critical roles in the perception of dangers from exteroceptive and interoceptive origins.

1. Kang SJ*, Liu S*, Ye M, Kim D, Pao GM, Copits BA, Roberts BZ, Lee KF, Bruchas MR, **Han S.** (2022) A central alarm system that gates multi-sensory innate threat cues to the amygdala. *Cell Reports*, 40(7):111222. (*Co-first authors)
2. Kang SJ*, Kim JH*, Kim DI, Roberts BZ, **Han S.** (2023) The neural basis of panic-like behavioral and somatic symptoms and their rescue in mice. *Under Revision*, doi: 10.21203/rs.3.rs-1840169/v1 (*Co-first authors)

Endogenous opioidergic systems that define opioid actions: We investigate three different clusters of μ -opioid receptor-expressing neurons in the lateral parabrachial nucleus that play critical roles in opioid actions. 1) the *Oprm1* neurons in the shell of the PBel that project to the medullary breathing centers are critically involved in breathing regulation, and therefore responsible for OIRD. 2) the *Oprm1* neurons in the core of the PBel that project to the central amygdala are critically involved in affective pain perception, and therefore responsible for opioid analgesia. 3) the *Oprm1* neurons in the PBdl that project to the ventral tegmental area are critically involved in opioid craving behaviors, such as hyperlocomotion and opioid seeking, and therefore responsible for opioid addiction.

3. Liu S, Kim D, Oh TG, Pao G, Kim J, Song M, Chu D, Evans RM, **Han S.** (2021) Neural Basis of Opioid-Induced Respiratory Depression. *PNAS*, 118(23):e2022134118.
4. Liu S, Ye M, Pao GM, Song SM, Jhang J, Jiang H, Kim J, Kang SJ, Kim DI, **Han S.** (2022) Divergent brainstem opioidergic pathways that coordinate breathing with pain and emotions. *Neuron*, 110(5):857-873.e9.

Established techniques: Optogenetics, chemogenetic, fiber photometry, miniscope single-cell imaging, viral tracing, slice electrophysiology

Techniques of interest: High resolution 3D mapping, two-photon fluorescence imaging *in vivo*, single-cell transcriptomic analysis