UCLA Engineering
HENRY SAMUELI SCHOOL OF
ENGINEERING AND APPLIED SCIENCE

BIOENGINEERING

PRESENTS

Glucagon-like peptide-1 receptor: small molecule agonists, 3-dimentional structures and beyond

TUESDAY, Feb 12, 2019
11:00AM – 12:30 PM
2101 ENGINEERING V

Mingwei Wang, M.D., Ph.D.
Fudan University
Dean, School of Pharmacy

ABSTRACT:

Glucagon-like peptide-1 receptor (GLP-1R) belongs to the class B family of G-protein coupled receptors. The non-peptidic GLP-1R agonist Boc5 was shown to mimic a full spectrum of physiological actions of GLP-1. However, its druggability is hampered by poor oral bioavailability and difficulties in chemical synthesis. This led us to conduct structural biology studies of the receptor. Upon stabilization by negative allosteric modulators, two crystal structures of the human GLP-1R 7-transmembrane domain were determined in an inactive conformation, revealing a common binding pocket present in both GLP-1 and glucagon receptors. Molecular modeling and mutagenesis experiments indicate that agonist positive allosteric modulators (PAMs) target the same general region, but in a distinct sub-pocket which may facilitate the formation of an intracellular binding site that enhances G-protein coupling. The structure of human GLP-1R in complex with the G protein-biased peptide, exendin-P5, and Gs protein was also determined, offering insights into the structural basis of biased agonism. Allosteric modulation provides high selectivity, broad mimicry and less over-activation in terms of pharmacological properties. Based on the structural information, new efforts are being made to discover PAMs targeting the GLP-1R, with an ultimate goal of developing novel small molecule therapeutics to treat metabolic disorders.

BIOGRAPHY:

Following medical practices in Shanghai, Dr. Ming-Wei Wang obtained his Ph.D. from University of Cambridge in 1989. He worked for a couple of US-based biotech companies a year later and served as a consultant to Merck and UNDP on China-related projects in the mid-1990's. Thereafter, he was engaged in various entrepreneur activities. Dr. Wang joined the faculty of Shanghai Institute of Materia Medica, Chinese Academy of Sciences in 2001 and became Director of the National Center for Drug Screening in 2003. In 2004, he was named by Shanghai Pudong New District Government as a Senior Business Advisor. He founded the Chinese National Compound Library and has been its first director since 2012. Dr. Wang was appointed as Dean, School of Pharmacy, Fudan University in 2015. He is also an editorial board member of *Trends in Pharmacological Sciences* (TiPS), *The Biochemical Journal, Acta Pharmacologica Sinica* and *ACS Pharmacology and Translational Science.* His research achievements include the discovery of a non-peptidic glucagon-like peptide-1 receptor agonist Boc5, determination of the 3-D structures of 7-TMD and full-length glucagon and glucagon-like peptide-1 receptors, elucidation of the insulinotrophic effect of insulin-like peptide 5 and identification of the link of GPR160 (an orphan GPCR) and prostate cancer.