Tsinghua-*Science* Workshops

Structural Biology and Drug Design

Session 4: Structural biology and drug discovery targeted at GPCRs

Friday, March 5th, 2021 8-10 pm (GMT +08:00, Beijing)

8:00pm-8:45pm

Xiangyu Liu, Tsinghua University, China

Structural biology and drug innovation for β-adrenergic receptors

8:45pm-9:00pm Q&A

9:00pm-9:45pm

Bryan L. Roth, University of North Carolina Chapel Hill School of Medicine, USA

Structure-guided discovery small molecule discovery at G protein coupled receptors (GPCRs)

9:45pm-10:00pm Q&A

Host

Prof. Hongwei Wang

Dr. Hong-Wei Wang is currently Professor and Dean of School of Life Sciences at Tsinghua University, Deputy Director of Tsinghua-Peking Joint Center for Life Sciences, and Executive Director of Beijing Advanced Innovation Center for Structural Biology at Tsinghua University. Dr. Wang received his B.S. degree in Biological Sciences & Biotechnology from Tsinghua University in Beijing, China in 1996. He did his thesis work under the supervision of Prof. Sen-Fang Sui, earning a Ph.D. degree from Tsinghua University in 2001. Subsequently, he worked as a Postdoctoral Fellow under the supervision of Prof. Eva Nogales, advancing to Research Scientist in 2006 at Lawrence Berkeley National Laboratory. He joined Yale University as a Tenure-Track Assistant Professor of Molecular Biophysics and Biochemistry in 2009 and returned to his alma mater as a Professor of Life Sciences in December, 2010.

Dr. Wang's current research interests include methodology development for more efficient and high resolution cryo-EM, the coordination mechanisms of cytoskeleton and membrane systems, and the mechanism and regulations of nucleic acid quality control.

Dr. Wang received numerous awards, including Science and Technology Breakthrough Award (with Jijie Chai) of School of Life Sciences, Tsinghua University (2020), XPLORER PRIZE of Tencent Foundation (2019), Chinese Cryo-EM Outstanding Contribution Award (2019), Tan Jiazhen Life Sciences Innovation Award (2018), Beijing Teachers' Role Model (2018), Beijing Outstanding Teacher Award (2017), The Best Mentor Like A Friend of Tsinghua University (for two consecutive sessions, 2016 and 2018), National Award of Natural Science (2nd rank, 2005), and Outstanding Performance Award of Lawrence Berkeley National Laboratory (2005).

Speakers

Dr. Xiangyu Liu

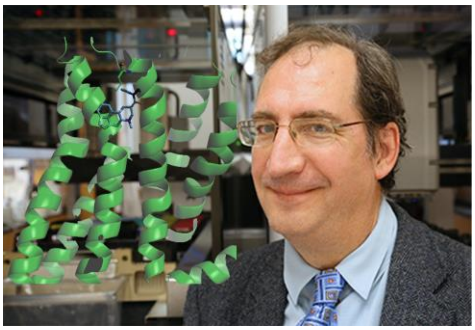
Dr. Xiangyu Liu obtained his BS and PhD at Peking University in 2004 and 2011, respectively. From 2008 to 2010, he studied as an exchange PhD student at Aarhus University, Denmark, with the support from Chinese Scholarship Council. Dr. Liu conducted his first postdoctoral research at School of Life Sciences, Peking University from 2011 to 2013, and his second postdoctoral research at School of Medicine, Tsinghua University from 2013 to 2017. Then he worked as assistant researcher at School of Medicine, Tsinghua University. In August 2019, Dr. Liu joined School of Pharmaceutical Sciences as an assistant professor and a principle investigator, his research interest focuses on structural biology of G protein coupled receptors and structure guided drug development. His major scientific contributions include revealing the modulation mechanisms of the first intracellular negative allosteric modulator (NAM) and the first intracellular positive allosteric modulator (PAM) for beta2 adrenergic receptor, as well as providing structure insights into the process of GPCR-G protein complex formation.

Structural biology and drug innovation for β-adrenergic receptors

Beta adrenergic receptors (βARs) mediate physiologic responses to the catecholamines epinephrine and norepinephrine released by the sympathetic nervous system. While the hormone epinephrine binds β1AR and β2AR with similar affinity, the smaller neurotransmitter norepinephrine is approximately 10-fold selective for the β1AR. To understand the structural basis for this physiologically important selectivity, we solved the crystal structures of the human β1AR bound to different antagonists and agonists including norepinephrine and epinephrine. Structural comparison revealed that the catecholamine binding pockets are identical between β1AR and β2AR, but the extracellular vestibules have different shapes and electrostatic properties. Metadynamics simulations and mutagenesis studies revealed that these differences influence the path norepinephrine takes to the orthosteric pocket and contribute to the different association rates and thus different affinities. To examine the effect of conformation restriction on ligand binding kinetics and ligand affinity, we developed a rigidified epinephrine. To our surprise, the rigidified epinephrine exhibited over 100 fold preference for the β2AR over the β1AR. The results suggest it's possible to develop selective drugs for receptors with identical orthosteric binding pockets.

While it's possible to develop subtype selective drugs targeting the orthosteric pockets, the efforts are still highly challenging due to the high homology of the orthosteric binding pockets among different subtypes of receptors. Allosteric modulators are more likely to be selective because they bind to less conserved allosteric binding sites. I will also introduce our work on identifying the binding pockets for the first negative allosteric modulator and the first positive allosteric modulator of the β2AR.

Prof. Bryan L. Roth



Bryan L. Roth MD, PhD is the Michael Hooker Distinguished Professor of Pharmacology at the University of North Carolina Chapel Hill School of Medicine. Dr. Roth received his MD and PhD (Biochemistry) from St. Louis University in 1983 and subsequently trained in pharmacology (NIH), molecular biology (Stanford) and Psychiatry (Stanford). Prior to coming to UNC, Dr. Roth was a Professor of Psychiatry and Biochemistry at Case Western Reserve University School of Medicine where his clinical specialty was treatment-resistant schizophrenia. Dr. Roth has published more than 450 papers in the general areas of molecular pharmacology, structural biology and synthetic biology including 29 papers published in Science, Nature and Cell over the past decade. Dr. Roth was elected to the National Academy of Medicine of the National Academy of Sciences in 2014 and the American Academy of Arts and Sciences in 2019. He has received many honors including the Goodman and Gilman Award for Receptor Pharmacology, the PhRMA Foundation Excellence in Pharmacology Award, a NARSAD Distinguished Investigator Award and the IUPHAR Analytical Pharmacology Lectureship. Dr. Roth also given more than 20 named lectures including the 2017 Martin Rodbell Lecture and a Presidential Special Lecturer at the 2018 Society for Neurosciences meeting.

Structure-guided discovery small molecule discovery at G protein coupled receptors (GPCRs)

Over the past several years a revolution in our understanding of GPCR structure and function has been catalyzed by crystallographic and cryo-EM based structure determination. Here I will focus on one important family of GPCRs highlighting unpubished data and will show how a detailed understanding of the structure and function of GPCRs can accelerate drug discovery.