236th WPI-IIIS Seminar
-Mini Symposium-

Designing novel therapeutics with minimized side-effects

G protein-coupled receptors (GPCRs) represent the largest class of cell surface receptors in the human genome, and they are involved in almost every physiological process in our body such as cardiovascular regulation, immune response, neurotransmission, behavior and mood regulation. About half of the currently prescribed drugs target this class of receptors including those used in congestive heart failure, hypertension, asthma, allergies, schizophrenia, Parkinson's disease, and cancer. GPCRs harbor a conserved seven transmembrane (7TM) architecture and typically signal through heterotrimeric G-proteins and β-arrestins. The overarching goal of our laboratory is to understand the activation, signaling and regulation of GPCRs, and leverage this information to design novel therapeutics with minimized side-effects.

Dr. Arun Shukla

Department of Biological Sciences and Bioengineering

Indian Institute of Technology

Date: **Thursday, November 6, 2025**

Time: **9:30 – 10:25**

Venue: **1F Auditorium, IIIS Building**

＊On-site participation only

IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

筑波大学 高等研究院 Tsukuba Institute for Advanced Research

wpi

MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

Contact: International Institute for Integrative Sleep Medicine, University of Tsukuba
029-853-5857 (ext.5857) | wpi-iiis-alliance@ml.cc.tsukuba.ac.jp

237th WPI-IIIS Seminar
-Mini Symposium-

Gαs slow conformational transition upon GTP binding and a novel Gαs Regulator

G proteins are major signaling partners for G protein-coupled receptors (GPCRs). Although a number of high-resolution structures of GPCR-G protein complexes have been revealed by X-ray crystallography and cryo-electron microscopy (cryo-EM), the stepwise structural changes during GPCR–G protein coupling have not fully been understood fully. In this study, we analyzed step-wise conformational changes during GPCR-G protein coupling using beta2-adrenergic receptor (beta2AR) and Gs as a model GPCR and G protein. To understand the step-wise conformational changes, we used pulse-labeling hydrogen-deuterium exchange mass spectrometry (HDX-MS). HDX-MS can analyze the conformational dynamics of proteins and can tolerate conformational heterogeneity. To monitor the movement of alpha-helical domain (AHD) of Gα subunit, we developed an assay system using tryptophan-induced fluorescence quenching technique. The pulse HDX-MS showed that there are delayed structural changes even after GDP-release or GTP-binding. Specifically, the C-terminus of Gαs undergoes sustained conformational changes during beta2AR-Gs complex formation even after GDP is released. Likewise, AHD of Gαs undergoes sustained conformational changes after GTP is incorporated and Gαs is dissociated from the receptor and Gβγ. We further identified a novel AHD-binding protein, melanoma-associated antigen D2 (MAGE D2), which regulates the G proteins activation cycle by accelerating the GTP-induced closing of the Gαs AHD. Our data revealed the conformational changes during GPCR-Gs coupling that have not been observed by currently available high-resolution structures. The data suggest that the GPCR-G protein coupling specificity is determined by one or more transient intermediate states that serve as selectivity filters and precede the formation of the stable nucleotide-free GPCR-G protein complexes observed in crystal and cryo-EM structures. Furthermore, we observed that the GTP-binding mediated G protein activation kinetics can be regulated by proteins interacting at AHD.

Dr. Ka Young Chung

School of Pharmacy

Sungkyunkwan University

Date: **Thursday, November 6, 2025**

Time: **10:30 – 11:25**

Venue: **1F Auditorium, IIIS Building**

✻On-site participation only

INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

Contact: International Institute for Integrative Sleep Medicine, University of Tsukuba
029-853-5857 (ext.5857) | wpi-iiis-alliance@ml.cc.tsukuba.ac.jp

238th WPI-IIIS Seminar
-Mini Symposium-

Spying on Neuromodulator Dynamics In Vivo by Constructing Multi-Color GRAB Sensors

The human brain consists of billions of neurons, most of which communicate with each other by releasing different kinds of neuromodulators through chemical synapses, and therefore is able to control different physiological functions like perception, motion, learning and memory. To dissect the mechanism underlying how brain take part in different physiological functions and pathological conditions, it's important to monitor the dynamics of neuromodulators in vivo. In the past few years, we and others have developed a series of multi-color GPCR-activation–based (GRAB) sensors for monitoring extracellular neuromodulator dynamics with high sensitivity, specificity, and spatial-temporal resolution in living animals. In this report, I will share our recent progress in developing sensors for monitoring monoamines, nucleotides, neurolipids and neuropeptides. With these GRAB sensors, we have monitored the dynamics of neuromodulators in mice in a wide range of physiological processes (sleep-wake cycle, motion, etc.) and pathological conditions (epilepsy, etc.).

Dr. Yulong Li

School of Life Sciences

Peking University

Date: **Thursday, November 6, 2025**

Time: **12:30 – 13:25**

Venue: **1F Auditorium, IIIS Building**

＊On-site participation only

IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

筑波大学 高等研究院 Tsukuba Institute for Advanced Research

wpi

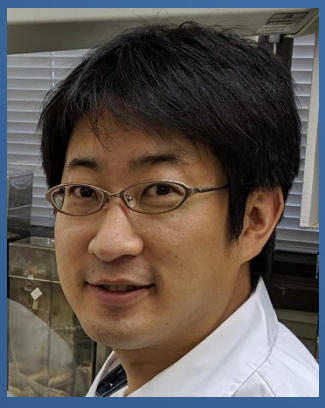
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

Contact: International Institute for Integrative Sleep Medicine, University of Tsukuba
029-853-5857 (ext.5857) | wpi-iiis-alliance@ml.cc.tsukuba.ac.jp

239th WPI-IIIS Seminar
-Mini Symposium-

Chemogenetic activation of G12 signaling illuminates therapeutic potential for G12-coupled GPCRs

Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) are powerful chemogenetic tools that enable selective modulation of specific G protein signaling pathways in vivo. Existing DREADDs for Gs, Gi, and Gq pathways have proven invaluable for dissecting diverse physiological processes ranging from neuronal activity to metabolic regulation. However, G12/13 signaling has remained largely unexplored due to the absence of selective pharmacological tools. To address this gap, we developed G12D, a DREADD that preferentially activates G12 signaling upon clozapine-N-oxide (CNO) administration. By combining G12D with Cre-loxP systems, we generated adipocyte-, hepatocyte-, and POMC neuron-specific models to interrogate tissue-specific G12 functions. Our studies revealed striking context-dependent metabolic outcomes: synergistic enhancement of adipose browning with β-adrenergic signaling, divergent regulation of hepatic lipid versus glucose metabolism, and central control of appetite and energy balance. We are currently developing G13-selective DREADDs to further distinguish G12 from G13 signaling. These chemogenetic approaches establish G12/13-coupled GPCRs as promising therapeutic targets for obesity and metabolic disease.



Dr. Asuka Inoue

Graduate School and Faculty of Pharmaceutical Sciences, Kyoto University

Date: **Thursday, November 6, 2025**

Time: **13:30 – 14:25**

Venue: **1F Auditorium, IIIS Building**

＊On-site participation only

IIIS
INTERNATIONAL INSTITUTE FOR INTEGRATIVE SLEEP MEDICINE

筑波大学 高等研究院 Tsukuba Institute for Advanced Research

wpi

MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

Contact: International Institute for Integrative Sleep Medicine, University of Tsukuba
029-853-5857 (ext.5857) | wpi-iiis-alliance@ml.cc.tsukuba.ac.jp