



DECEMBER 5, 2015

KOLIS

WINTER CONFERENCE 2015
(KOLIS-IBS Global Talent Forum)

Berg Hall, Li Ka Shing Center, Stanford University

PROGRAM

9:00 – 10:20 AM

Registration

10:20 – 10:30 AM

Opening Remarks
Congratulatory Address (Doochul Kim, IBS)

10:30 – 11:10 AM

Gou Young Koh
IBS, KAIST

11:10 – 11:50 AM

Seong-Gi Kim
IBS, Sungkyunkwan University

11:50 AM – 12:30 PM

Jin-Soo Kim
IBS, HQ & Seoul National University

12:30 – 2:00 PM

Lunch

Symposia I

Symposia II

2:00 – 2:30 PM

Peter Dongmin Sohn
UC San Francisco

Hee Won Yang
Stanford University

2:30 – 3:00 PM

Jae-Ick Kim
Stanford University

Hee Jung Yang
UC Davis

3:00 – 3:20 PM

Coffee Break

3:20 – 3:50 PM

Changhui Pak
Stanford University

Gyeng Jin Kang
UC Berkeley

3:50 – 4:20 PM

Keunhong Jeong
UC Berkeley, LBNL

Minah Kim
UC San Francisco

4:20 – 4:30 PM

Photo Time

4:30 – 4:45 PM

Yung Joon Yoo
'Institute for Basic Science(IBS)-Past, Present & Future'

4:45 – 5:10 PM

Sponsors Info Session

5:10 – 5:30 PM

Raffle & Annual Report
Closing Remarks

5:30 PM -

Dinner & Happy Hour
(The Lorry I. Lokey Stem Cell Bldg. 1F,
Stanford University)

KOLIS WINTER CONFERENCE 2015

KEYNOTE PRESENTATION

(10:30 – 12:30)

KEYNOTE TALK I



Gou Young Koh

Center for Vascular Research, IBS
Graduate School of Medical Science and Engineering, KAIST

Leading vascular research through ground-breaking discoveries and innovative challenges

Endothelial cells (ECs) constitute the inner lining of blood and lymphatic vessels as monolayers and play essential roles in regulating and maintaining the viability of all organs in the human body. The shape and response of ECs differ depending on the organ, location, situation, and stimuli. This diversity and heterogeneity of ECs have been a long-standing interest, because such characteristics are essential in displaying and maintaining diverse functions of different organs and tissues. Despite the significant conceptual advances we have already achieved, a large portion of the characteristics remains to be elucidated to further our understanding of the diversity and heterogeneity of ECs at the molecular level. Our ultimate goal is to make ground-breaking discoveries,

conceptual advances and paradigm shifts in vascular biology through basic and fundamental research. In particular, we will focus on further understanding of "organotypic" EC heterogeneity, angiogenesis, lymphangiogenesis, cardiogenesis, vascular remodeling, and vascular niche with the integration of biomedical science and innovative technology. Successful achievement of these aims will not only shed light on unexplored paths to understand the regulations of cardiovascular functions in an organ-specific manner, but also enable us to develop new drugs and stem cells to treat cardiovascular diseases, including cancer, diabetic vasculopathy and ischemic heart diseases, as translational medicine.

KEYNOTE TALK II



Seong-Gi Kim

Center for Neuroscience Imaging Research, IBS
Department of Biomedical Engineering, Sungkyunkwan University

Introduction of IBS Center for Neuroscience Imaging Research

The IBS Center for Neuroscience Imaging Research (CNIR) is located in the Suwon campus of Sungkyunkwan University (<http://cnir.ibs.re.kr>), and focuses on integrative imaging methods and systems neuroscience research. We have dedicated three-floor space (~46,000 sqft) with core imaging facilities (human MRI, animal MRI, multi-photon microscope, and confocal microscopes), histology, rodent and non-human primate housing, and clustered computer. The CNIR consists of inter-disciplinary research programs, including

neurophysiology, rodent fMRI, human fMRI, neurovascular coupling, and neurophotonics. Our center is closely linked to the Department of Biomedical Engineering, which has all scholarship-based undergraduate as well as graduate program with three sub-majors (neuroscience, biomedical imaging, and biomaterials). Consequently, two types of faculty positions are available: tenure-track SKKU faculty and IBS research faculty. I will present the center's vision, facilities, research programs, and biomedical engineering department.

KEYNOTE TALK III



Jin-Soo Kim

Center for Genome Engineering, IBS
Department of Chemistry, Seoul National University

Genome Editing in Human Stem Cells, Animals, and Plants

Genome editing that allows targeted mutagenesis in higher eukaryotic cells and organisms is broadly useful in biology, biotechnology, and medicine. We have developed ZFNs, TALENs, and Cas9 RNA-guided endonucleases (RGENs), derived from the type II CRISPR-Cas prokaryotic adaptive immune system, to modify chromosomal DNA in a targeted manner. In particular, we used purified Cas9 protein and in vitro transcribed guide RNAs rather than plasmids encoding these components to correct large chromosomal inversions in the blood coagulation factor VIII gene that cause hemophilia A in patient-derived induced pluripotent stem cells (iPSCs) and to modify diverse genes in large animals and plants. The resulting animals and plants contained small insertions or deletions (indels) at target sites, which are indistinguishable from naturally-occurring variations, possibly bypassing

regulatory requirements associated with use of recombinant DNA. Despite broad interest in RNA-guided genome editing, RGENs are limited by off-target mutations. We developed Cas9 nuclease-digested whole genome (digenome) sequencing (Digenome-seq) to profile genome-wide specificities of Cas9 nucleases in an unbiased manner. Digenome-seq captured nuclease cleavage sites at single nucleotide resolution and identified off-target sites at which indels were induced with frequencies below 0.1%. We also showed that these off-target effects could be avoided by using modified guide RNAs that contain two extra guanine nucleotides at the 5' end. Digenome-seq is a robust, sensitive, unbiased, and cost-effective method for profiling genome-wide off-target effects of programmable nucleases including Cas9.

KOLIS WINTER CONFERENCE 2015

SYMPOSIA I

(14:00 – 16:20)

SYMPOSIA I



Peter Dongmin Sohn

UC San Francisco

Tau-mediated cytoskeletal alterations in Alzheimer's disease

Neurons are highly polarized cells in which asymmetric axonal-dendritic distribution of proteins is crucial for neuronal function. Somatodendritic mislocalization of the axonal protein tau is an early sign of Alzheimer's disease (AD) and other neurodegenerative disorders. However, the pathogenic molecular mechanisms are incompletely understood. Here we report that tau acetylation and consequent destabilization of the axon initial segment (AIS) cytoskeleton are important in the somatodendritic mislocalization of tau. AD-relevant acetylation at K274 and K281 in the microtubule (MT)-binding domain of tau reduced tau binding to MTs. In primary neuronal cultures, acetylation at these sites led to hyperdynamic MTs in the AIS, shown by live-imaging of MT mobility and

fluorescence recovery after photobleaching. AIS cytoskeletal proteins, including ankyrin G and β IV-spectrin, were downregulated in AD brains and in the brains of transgenic mice expressing tauK274/281Q, which mimics acetylation. Using photoconvertible tau constructs, we found that acetylated axonal tau is mislocalized to the somatodendritic compartment. Stabilizing MTs with epothilone D to restore the cytoskeletal barrier in the AIS prevented tau mislocalization in primary neuronal cultures. These findings suggest that tau acetylation contributes to neurodegenerative disease by compromising the cytoskeletal sorting machinery in the AIS.

SYMPOSIA I



Jae-Ick Kim

Stanford University

Aldehyde Dehydrogenase 1a1 Mediates a GABA Synthesis Pathway in Midbrain Dopaminergic Neurons

Midbrain dopamine neurons are an essential component of the basal ganglia circuitry, playing key roles in the control of fine movement and reward. Recently, it has been demonstrated that γ -aminobutyric acid (GABA), the chief inhibitory neurotransmitter, is co-released by dopamine neurons. Here we show that GABA co-release in dopamine neurons does not utilize the conventional GABA synthesizing enzymes, glutamate decarboxylases GAD65 and GAD67. Our experiments reveal an evolutionarily

conserved GABA synthesis pathway mediated by aldehyde dehydrogenase 1a1 (ALDH1a1). Moreover, GABA co-release is modulated by ethanol at binge drinking blood alcohol concentrations and diminished ALDH1a1 leads to enhanced alcohol consumption and preference. These findings provide insights into the functional role of GABA co-release in midbrain dopamine neurons, which may be essential for reward-based behavior and addiction.

SYMPOSIA I



Changhui Pak

Stanford University

Human Neuropsychiatric Disease Modeling using Conditional Deletion Reveals Synaptic Transmission Defects Caused By Heterozygous Mutations in *NRXN1*

The cellular and molecular mechanisms governing complex neuropsychiatric disorders, such as autism and schizophrenia (SZ), remain unclear. Multiple lines of human genetic research indicate that specific mutations in the genes encoding proteins involved in the development/and or function of synapses are repeatedly observed in patients with autism and SZ. Therefore, synaptic dysfunction has been postulated as a common mechanism underlying these disorders. However, the studies examining the functional effects of such mutations in the basis of human synaptic transmission are limited. In particular, mutations in the gene encoding a synaptic cell adhesion molecule, Neurexin-1 (*NRXN1*), have been repeatedly observed in individuals with autism and SZ. At present, *NRXN1* mutations represent the most frequent

single-gene mutation in SZ. This presentation will cover a recently published work describing the cellular and synaptic effects of human *NRXN1* mutations using engineered mutations in wild type human embryonic stem (hES) cells. hES cells that are conditionally mutant for *NRXN1* locus have been generated and differentiated into cortical-like excitatory human neurons. *NRXN1* mutant neurons display a prominent and specific impairment in the calcium-dependent neurotransmitter release by decreasing the initial release probability. This approach will identify disease-relevant phenotypes and mechanisms, which will serve to further our understanding of synaptic pathology in SZ and autism and eventually help discover potential therapeutics to patients with various psychotic disorders.

SYMPOSIA I



Keunhong Jeong

UC Berkeley, LBNL

Chemical Sensors Using Hyperpolarized ^{129}Xe NMR/MRI

Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI) have excellent potential in medical imaging and research because they are not invasive. These well-established techniques are commonly done on protons in the body or in sample tubes to generate signals; however, the sensitivity is low due to low thermal equilibrium polarization. To overcome this problem,

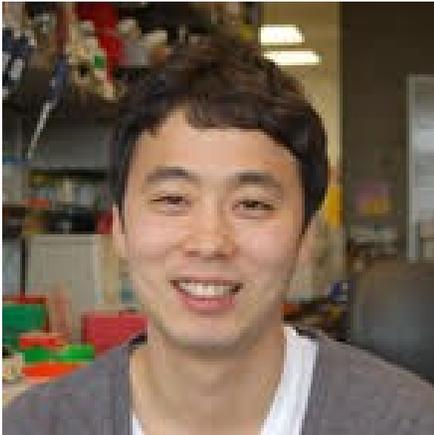
our lab is developing ^{129}Xe hyperpolarization, hyper-CEST (chemical exchange saturation transfer) techniques. We synthesized several molecular sensors detecting various metal ions and targeting cancer cells *in vitro*.

KOLIS WINTER CONFERENCE 2015

SYMPOSIA II

(14:00 – 16:20)

SYMPOSIA II



Hee Won Yang

Stanford University

Locally excitable Cdc42 signals steer cells during chemotaxis

Neutrophils and other immune cells use amoeboid movement and chemotaxis to reach sites of infection and inflammation. This process requires a polarization mechanism that directs actin polymerization, membrane protrusion and adhesion formation to the cell front. While Ras, Rac, Cdc42, and RhoA small GTPases all regulate chemotaxis, it has not yet been established how they spatially and temporally control polarization and steering. Using fluorescence biosensors and photorelease of chemoattractant, we show that upon cell stimulation, all four small GTPases initially respond cell-wide with similar kinetics. However, Cdc42 activity polarizes rapidly, antagonizes RhoA,

and maintains a steep spatial gradient during migration, while Ras and Rac polarize later forming shallow gradients. Strikingly, pre-existing local Cdc42 signals predict the future direction of movement upon stimulation, and asymmetric Cdc42 signals across the front of migrating cells predict chemotactic turning. Furthermore, in the absence of actin polymerization, cells trigger local recurring Cdc42 activity pulses, a hallmark of excitable networks. Thus, de novo polarization and steering towards chemoattractant are both directed by local self-amplified Cdc42 signals

SYMPOSIA II



Hee Jung Yang

UC Davis

Phosphorylation of ribosomal protein S3 and anti-apoptotic TRAF2 protein mediates radioresistance in non-small cell lung cancer cells

Radioresistance is considered as a main factor restricting efficacy of radiotherapy. However, the exact molecular mechanism of radioresistance has not been explained yet. To elucidate radioresistance mechanism in lung cancer, radiation responses in two types of non-small cell lung cancer (NSCLC) cells with different radiosensitivity were compared and then key molecules conferring radioresistance were identified. In radioresistant NSCLC cells, ionizing radiation (IR) led to casein kinase 2 α (CK2 α)- and PKC-mediated phosphorylation of rpS3 and TRAF2, respectively, which induced dissociation of rpS3-TRAF2 complex and NF- κ B activation, resulting in significant up-regulation of pro-survival genes (cIAP1, cIAP2, and survivin). Also, dissociated phospho-rpS3 translocated into nucleus and bound with NF- κ B complex (p65 and p50), contributing to p65 DNA binding property and specificity. However, in

radiosensitive NSCLC cells, IR-mediated rpS3 phosphorylation was not detected due to the absence of CK2 α overexpression. Consequently, IR-induced rpS3-TRAF2 complex dissociation, NF- κ B activation, and pro-survival gene expression were not presented. Taken together, these findings revealed a novel radioresistance mechanism through functional orchestration of rpS3, TRAF2, and NF- κ B in NSCLC cells. Moreover, it provided the first evidence for the function of rpS3 as a new TRAF2-binding protein and demonstrated that phosphorylation of both rpS3 and TRAF2 is a key control point of radioresistance in NSCLC cells. These results suggest that regulation of rpS3 and TRAF2 in combination with radiotherapy could have high pharmacological therapeutic potency for radioresistance of NSCLC.

SYMPOSIA II



Gyeong Jin Kang

UC Berkeley

Intravital Imaging Reveals Dynamics of Corneal Lymphangiogenesis

Lymphatic research signifies a field of rapid progression in recent years. Though lymphatic dysfunction has been found in a myriad of disorders, to date, few effective treatments are available for lymphatic diseases. It is therefore urgent to develop new experimental approaches and therapeutic protocols. The cornea offers an ideal site for lymphatic research due to its transparent nature, accessible location, and lymphatic-free but – inducible features. In this study, taking

advantage of the live imaging system we recently developed, we are able to reveal the multifaceted dynamics of corneal lymphangiogenesis from the initiation to regression phases. Further investigation holds the great potential for divulging new mechanisms and therapeutic strategies for lymphatic diseases occurring both inside and outside the eye.

SYMPOSIA II



Minah Kim

UC San Francisco

Opposing actions of Angiotensin-2 on Tie2 signaling in the presence or absence of inflammation

Angiotensin-2 (Ang2) promotes blood vessel remodeling in diverse pathological conditions through actions on endothelial Tie2 receptors. Ang2 inhibits Tie2 by competing with angiotensin-1 (Ang1), but paradoxically promotes Tie2 phosphorylation (p-Tie2) in some settings. We reconciled this paradox by manipulating conditions that govern Ang2 agonism or antagonism in the respiratory vasculature, where either action can lead to vascular remodeling. By using novel reporters, agonists, and inhibitors, we found that vascular remodeling during *Mycoplasma pulmonis* infection was preceded by p-Tie2 suppression. This change was accompanied by activation of Foxo1 transcription factor, a downstream target of Tie2 signaling, and by increased Ang2

and leakiness. Consistent with a mechanism involving Ang2 antagonism of Tie2, these changes were exaggerated by Ang2 overexpression or inhibition of Tie2 and were reduced by exogenous Ang1 or inhibition of Ang2. Ang2 also promoted vascular remodeling under pathogen-free conditions, but here Ang2 was an agonist: high p-Tie2, low Foxo1 activation, and no leakage. Together, the data show that the presence or absence of inflammation determines whether Ang2 is a Tie2 agonist or antagonist. Ang2 agonism promotes stable enlargement of normal vessels, but Ang2 antagonism in inflammation initiates a positive feedback loop where Foxo1-driven Ang2 expression leads to vascular enlargement and leakage.

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(주) 상신 랩텍



KOLIS WINTER CONFERENCE 2015

Berg Hall, Li Ka Shing Center, Stanford University

Directions to conference



From US-101

- Take the Embarcadero Road West Exit
- Follow Embarcadero Road through Palo Alto for 3-4 Miles
- As you approach the underpass, get into the right lane
- Once you have crossed El Camino Real, Embarcadero Rd. splits
- Turn right at the fork onto Arboretum Rd.
- Turn left at the second light onto Quarry Road
- Turn right at the first light onto Welch Road
- Turn left on Campus Dr. West
- LKSC is on the left, before Campus curves to the left

Parking

- If there is no special sign, the marked areas are free on Saturday.

From Interstate 280

- Take the Sand Hill Road exit and follow Sand Hill road East
- Follow Sand Hill Road for 5-6 miles
- Turn right onto Pasteur Drive -- you will see the main entrance to the hospital
- Turn right onto Welch Road
- Turn left on Campus Dr. West
- LKSC is on the left, before Campus curves to the left