



Association of Korean Neuroscientists



2nd AKN Research Symposium

August 27, 2021

10:00 am – 5:00 pm (Eastern time)



Association of Korean Neuroscientists

Date: August 27, 2021 (Eastern time)

Zoom link: <https://us02web.zoom.us/j/8796243387>

Morning Session

10:00 – 10:05	Opening	Dr. Daewoo Lee
10:05 – 11:10	Prof. Joh Memorial ceremony, Award announcement & lecture	Moderator Dr. Yoon-Seong Kim
11:10 – 12:30	Laboratory introduction	Moderator Dr. In Hyun Park
12:30 – 1:00	Break	

Afternoon Session

1:00 – 2:00	Dr. Joshua Park, SRO at NIA	Moderator Dr. Jungsu Kim
2:00 – 3:30	Group break room (Research/grant discussion)	Group leader
3:30 – 3:40	Break	
3:40 – 4:20	Group break room (Technology discussion)	Group leader
4:20 – 4:40	Official closing	Moderator Drs. Daewoo Lee & Yoon-Seong Kim



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Prof. Joh Memorial ceremony, Award announcement & Lecture

10:05 – 10:10 Welcome and Introduction Dr. Yoon-Seong Kim

10:10 – 10:15 Eulogy Dr. Jin Mo Chung

10:15 – 10:35 Reflections from Friends and Family
Dr. Un Kang Moderator
Dr. Sung Hee Cho Dr. Un Kang
Dr. Onyou Hwang
Ms. Mimi Joh-Carnella

10:35 – 10:40 Awardee Announcement
Mr. Heechul Jun (UC Irvine) Dr. Daewoo Lee
M.D./Ph.D. Candidate

10:40 – 11:10 Lecture
Title: Dopamine facilitates
associative memory encoding in
the entorhinal cortex Moderator
Dr. Yoon-Seong Kim



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Research Interest & Study Section Group

	Name	Affiliation
A	Jae Kyu Lee	University of Miami
	Sangmi Chung	New York Medical College
	Un Jung Kang	NYU Grossman School of Medicine
	Shawn Je	Duke-NUS Medical School
	Eun Su Park	UTH at Huston
	Daewoo Lee	Ohio University
	Hoonkyo Suh	Cleveland Clinic
B	Soo-Kyung Lee	SUNY Buffalo
	Yungki Park	SUNY Buffalo
	Hojoon Lee	Northwestern University
	Yu Shin Kim	University of Texas Health Science Center at San Antonio
	Haesun Kim	Rutgers University
	Shin Kang	Temple University
	Young-Jin Son	Temple University
C	Sunghee Cho	Burke Institute, Cornell University
	Yong Hwan Kim	University of Delaware
	Jae Kyung Lee	University of Georgia College of Veterinary Medicine
	Yong Kim	Rutgers University
	Jungsu Kim	Indiana University
	Hanseok Ko	Johns Hopkins School of Medicine
	Hyoung-gon Lee	University of Texas Health Science Center, San Antonio
JungA (Alexa) Woo	Case Western Reserve University	
D	Doo-Sup Choi	Mayo Clinic
	Kyung-An Han	The University of Texas at El Paso
	Yongsoo Kim	Penn State University
	Bokkyu Kim	SUNY Upstate Medical University
	Jin Mo Chung	University of Texas Medical Branch
	Yoonbae Oh	Mayo Clinic
	Eun Hee Kim	UTH at Huston
Yoon-Seong Kim	Rutgers University	
E	Ki Bum Lee	Rutgers University
	Jun Hee Kim	University of Texas Health Science Center, San Antonio
	Sung Eun Kwon	University of Michigan
	In-Hyun Park	Yale University
	Deok-Ho Kim	Johns Hopkins
	Mi Hyeon Jang	Rutgers University
	Doo Yeon Kim	Harvard University
Won Chan Oh	University of Colorado School of Medicine	



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Technology Discussion Group

A. Single-Cell Transcriptomic Analysis

- **Dr. Jae K. Lee:** Single cell dissociation method for brain and spinal cord
- **Dr. Jungsu Kim:** 10x Genomics vs BD Rhapsody platform: Whole vs Targeted single-cell transcriptomics”?

B. Advanced Electrophysiology & 3D Brain Mapping

- **Dr. Jun Hee Kim:** Single-cell transcriptomics paired with whole-cell patch-clamp recordings
- **Dr. Yu Shin Kim:** Electrophysiology combined with multi-photon confocal imaging technology
- **Dr. Yongsoo Kim:** High resolution 3D whole mouse brain mapping to examine cell type architecture

C. iPSCs & Brain Organoids

- **Dr. In-Hyun Park:** Reprogramming and brain organoids
- **Dr. Sangmi Chung:** Modeling psychiatric disorder using iPSC-derived developmental neurons



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Dr. Sunghee Cho

Burke Neurological Institute/Weill Cornell Medicine

A. Research Interests

My lab investigates neuroimmunology of stroke pathology and repair mechanisms with a focus in translational studies. We specifically address on the role of immune receptor *CD36* that is highly expressed in monocytes/macrophages. Their role on stroke-induced inflammation and injury and how these immune cells interact with a neuronal system to influences stroke outcome and functional benefits are the main subjects.

1. The role of CD36 in stroke-induced inflammation/injury and recovery

Since CD36 is expressed in many different tissues and cell types, including peripheral monocytes/macrophages, we investigate the effect of CD36 expressed in the peripheral organs including bone marrow, spleen and blood. The major questions to address in this study are the recognition of peripheral immunity on CNS injury, validating CD36 as a target in acute pathology, and characterizing a pharmacological agent that modulate CD36 pathways.

2. Comorbid-modified inflammation and brain injury in stroke

The recurring failure to translate neuroprotective strategies in animal models into clinical settings prompted us to reevaluate existing preclinical stroke models. One major issue in preclinical studies has been the lack of inclusion of prevalent risk factors in animal models of stroke. We have been addressing this issue by including hyperlipidemia and diabetes, prevalent co-morbid conditions, in our experimental model of stroke. These studies will define if and how these risk factors modify peripheral immunity and influence stroke outcome and functional recovery and provide an importance of the inclusion of comorbidities in animal models of stroke.

3. Stroke recovery mechanism/Genetics

Because strategies that reduce acute stroke-induced injury and inflammation in preclinical studies have not successfully translated into clinical practice, studies to understand repair/recovery mechanisms that promote functional recovery have been emerged. Genetics is among several factors that influence stroke recovery. We address a role of the BDNF single nucleotide polymorphism (SNP) on stroke recovery, which is common in humans. Using mice that contain the human BDNF SNP variant, we investigate the impact of the BDNF SNP on stroke recovery and underlying event for functional recovery with BDNF SNP carriers, by dissecting structural and molecular plasticity in the brain in chronic stroke.

B. Major techniques established in the lab.

1. Animal model of stroke

We generate animal model of stroke using an intraluminal thread method to occlude middle cerebral artery (MCAO). This is the most widely used animal model of stroke that produce injury in the striatum and part of cortex. The model has been used to study the pathology on acute (hours to days) and subacute (days to weeks) period and long-term recovery mechanisms (weeks and up to 6 month).

2. Behavior testing on motor/gait function and cognition.

We have established comprehensive behavior testing modules for motor and cognitive function. The behavior tests include rotarod and gait functions by digitized Nordus Catwalk analyses system for stride length, walk speed, interlimb coordination, swing speed. For cognition, we use an automated system to record noble object recognition, Y-maze, elevated platform for anxiety test, and water maze for hippocampal memory.



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Dr. Sunghee Cho

Burke Neurological institute/Weill Cornell Medicine

3. Flow cytometer determination of immune cell.

We have established a protocol to isolate immune cells from CNS and periphery in normal and stroked animals. Flow cytometric measurement of immune cell population using 3-laser, 8-channel flow cytometer, this technique has been used to identify specific immune cell populations and sub-populations in the brain and peripheral organs.



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Dr. Doo-Sup Choi

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A. Research interests

1. Astrocyte-Neuron Interaction in the Dorsal Striatum and Ethanol-Seeking Behaviors. We investigate the role of astrocytes in the dorsal striatum, which regulates goal-directed and habitual ethanol-seeking behaviors in mice. Maladaptive shifts in goal-directed to habitual actions may lead to severe psychopathologies such as obsessive-compulsive disorder, impulsivity, and addiction. Our study will elucidate the neural mechanisms encoding goal-directed and habitual ethanol-seeking behaviors. We will provide a rational path for developing new therapeutic methods for the treatment of alcohol use disorder.

2. Chronic Alcohol Exposure and Pathophysiology of Alzheimer's Disease. We investigate the sex- and age-dependent effect of alcohol on AD development using translational biomarkers and mouse models of familial and late-onset AD. Our central hypothesis is that repeated alcohol exposure leads to altered energy homeostasis, mitochondrial dysfunction, synaptic alterations, and cognitive decline in a sex- and age-dependent manner. This hypothesis is based on robust preliminary data generated in our laboratory demonstrating that multiple pathological mechanisms critical for AD development, including abnormal energy homeostasis, mitochondrial dysfunction, and A β exocytosis, are present in a mouse model of alcohol use disorder (AUD). We will utilize male and female APP/PS1 mice representing a familial AD and human ApoE4KI mice, a model of susceptibility to dementia that resembles a late-onset AD, the most prevalent form of the disease in humans.

3. Neural Basis of Ethanol Withdrawal-Induced Sleep Disturbance. Our study will reveal the neural basis of how NAc-BF circuits contribute to chronic ethanol-induced sleep disturbance in a sex-dependent manner. The outcomes of our study will be critical to discover and comprehensively characterize neural circuits and molecular mechanisms underlying ethanol-induced sleep disturbance, which may translate into clinical studies and identify novel therapeutic targets.

B. Major techniques established in the lab

1. Chemogenetics and optogenetics. We routinely utilize the chemogenetic and optogenetic methods to understand whether activation or inhibition of the cell-type specific astrocyte and neurons alter the circuits and behaviors.

2. GCaMP-based calcium imaging using fiber photometry and endomicroscopy. To examine astrocyte and neuronal activities aligned with behaviors, we employ the Cre-dependent GCaMP virus and transgenic mice. We have both a multichannel fiber photometry system and Inscopix nVista endomicroscopy system. We are also conducting MATLAB-based computational neuroscience with collaborators.

3. Whole-brain mapping using iDISCO. We have recently established a new approach called iDISCO (immunolabeling-enabled three-dimensional imaging of solvent-cleared organs), which is a convenient method for examining brain activities (c-fos labeling) or gene expression.



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4. Caspase 3-dependent circuit ablation. To understand the role of the specific circuit, we are using the Cre-dependent caspase expression, which ablates neurons in a cell-specific manner while limiting necrosis to surrounding tissue.

5. Proteomics and metabolomics: We use LC MS-based proteomics and metabolomics to identify biomarkers or signatures from animal and human samples (tissues, blood, and CSF).

C. Techniques of interest

Single-cell RNA sequencing, computational neuroscience



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Dr. Kyung-An Han

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A. Research Interests:

Neuromodulatory mechanisms underlying behavior and reproduction

Model organism: *Drosophila melanogaster* (fruit flies)

Overarching goals: the molecular, cellular and neural mechanisms by which monoamines regulate behavioral plasticity (learning, memory and addiction), motivation, attention, inhibitory control and reproduction (courtship behavior and oviposition).

1. Natural stimuli-induced learning/memory processes: aversive and appetitive olfactory conditioning (classical conditioning), aversive and appetitive visual conditioning (classical conditioning), conditioned courtship (operant conditioning)
2. Alcohol-induced behavioral adaptation: behavioral disinhibition (cognitive and motor impulsivity), behavioral sensitization, sensitivity and tolerance to the sedative effect
3. Response inhibition and impulsivity
4. Dementia: mechanisms by which genetic and non-genetic factors cause neurodegeneration
5. Courtship and copulation behaviors
5. Ovulation/egg laying

B. Research/technical expertise

Genetic manipulation of genes and neuronal activities

Behavioral analyses

Immunohistochemical and molecular analyses



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A. Research Interests

My research focuses on how brain circuitry is perturbed by dopamine loss and produces Parkinson's disease (PD) symptoms and how the compensatory plasticity contributes to the motor complications (including levodopa-induced dyskinesia [LID]) from pharmacological treatment of PD. Specific topics include (1) understanding the striatal circuit plasticity that underlies the long-duration response to dopamine replacement therapy (LDR), which is an ignored, but most beneficial component of the therapeutic effect of dopamine replacement, (2) the contribution of aberrant activity in the basal ganglia output nuclei, the substantia nigra reticulata (SNr) and globus pallidus internus (GPi) to LID, (3) how striatal cholinergic interneurons contribute to motor dysfunction and LID, and (4) the role of the pedunculopontine nuclei in gait abnormalities and freezing in PD. We address these questions at molecular, cellular, and circuit levels in mouse models, emphasizing the contribution of specific types of neurons.

I am also interested in the molecular dysfunctions that contribute to neuronal dysfunction and loss in PD, and translating these knowledge into PD-specific biomarkers that inform disease pathogenesis. These biomarkers may allow the earlier diagnosis of PD, better monitoring disease progression, and assessment of target engagement in therapeutic trials. Moreover, these studies allow us to understand the heterogeneity in PD pathogenesis, allowing us to better individualize therapeutic approaches. I work with international biomarker consortiums supported by MJFF and NIH for these studies.

B. Major techniques established in the lab

As in C.

C. Techniques of Interest

Behavioral monitoring in PD rodent models

Optogenetic and chemogenetic modulation of specific cell types in mouse brain

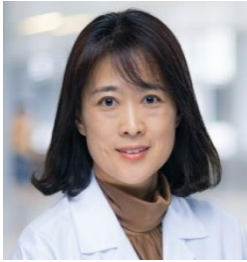
In vivo multichannel electrophysiology recording and optic recording in mouse brain

Single cell transcriptomics of human brain cells

Biomarkers of human PD biofluids



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Dr. Jun Hee Kim

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Research Interest

Neuron-glia interaction for activity-dependent myelination and brain plasticity

Dynamic communication between neurons and myelin-forming oligodendrocytes (OLs) is pivotal in the strength and speed of neurotransmission by influencing myelination in the brain. We found that a subpopulation of OLs expresses glutamate receptors and voltage-gated Na⁺ and Ca²⁺ channels, which underlie OL depolarization, Na⁺ current-mediated spiking, and Ca²⁺ dynamics in OLs (Berret et al., 2017, Barron et al., 2019). A Ca²⁺ transient in OLs triggers release of brain-derived neurotrophic factor (BDNF), important in synaptic strength and plasticity in the auditory brainstem (Jang et al., 2019). We are investigating how neurons and OLs communicate to control activity-dependent myelination in the mammalian brain.

Presynaptic physiology, synaptic transmission and plasticity

The synapse is the critical structure where neuronal information is transmitted, and presynaptic excitability is crucial for the reliable transmission of this information. To study presynaptic properties directly, we take advantage of the calyx of Held, a large terminal in the central auditory system that allows direct recordings. Using patch-clamp recordings and in vivo electrophysiology, we are studying synaptic activities and plasticity in hearing disorders such as deafness and auditory processing disorder (Xu et al., 2018, Barron et al., 2018, Kim et al., 2019, Barron et al., 2020, Kim et al., 2021).

Oligodendrocytes and Autism Spectrum Disorders (ASD)

The gene, *Scn2a*, encoding the alpha subunit of the voltage-gated Na⁺ channel 1.2 (Na_v1.2), is highly linked to ASD and developmental delay. We recently characterized a subpopulation of oligodendrocytes lineage cells (OLs), the myelin-producing glial cells that express Na_v1.2 channels (Berret et al., 2017, Gould et al., 2021). We are studying how the loss of oligodendroglial *Scn2a* impacts myelination and neural connectivity.

Research Tools

1. Ex vivo electrophysiology (Patch-clamp recordings in brain slices)
2. In vivo electrophysiology (e.g. auditory brainstem responses)
3. Intracellular Ca²⁺/Na⁺ imaging in brain slices.
4. Single-cell patch seq (Combined patch-clamp recordings with single cell sequencing)



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Dr. Jungsu Kim

Stark Neuroscience Research Institute,
Indiana University

A. Research Interests

1. The role of ApoE and its binding proteins in the pathogenesis of Alzheimer's disease.

Research in our lab is aimed at developing therapeutic strategies for Alzheimer's disease by targeting brain lipid-regulating proteins, such as apolipoprotein E (ApoE) isoforms, low density lipoprotein receptor (LDLR), ATP-binding cassette transporter A1 (ABCA1), and Increased Degradation of LDL Receptor Protein (IDOL, official gene name: MYLIP).

2. The contribution of transcriptional dysregulation in the pathogenesis of Alzheimer's disease.

Using multiple omics approaches, such as whole transcriptome single cell RNA sequencing, targeted single cell RNA sequencing, spatial transcriptomics, bulk RNA sequencing, and proteomics, we study the role of microglial transcription factors in Alzheimer's disease phenotypes.

3. The role of microglial actin binding proteins in the pathogenesis of Alzheimer's disease, neuroimmune function, peripheral immune, and brain aging

Recent human genetics and transcriptomics studies have demonstrated actin binding proteins in microglia affect Alzheimer's disease, immune function, and brain aging. Using multiple mouse models and microglia-like cells derived from induced pluripotent stem cells, we are investigating the role of actin binding proteins in microglia and their secondary effects on neurons and other cell types in the brain and peripheral tissues.

4. The role of microRNAs in the pathogenesis of Alzheimer's disease, neuroimmune function, and brain aging

We study the role of microRNA-33, microRNA-21, microRNA-17-92 cluster, and others in Alzheimer's disease, neuroimmune function and brain aging using mouse models and cell biology approaches.

5. Developing or establishing single cell RNA sequencing methods

In addition to performing the routine whole transcriptome single cell RNA sequencing, we are developing or establishing new single cell RNA sequencing approaches, such as targeted single cell RNA sequencing method and other methods to decrease the cost of single cell RNA sequencing and to increase the sensitivity.

B. Major techniques established in the lab

Wet and dry lab expertise in whole transcriptome single cell RNA sequencing, targeted single cell RNA sequencing, bulk RNA sequencing, proteomics, and DNA methylation, AAV-mediated gene manipulation Multiple mouse models of amyloid and tau pathology eQTL, pQTL, and other QTL analysis MRI brain imaging

C. Techniques of Interest

Spatial transcriptomics, SPLIT-seq, miniScope, Cell-type specific or single cell proteomics, Multielectrode array for neural activity



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A. Research Interests

1. Targeting senescence markers for therapeutic intervention in PD pathology: Our recent publication in collaboration with the Ko lab at Johns Hopkins suggests that α -syn preformed fibrils (PFF)-induced pathology could lead to astrocyte and/or microglia senescence in PD brains, which may contribute to neuropathology in this model (Verma et al., 2021). Targeting senescent cells using senolytics could therefore constitute a viable therapeutic option for the treatment of PD. As a follow-up study, we test a hypothesis that cellular senescence processes result in the failure of maintaining the homeostasis in dopamine neurons or surrounding astrocytes/microglia, which is associated with PD pathology. With measuring the levels of senescence markers in the PD-related regions including the striatum and Substantia nigra from PFF-injected PD mouse model or human PD brains, we will determine the effects of cellular senescence in inducing dopaminergic neuronal loss and PD pathology and verify the validity of using senolytics in halting PD pathology. This study will allow us to understand the senescence aspects of neuropathology of PD, which may reveal potentially new therapeutic targets using senolytics for preventing neurodegeneration including PD.

2. Oxidative stress increases the levels of deSUMOylation in PD related proteins for inducing PD pathology: We turned our efforts to determine if the levels of SUMO proteases (**SENPs**) are higher in the striatum and brainstem from human PD tissues than those in age-matched normal brains. We found that the level of SENP1 in human PD patient brains was higher than that in age-matched controls (a manuscript in prep). Thus, we set up a hypothesis that SENP1 level and/or activity is stimulated by oxidative stress, which is a part of pathological mechanisms of PD. Our preliminary results demonstrated that MPTP- or PFF-induced oxidative stress removes SUMO1 from α -synuclein in mouse striatum and midbrain, while SUMO conjugase, Ubc9 overexpression-mediated SUMOylation protects the dopaminergic neurons in the striatum and Substantia nigra against the toxicities (Verma et al., eNeuro, 2020). Therefore, we are investigating whether SENP1 inhibitions protect dopaminergic neurons in the striatum and SNc in PFF-injected mice. We also expect to see that higher levels of SENP1 in the Lewy bodies than those in normal brainstem tissues. This approach will help us determine if stimulating SENP1 is related to induce the PD pathology in the human and mouse brains, and blocking SUMO1 removal by SENP1 inhibition can be a novel therapeutic target in PD pathology.

3. Assessing regulatory roles of SUMOylation in DAT, alpha-synuclein, and LRRK2 in Parkinson's disease pathology.

4. Developing neuroprotective compounds as potential therapeutics in Parkinson's disease mouse models.

5. Developing a combination therapy for halting PD pathology and identifying a biomarker from human PD patients' saliva.

B. Common Lab techniques: Western blot, qRT-PCR, cell viability/cytotoxicity assays (MTT & LDH), ELISA, protein activity assays (including DAT, HAT & HDAC), ROS measurements, Protein aggregation (Thioflavin T) assay, primary neuron/astrocytes/microglia culture, microarray, Immunoprecipitation, immunohistochemistry, confocal microscopy, stereology, and Mass Spectrometry & MS imaging (collaboration).

C. Techniques of Interest

Mass-Spectrometry brain imaging (Bruker) and midbrain-derived organoids culture.



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Dr. Yong Kim

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A. Research Interests

My lab is interested in the molecular and cellular compensatory mechanisms by which brain cells maintain homeostasis following exposure to brain injury or risk factors related to neurodegenerative or psychiatric disorders. Our long-term goal is to understand how brain-cell-type-specific natural compensatory mechanisms are altered in disease conditions for the purpose of finding novel disease mechanisms and promising therapeutic targets.

Our specific research interests are:

Molecular mechanisms in endothelial cells regulating blood-brain barrier permeability and neural circuit activity. In this particular project, we are focusing on molecular pathways mediated by Ahnak, which is one of molecular factors we discovered from our long-term depression research. One of our goals is to understand how Ahnak-mediated pathways in endothelial cells regulate depressive behavior.

Role of actin regulators in homeostatic control of neuronal activity or survival. In this particular project, we are focusing on the heteropentameric WAVE1 protein complex that we initially discovered as a binding partner of cyclin-dependent kinase 5. Our previous studies uncovered WAVE1, a key component of the protein complex, as a neuronal activity-dependent regulator of actin polymerization in the brain. We have also found that a reduction of WAVE1 expression observed in Alzheimer's disease (AD) brains is a critical part of cellular compensatory mechanism to control amyloid β production. Importantly, we have found novel coding variants of the WAVE1 complex in AD patients. Current ongoing research is to elucidate the function of the coding variants using human iPSCs-derived neuronal models and knockin mouse models.

Molecular and cellular pathways mediating comorbidities in neurological and psychiatric disorders.

Depression is the most common comorbid condition of epilepsy. Our previous studies indicate that parvalbumin (PV)-positive GABAergic interneuron is a pivotal node controlling depressive behavior. Alterations of PV interneurons are highly implicated in epilepsy as well. We have developed several PV interneuron-selective knockout mouse lines for depression research. We are currently using them as a powerful tool to study common molecular pathways mediating seizure activity and depression-like behavior.

B. Major techniques established in the lab

1) Translating Ribosome Affinity Purification (TRAP)/RNAseq: We have established parvalbumin-positive interneuron-selective TRAP/RNAseq technique and endothelial cell type-specific TRAP/RNAseq technique to analyze cell-type-specific translating mRNAs from brain tissues.

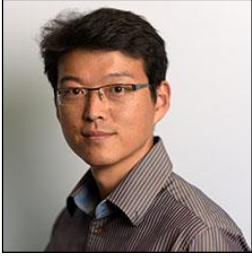
2) Multi-step *in vitro* fertilization and embryo transfer technique: We have numerous transgenic lines for the studies of key molecular factors we have discovered so far. As a collaboration with the Genome Editing Shared Resource (GESR) facility at Rutgers, we are using multi-step *in vitro* fertilization (IVF) together with embryo transfer to surrogates or cryopreservation of fertilized embryos in order to rapidly cross multiple transgenes and produce sufficient number of experimental mice or efficiently store transgenic mouse lines with a minimal number of breeding cages.

C. Techniques of Interest

Cell-type-specific proteomics



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Dr. Yongsoo Kim

Department of Neural and Behavioral science, College of Medicine

The Pennsylvania State University.

Lab website: <https://kimlab.io/>

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.



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A. Research Interests

1. The role of NADPH oxidases (NOXs)-mediated oxidative stress in the pathogenesis of Parkinson's disease. 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. Chromatin landscape and epigenetic regulation of α -SYN in PD. In human, the α -SYN gene (*SNCA*) contains high CpG rich region around transcription start site. We have found that CpGs in this region of dopaminergic neurons and human brain tissue are largely unmethylated in both control and PD conditions. Histone marks, however, demonstrate significant differences between them with for example much higher H3K4me3 levels in PD, supporting elevated α -SYN levels. To modulate epigenetic marks in a precise target-specific manner, a CRISPR/dCas9-Suntag technique has been developed.

B. Major techniques established in the lab

1. 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.

2. Single-molecule fluorescence in situ hybridization (smFISH) 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



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localization of single RNA molecule can be visualized.

3. Multiomic analysis using single nuclei (sn) 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.

C. Techniques of Interest

Multielectrode array for neural activity



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https://www.hopkinsmedicine.org/institute_cell_engineering/research_programs/neuroregeneration/

A. Research Interests: My laboratory is currently at the forefront of research into the biology and pathobiology of the proteins and mutant proteins linked to Parkinson's disease (PD) and Dementia Lewy bodies (DLB) and discovering new targets for therapeutic intervention. The studies below are providing major insights into understanding the pathogenesis of neurologic disorders and are providing novel opportunities for therapies aimed at preventing neurodegenerative disorders.

- We showed that c-Abl is active in PD and contributes to pathogenesis of PD through tyrosine phosphorylation of α -synuclein and parkin and genetic depletion and pharmacological inhibition of c-Abl protects against α -synuclein-induced neurodegeneration (PMID: 29103051). We are investigating potentially safer and more effective c-Abl inhibitor drug options in mouse models of PD in collaboration with 1stbio therapeutic Inc and Neuraly, Inc.
- We recently discovered that lymphocyte activation gene 3 (LAG3) is the major internalization receptor for pathological α -synuclein that has important implications in PD and Dementia with Lewy bodies (PMID: 27708076). We are investigating the role of APLP-1/LAG3 complex on cell-to-cell transmission of pathologic α -synuclein.
- Recently, we discovered that pathologic α -synuclein activates microglia converting astrocytes to activated A1 astrocytes, which drives non-autonomous cell death in PD. Also, we recently showed that a potent, brain penetrant long-acting glucagon like peptide-1 receptor (GLP-1R) agonist NLY01 protects against neurodegeneration and behavioral deficits in mouse models of PD and AD via the direct prevention of microglial mediated conversion of astrocytes to an A1 neurotoxic phenotype (PMID: 29892066, PMID: 33902708). The drug NLY01 is under clinical phase 2 trials for PD and AD patients.
- We discovered that microglial NOD2/RIPK2 could be a key regulator driving neurodegeneration induced by pathologic α -synuclein. Genetic deletion and pharmacological inhibition of NOD2/RIPK2 signaling protects against neurodegeneration in PD and AD. We are investigating potentially safer and more effective RIPK2 inhibitor drug options in mouse models of PD, AD, and ALS in collaboration with 1stbio therapeutic Inc and Neuraly, Inc.
- My group discovered that graphene quantum dots (GQDs) have notable potency in not only inhibiting fibrillization of α -synuclein but also disaggregating mature fibrils mainly by virtue of their amphiphilic nature via direct interaction with α -synuclein and treatment of GQDs rescue PD phenotypes in mouse models of PD (PMID: 29988049). These discoveries have led to innovative approaches and enhanced the development of new agents to treat PD. We are investigating the neuroprotective effect of GQDs in mouse models of AD.
- We have been investigating how glucocerebrosidase 1 (GCase) is dysregulated in sporadic PD and GBA1-linked PD. My group discovered TRIP12, a ubiquitin E3 ligase, as a major regulator of wt GCase turnover. We uncovered that TRIP12 tightly controls the GCase level via the ubiquitin-proteasome system (UPS), and TRIP12-induced ubiquitination and subsequent degradation of GCase lead to mitochondrial dysfunction. Depleting TRIP12 in the human dopaminergic neurons and SN provides neuroprotection against α -synuclein preformed fibrils-provoked PD by increasing the GCase activity. This study offers novel therapeutic strategies to restore GCase activity and reverse PD. We are identifying agents that inhibit GBA1:Trip12 interaction or inhibit Trip12 E3 ligase activity.



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• We have been contributing to establish mouse models of PD. Recently we have developed an mouse model that supports the Braak's theory that PD could start in the gut and spread to the brain via the vagus nerve to cause PD (PMID: 31255487). This new model recapitulates the clinical syndrome and manifestations of idiopathic PD including both motor and non-motor symptoms. We are dissecting the circuits involved in the transmission of α -synuclein from the gut to brain. We are also characterizing E326K GBA1 KI mouse line, TH-tTA/D620N VPS35 Tg mouse line, and E326KGBA1/APOE4 KI mouse line.

B. Major techniques established in the lab: My laboratory employs advanced technologies in next generation sequencing including RNA Seq and ChIP Seq and single nucleus seq, circuit mapping, human stem cell biology, high throughput screening, and high throughput proteomic analysis coupled with advanced computational biology to investigate signaling networks important in neurologic disorders. We also use many advanced imaging approaches including stereology, confocal microscopy, super resolution microscopy, electron microscopy, in our analyses.

C. Techniques of Interest

SHIELD and 3D high-resolution tissue imaging, light-sheet microscopy with iDISCO and CUBIC, CryoEM, Human mini brain models, Single cell proteomics.



Association of Korean Neuroscientists



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A. Research Interests

1. Neural mechanisms of category learning. Our ability to categorize sensory stimuli according to their behavioral relevance is an important adaptive function with unknown mechanisms. Important questions are where in the brain and how the categorical information is represented. We trained head-restrained mice to perform a vibration frequency categorization task and monitored neuronal activity in the somatosensory cortex using in vivo two photon imaging. Our preliminary data show that neurons preferring the same categorical stimuli increase correlated activities while neuronal tuning curves do not change. We are characterizing which neurons participate in the neuronal 'assemblies' and testing their causal contribution in encoding of categorical information.

2. Neural circuit underlying the contribution of somatosensory cortex in motor coordination. The primary somatosensory cortex (S1) is involved in the control of movement, but underlying mechanisms remain poorly understood. Our data show that S1 inactivation impairs simple coordinated movements like locomotion and that cortico-cortical connections in S1 are required for the efficient control of locomotion. These cortical pathways preferentially innervate inhibitory interneurons in S1. Building on these results, we aim to identify key neural components required for sensory-motor interaction and determine the nature of information that is routed from S1 to locomotor centers.

3. Inhibitory circuit dysfunction in neurodevelopmental disorders. De novo haploinsufficiency in SynGAP1 is strongly linked to neurodevelopmental disorders. Sensory processing deficits are common among human SynGAP1 patients. While existing studies suggest the importance of excitatory neocortical neurons in the pathogenesis of SynGAP1 disorders, recent evidence suggests a role for inhibitory interneurons as well. We test whether and how inhibitory circuit contributes to neural and behavioral deficits observed in a mouse model of SynGAP1 haploinsufficiency using cell-type specific recording and manipulation methods.

B. Major techniques established in the lab

Head-fixed behavioral tasks, In vivo calcium imaging, photoablation, gait assay, opto/chemogenetics.

C. Techniques of Interest

Computational analysis of movement



Association of Korean Neuroscientists



Dr. Daewoo Lee

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A. The Main Research Interest is to understand pathogenic mechanisms underlying neurodegenerative diseases (NDs). In particular, we are interested in prion-like propagation of pathogenic proteins such as α -Synuclein and tau.

1. 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 such as Parkinson's disease. 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. Our key interest is to study how neuronal subtypes, α -Syn mutants, and functional/molecular factors affect pathological transmission of α -Syn.

2. Phosphorylation-dependent human tau release: Intracellular neurofibrillary tangles are composed of tau (MAPT), which is hyper-phosphorylated and aggregated. Tau is an intracellular protein but also released to the extracellular fluid. Studies have shown that a prion-like mechanism involving the transfer of hyper-phosphorylated tau between synaptically connected neurons underlies the seeding and spread of tau pathology throughout the brain. Interestingly, neuronal excitability increases during the early stages of AD 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 is not known what phosphorylation sites modulate activity-dependent tau release and kinases have yet to be identified for their role in activity-dependent tau release. We have developed a tractable and highly reproducible method of studying activity-dependent tau release in *Drosophila* primary neuronal culture and a human neural progenitor cell line (ReNCell), which form the experimental framework of this study. Optogenetic method has been also used to induce activity-dependent tau release.

Other research projects:

3. Dopamine signaling and Parkinson's disease: We have studied neurodegenerative and neuroprotective role of dopamine signaling in PD. Dysregulation of dopamine homeostasis causes selective neurodegeneration while activation of D2 receptors is neuroprotective.

4. Biogenic amine signaling and olfactory learning. The main goal of this project is to investigate functional roles of dopamine and serotonin receptors in synaptic plasticity and olfactory learning. We also study their downstream G-protein signaling mechanisms. It is of our particular interest to understand the role of DA autoreceptors in modulating excitability and synaptic inputs which underlie olfactory learning.

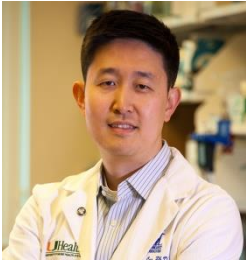
B. Technical expertise in my lab:

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

C. Techniques of Interest: Next generation sequencing, Single-cell analysis



Association of Korean Neuroscientists



Dr. Jae K. Lee

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A. Research Interests

1. Mechanisms of fibrosis after CNS injury. In contrast to the glial scar, the fibrotic scar that forms after CNS injury has received little attention. Although the traditional view was that fibroblasts originate from the meninges, we and others have shown that the perivascular niche is another major source and contributes to fibrosis even after injuries in which the meninges remain intact. These infiltrating fibroblasts contribute to maintenance of tissue integrity, but also create an environment that is detrimental to axon and oligodendrocyte regeneration. We are investigating signaling mechanisms that can be targeted to reduce fibrosis and create an environment that is more conducive to CNS regeneration.

2. Lipid metabolism in macrophages after spinal cord injury. After traumatic injuries to the CNS, such as spinal cord injury, there is a massive influx of monocyte-derived macrophages at the injury site whose primary role is to phagocytose and clear cellular debris. In the case of spinal cord injury, a large part of this debris is from myelin, which is comprised mainly of lipids. The excessive amount of myelin debris leads to accumulation of lipid droplets in macrophages (i.e. foamy macrophages) that results in metabolic dysfunction and increased inflammatory response. We are investigating the molecular mechanisms of foamy macrophage formation and their effects on spinal cord injury pathology.

3. Contribution of oligodendrocyte progenitor cells to gliosis. The glial scar is usually synonymous with the astroglial scar, but there are many other cellular components of the glial scar than just astrocytes, including oligodendrocyte progenitor cells (OPCs). In the injured CNS, OPCs do more than just give rise to oligodendrocytes. They play immunomodulatory roles and even differentiate into astrocytes as well as Schwann cells. These diverse functions of OPCs in the glial scar are poorly understood. We are investigating how OPCs can be targeted to promote neural repair after spinal cord injury.

B. Major techniques established in the lab

1. Tissue clearing and light sheet microscopy.
2. Bulk and single cell RNA-seq.
3. Rodent models of spinal cord injury and axon regeneration.

C. Techniques of Interest

Advanced imaging techniques; spatial transcriptomics



Association of Korean Neuroscientists



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A. Research Interest

My research background in immunology and neuroscience has equipped me with a broad spectrum of interdisciplinary research experiences. As a tenure-track faculty at the University of Georgia, my research programs have been geared towards understanding the mechanism of inflammation in the CNS and the periphery modulating neurodegenerative diseases. The long-term goal of my lab is to understand the relationship between innate immunity and proteinopathy and provide a novel immunotherapeutic strategy.

1. To investigate the role of innate immune cells in Lewy body diseases. I have developed a novel research program investigating 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.

2. To investigate the mechanism of aged-associated changes modulating neurodegenerative 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 showed the level of RGS10 in microglia significantly decreased with age. I am currently investigating studies as follows: 1) To determine if RGS10 plays a protective role in metabolic disorders by maintaining glucose tolerance and insulin sensitivity. 2) To determine if the loss of RGS10 with aging exaggerate chronic inflammation, metabolic syndromes, and cognitive deficits in the CNS. 3) To determine the detailed mechanism of RGS10 in modulating glucose homeostasis and inflammation in microglia and its role in synuclein-induced inflammation and neurotoxicity. To do so, we propose to generate microglia-targeting nanotherapeutics carrying RGS10 plasmid for the amyloid fibril-induced mouse model of Lewy body diseases. Our goal is to demonstrate that RGS10 enrichment in microglia restores microglia homeostasis, enhances amyloid fibril clearance, and exerts neuroprotection for amyloid fibril-induced neuronal death.

B. Major techniques established in the lab

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 preformed fibril (PFF) alpha-synuclein (α -syn) mouse model 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. Our study demonstrated that intracerebral-initiated



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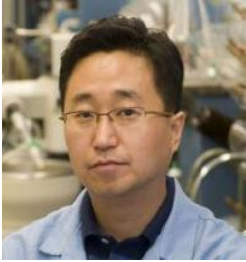
synucleinopathies alter immune cell profiles not only in the CNS but also in peripheral lymphoid organs prior to neurodegeneration. Based on these findings, we investigate the crosstalk mechanism to link α -syn pathology in the CNS and its effect on the peripheral immune system. The long-term goal is to explain how the immune system influences PD-associated brain changes, which may represent a novel mechanism and an avenue for treating neurodegenerative diseases.

C. Techniques of Interest

Single cell analysis, Proteomics, Metabolomics



Association of Korean Neuroscientists



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A. Research Interests

1. Promoting Axonal Regeneration in the injured CNS using a Non-viral Gene Manipulation method.

Given the intrinsically limited regenerative potential of the central nervous system (CNS) and the complex inhibitory environment, there is an urgent need for effective strategies towards robust axon regeneration and neurite outgrowth of neurons to re-establish the damaged neural circuitry. In this project, we plan to integrate several fields of research, Nanotechnology, Biomaterials, Chemical Biology, Neuroscience, and Stem Cell Biology, to develop a novel nanomaterial-based platform that induces axon regeneration and neurite outgrowth, which are safe, effective, and innovative for in vivo transplantation and potential clinical applications.

2. In Vivo Cell Reprogramming of Reactive Astrocytes into Neurons for Enhancing CNS Repair.

Reactive astrogliosis has been considered a major hurdle in the recovery after CNS injuries. Reactive astrocytes can, therefore, be a good target for therapy to both suppress the secondary injury as well as provide a means of neuron replacement therapy. To this end, we are developing a non-viral transcription factor (TF) method to in vivo reprogram reactive astrocytes to neurons.

3. Advanced Stem Cell Therapies for CNS injuries and Advanced in vivo Drug/Gene Delivery using Bioinspired Hybrid Nanoscaffolds.

Stem cell transplantation, as a promising treatment for central nervous system (CNS) diseases, has been hampered by crucial issues such as low cell survival rates, incomplete differentiation, and limited neurite outgrowth in vivo. We designed and developed a biodegradable hybrid inorganic (BHI) nanoscaffold-based method to improve the transplantation of human patient-derived neural stem cells (NSCs) and to control the differentiation of transplanted NSCs in a highly selective and efficient way. [*Nature Communications*, 2018]. The development and the use of biomaterials for stem cell-based tissue engineering to treat CNS diseases/injuries to date have focused on: (i) providing favorable microenvironments for endogenous and exogenous cellular regeneration and (ii) serving as a spatiotemporally controlled drug release platform to regulate pro-neuroregenerative signaling pathways. In summary, our work [*Nature Communications*, 2018] is based on the development of a biodegradable hybrid inorganic nanoscaffold and its utilization for the enhanced transplantation of stem cells into SCI sites. Our demonstrated nanoscaffold technology platform [*Advanced Materials*, 2021] can further be combined with other neurogenic drugs, as well as stem cell therapeutic efforts currently in development.

B. Major techniques established in the lab

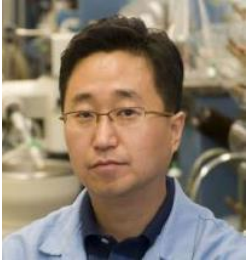
1. Nanoparticle-based Artificial Transcription Factor (NanoScript) for Effective Gene Regulation in Cellular Reprogramming.

2. Integrating Epigenetic Modulators into Non-viral gene delivery.

3. Nanotechnology Approaches to Advance CRISPR-Cas-based Gene Therapies.



Association of Korean Neuroscientists



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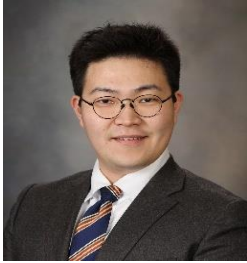
4. Developing hybrid RNAi-Nanoparticle-based gene therapy to enhance cellular reprogramming *in vivo*: We are developing a novel platform technology to design and synthesize RNAi (siRNA) nanoparticles using the rolling circle transcription (RCT) process. The key concept of this method is to develop a naturally biodegradable multigene regulator by integrating several different types of RNAi approaches (dsRNA and ssRNA) onto a single nanopatform to control a transcriptional cascade for the targeted cell reprogramming.

C. Techniques of Interest

MEA/NEA for neural activity, In Vivo Molecular Imaging, and Gene/Drug Delivery



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Personal statement

I received my PhD in Neural Engineering from the Department of Biomedical Engineering, Hanyang University, South Korea. My work at the Neural Engineering Laboratory of Hanyang University involved developing novel neurochemical recording techniques to measure neurotransmitters in the brain, especially dopamine. My experience is in the areas of in vitro and in vivo electrochemistry and electrophysiological recordings in addition to signal processing. I have published a number of papers on these developments and basic mechanisms in electrochemistry. Currently, I am an Assistant Professor in the Department of Neurologic Surgery and Associate Director at Neural Engineering Laboratories, Mayo Clinic in Rochester Minnesota.

A. Research Interests

1. Advancing voltammetry techniques.

Fast scan cyclic voltammetry (FSCV) has long been used in neuroscience to interpret neurochemical fluctuations in various physiological and behavioral settings. Due to its high spatial/temporal resolution and biocompatibility, FSCV is most commonly used for neurochemical recordings in vivo, especially biogenic amines (e.g., dopamine). However, several limitations exist with FSCV such as biofouling, unclear redox reaction, selectivity, and unstable background current. One main focus of my research is to adopt engineering techniques to electrochemistry for enhancing signal quality acquired from carbon-fiber microelectrodes. These studies include measuring dopamine and serotonin with higher selectivity, sensitivity, and with stable background signals.

2. Development of techniques for basal concentration measurements.

Present voltammetric techniques are only able to measure changes (electrical or pharmacological) in the concentrations of neurotransmitters in the living brain. There remains a critical need for new technologies that allows the measurement of basal concentrations in both normal and disease states. I have been developing and validating a neurochemical recording and data analysis method that fulfills this need and allows accurate, continuous, and real-time quantification of basal levels of dopamine and serotonin in the brain. The ability to measure discrete and rapid changes in basal concentrations of these neurotransmitters in the mammalian brain, presently impossible with existing methods, would provide an unprecedented advancement in neuroscience and means to understand and treat neuropsychiatric disorders.

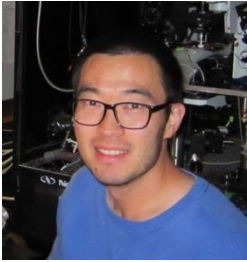
B. Major techniques established in the lab

1. Multiple Cyclic Square Wave Voltammetry. I recently developed a novel voltammetric technique, multiple cyclic square wave voltammetry (MCSWV, patent pending), for analytical quantification of tonic dopamine concentrations in vivo with relatively high temporal resolution (10 s). M-CSWV enriches the electrochemical information by generating two dimensional voltammograms which enable high sensitivity (limit of detection, 0.17 nM) and selectivity against ascorbic acid, and 3,4-dihydroxyphenylacetic acid (DOPAC), including changes in pH. Using M-CSWV, a tonic dopamine concentration of 120 ± 18 nM ($n = 7$ rats, \pm SEM) was determined in the striatum of urethane anesthetized rats. MCSWV is also modified for tonic serotonin extracellular levels recording termed N-MCSWV. Serotonin is known as a key neurochemical for depression and drug addiction.

C. Techniques of Interest: Electrochemistry, Fast-scan cyclic voltammetry, dopamine, serotonin, drug addiction



Association of Korean Neuroscientists



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A. Research Interest

Neocortical neurons receive thousands of excitatory and inhibitory synaptic inputs driven by varying patterns of neuronal activity. The spatial arrangement and temporal regulation of *excitatory* and *inhibitory* synapses determine the functional consequences of excitation and inhibition for synaptic integration, action potential generation, and neural activity. We use advanced optical imaging techniques to examine the spatiotemporal mechanisms that govern activity-dependent excitatory and inhibitory synaptic and circuit plasticity in the developing cortex. We study (1) how the integrative properties of single excitatory and inhibitory synapses and neurons support the early neural circuit formation and (2) whether early dysregulation of synaptic signaling gives rise to the pathogenesis of neurodevelopmental disorders. The goal of my research is to determine the functional impact of the neurotransmitters and neuromodulators (e.g. glutamate, GABA, dopamine, serotonin) on cortical circuits during development, plasticity, and in disease.

Key findings from my research program in the last three years are that:

We found that serotonin signaling promotes the initiation of excitatory synapse formation and controls the maturation of excitatory synapses in the developing prefrontal cortex (PFC), which is associated with higher cognitive processes that may be disrupted in illnesses such as Autism Spectrum Disorders (ASDs). This work is currently funded by R01 grant.

We found that early life stress-induced dysregulation of dopamine neurons constitutes a neural mechanism by which adverse events early in life alter excitatory, but not inhibitory, synapses in the PFC and may cause behavioral dysfunction in adulthood. This work was recently published in *Cell Reports* and supported by NARSAD YI Award and R21 grants.

We found that inhibitory synapses and their plasticity are essential for controlling excitatory synapses, neuronal excitability, and function, thereby giving them crucial roles in cognition and behavior. This work is supported by Brain Research Foundation Seed Grant and CSU/CU-Pilot Collaboration Grant and has been recently submitted for publication.

Together, our recent work has revealed cellular and synaptic mechanisms by which neurotransmitters and neuromodulators shape the early establishment of neuronal circuitry in mouse developing cortex and identified the neuromodulatory system that may contribute to the etiologies underlying mental health disorders such as ASDs.

B. Techniques of Interest

Two-photon imaging, Two-photon uncaging, Optogenetics, Electrophysiology



Association of Korean Neuroscientists



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A. Research Interests

As a bioinformatician-turned neurobiologist, we combine computational and experimental methods to elucidate the regulatory mechanisms that underlie oligodendrocyte development and its disease relevance.

1. Enhancers governing oligodendrocyte development Enhancers are *cis*-regulatory DNA elements that promote gene expression in a cell type-specific manner. We try to elucidate enhancers underpinning oligodendrocyte development and their role in neurological and neuropsychiatric disorders.

2. Silencers governing oligodendrocyte development Silencers are *cis*-regulatory DNA elements that repress gene expression in a cell type-specific manner. Virtually nothing is known about oligodendrocyte silencers. We try to elucidate them and their role in neurological and neuropsychiatric disorders.

3. Functional mechanism of Myrf for oligodendrocyte development Myrf, a membrane-bound transcription factor, is a master regulator of oligodendrocyte development. We try to elucidate its functional mechanism.

4. Identifying new transcription factors for oligodendrocyte development We try to uncover new transcription factors that are required for oligodendrocyte development.

B. Major techniques established in the lab

1. Bioinformatics
2. Epigenome editing tools: dCas9-KRAB
3. Genome editing tools
4. Mouse genetics



Association of Korean Neuroscientists



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Lewis Katz School of Medicine at Temple University,
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SPINAL CORD AND PERIPHERAL NERVE REGENERATION

The long-term goals of my research are to elucidate the mechanisms that govern maintenance and regeneration of synaptic connections in the spinal cord and muscle, particularly those associated with glial cells, and to use this knowledge to promote repair of spinal cord-muscle connections in patients with injury, disease, disuse or aging.

Research projects (current)

1. Oligodendrocyte progenitor cells as a novel inhibitor of CNS regeneration.

We are testing if Dorsal root axons fail to regenerate into the spinal cord by forming aberrant synapses with OPCs (or NG2 glia).

2. Coactivation of BRAF and mTOR signaling to promote spinal cord regeneration.

We have found that concurrent activation of BRAF and inhibition of PTEN induces unprecedented robust regeneration of dorsal root axons into the spinal cord after dorsal root injury. We are extending the finding to test further the strategy can lead to robust regeneration of primary sensory axons after direct SCI.

3. Novel Spinal cord ischemic stroke induced by spinal root injury.

We are studying unexpectedly robust ischemic damage dorsal root injury can elicit in the spinal cord and related mechanisms.

4. Role of YAP and TAZ in Schwann cell myelination and nerve repair.

We are studying the roles of Hippo signaling and the oncoproteins, YAP/TAZ in the development and maintenance of peripheral nerve myelination, Schwann cell plasticity and nerve repair.

5. Enhancing peripheral nerve regeneration.

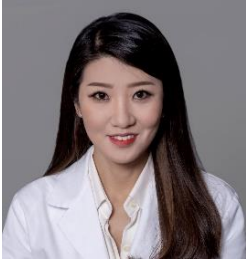
We are manipulating BRAF, PTEN, ErbB2 signaling in motor and sensory axons, and/or Schwann cells to facilitate nerve regeneration after peripheral nerve injury (proximal and chronic injury models).

Research methods

We primarily use mouse to study these projects. Our techniques include transgenic and knockout mice, cell type specific conditional and inducible gene or cell manipulation, in vivo time-lapse imaging, TEM, mouse microsurgery for spinal cord and DRG neurons, virus injection and transduction of DRG and sciatic nerve (AAV and lentivirus), tissue clearing, in vitro co-culture of DRG neurons, OPCs, and/or Schwann cells, and other standard molecular, cellular and behavioral analyses.



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A. Research Interests

Tau pathology is a prevailing hallmark of Alzheimer's disease and multiple other neurodegenerative diseases. Our research focuses on understanding how beta-arrestins, proteins known to regulate various neuronal signaling receptors, contribute to neurodegeneration in Alzheimer's disease (AD) and related dementias (ADRD). My laboratory first identified beta-arrestin2 to be significantly increased in brains of FTD patients and functions as a key positive regulator of tau pathology. Her team also demonstrated that beta-arrestin2 oligomers but not monomers drive tauopathy in vivo.

B. Research Projects and established techniques

Molecular mechanisms and therapeutic targeting of beta-arrestins in ADRDs

More than 50% of AD patients have comorbidities, including TDP-43 and Lewy body pathologies, which are hallmarks of FTD and PD, respectively. Beta-arrestin1 and beta-arrestin2 are ubiquitously expressed but show the highest expression in brain and spleen. While beta-arrestin1 and beta-arrestin2 share high sequence similarity (78% identical) and show functional overlap, significant differences exist. My lab is interested in further dissecting the molecular mechanisms by which beta-arrestin1 and beta-arrestin2 similarly or differentially drive multiple pathologies in ADRDs. We use interdisciplinary approaches from cell biology of neurons, live-cell imaging of genetically encoded fluorescent reporters, genetic models of AD/ADRD, recombinant AAVs, electrophysiology, and behavior to delve into an unexplored role of beta-arrestins in neurodegeneration in AD and ADRDs. Utilizing these state-of-art techniques, we aim to identify novel molecular insights to beta-arrestin1/2 activity, which enables us to find multiple ways target beta-arrestins to mitigate the pathogenesis in ADRDs. As oligomerized but not monomeric beta-arrestin2 drives tauopathy, one approach my lab is currently undertaking is the identification and characterization of small molecular inhibitors of beta-arrestin oligomerization as a therapeutic approach to mitigate tauopathy and possibly other signature brain pathologies.

Mitochondrial protein CHCHD2 in Lewy body disorders

Rare mutations in the gene coding for the mitochondrial protein CHCHD2 are associated with PD and other Lewy body disorders. Utilizing a multidisciplinary approach in vitro and in vivo, we aim to unveil how pathological CHCHD2 contributes to the pathogenesis of PD and other Lewy body disorders. In collaboration with the David Kang lab, we are also interested in identifying the similarities and differences between pathological CHCHD2 versus its homolog CHCHD10, the latter which is mutated in familial and sporadic FTD and ALS.

C. Techniques of interest

Two-photon imaging, iPSCs, Human neuronal cultures, neural organoids, dopaminergic neuronal culture.



Association of Korean Neuroscientists

2nd AKN Research Symposium Committee

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- Dr. Mi-Hyeon Jang at Rutgers University
- Dr. Jae K. Lee at University of Miami
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- Dr. Daewoo Lee at Ohio University (President)