## Tsinghua-*Science* Workshops

**Structural Biology and Drug Design**

**Session 6: Structural Biology and Drug Design – Kinases**

Friday, May 14th, 2021 8-10 pm (GMT +08:00, Beijing)

20:00-20:45

**Hao Wu**, Harvard University, USA

Inflammasomes: unconventional protein secretion and regulation by DPP9

20:45-21:00 Q&A

21:00-21:45

**Christopher Garcia**, Stanford University, USA

Exploiting T cell and cytokine receptor structural principles to engineer immunotherapeutics

21:45-22:00 Q&A

## Host

**Prof. Hongwei Wang**

Dr. Hong-Wei Wang is currently Professor 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

**Prof. Hao Wu**

Dr. Wu's research focuses on elucidating the molecular mechanism of signal transduction by innate immune receptors using core approaches of structural biology. Her lab has elucidated signaling complexes in the TNF receptor family, the interleukin-1 receptor (IL-1R) family, the Toll-like receptor (TLR) family, and more recently, inflammasomes which are supramolecular complexes that activate inflammatory caspases such as caspase-1. Her studies further revealed how gasdermin D (GSDMD), which is the downstream effector cleaved by inflammatory caspases, leads to membrane pore formation, cytokine release and pyroptotic cell death. Dr. Wu's structural studies revealed a recurrent theme that upon ligand stimulation, many innate immune receptors assemble large oligomeric intracellular signaling complexes, or "signalosomes," to induce the activation of caspases, kinases and ubiquitin ligases, leading to cell death, cytokine maturation or expression of gene products for immune and inflammatory responses.

Dr. Wu received her pre-medical training in Peking University and studied Medicine at Peking Union Medical College. She obtained her PhD in Biochemistry from Purdue University as an HHMI predoctoral fellow. After performing postdoctoral research at Columbia University as an Aaron Diamond Foundation Fellow, Dr. Wu started her faculty appointment at Weill Cornell Medical College

in 1997 and was promoted to Professor in 2003. In 2012, Dr Wu became the Asa and Patricia Springer Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School and Boston Children's Hospital. Dr. Wu received a number of honors including Pew Scholar Award, Rita Allen Scholar Award, New York Mayor's Award for Excellence in Science and Technology, Biophysical Society Margaret Dayhoff Memorial Award, Protein Society Dorothy Crowfoot Hodgkin Award, International Cytokine and Interferon Society Seymour & Vivian Milstein Award, and Biophysical Society Fellows Award. She serves on the Scientific Advisory Council of Cancer Research Institute and the Editorial Board of Cell, Cancer Cell, Structure and Science. She has been an elected member of the National Academy of Sciences since 2015 and an elected fellow of the American Academy of Arts and Sciences since 2021. (http://wulab.tch.harvard.edu/)

**Inflammasomes: unconventional protein secretion and regulation by DPP9**

Inflammasomes are cytosolic supramolecular complexes that activate inflammatory caspases, which in turn process cytokines in the IL-1 family and the pore forming protein gasdermin D (GSDMD) to induce cytokine release as well as pyroptotic cell death. In this talk, I would like to elaborate on two vignettes from our recent work: "selective" unconventional protein secretion by GSDMD, and regulation of the NLRP1 inflammasome by the enzyme dipeptidyl peptidase 9 (DPP9) and its small molecule inhibitors. If there is time, I will also summarize a few of our findings on the role of inflammasomes on COVID-19.

**Prof. Christopher Garcia**

K. Christopher Garcia, Ph.D is a Professor of Molecular and Cellular Physiology, and of Structural Biology at the Stanford University School of Medicine. He received his B.S. in Biochemistry from Tulane University, and his Ph.D in Biophysics from Johns Hopkins University. After two years of post-doctoral work at Genentech, Inc. under Dr. David Goeddel in the Dept. of Molecular Biology, where he learned the emerging technologies of protein engineering and recombinant protein expression, Dr. Garcia moved to a second post-doctoral fellowship at The Scripps Research Institute in the laboratory of Prof. Ian Wilson, where he succeeded in determining the first crystal structures of the T cell receptor and then its complex with peptide-MHC. In 1999, Dr. Garcia started his lab at Stanford University School of Medicine in 1999 where he also became an Investigator in the Howard Hughes Medical Institute. Dr. Garcia was elected to the National Academy of Sciences in 2012, and the National Academy of Medicine in 2016.

Dr. Garcia's interests reside at the cell surface, and his laboratory is investigating structural and functional aspects of cell surface receptor recognition and activation, in receptor-ligand systems with relevance to human health and disease. Structural information on receptor-ligand complexes is used to engineer variant proteins and/or surrogates to manipulate receptor signaling and cellular function, with an eye towards therapeutic applications. The receptor systems studied derive principally from the immune system (TCR/MHC, cytokines, chemokine GPCR), but additionally encompass several systems that are also important in neurobiology (Neurotrophins, Semaphorins) and development (Notch, Wnt). A focus is on "shared" pleiotropic receptors, to understand the biophysical basis by which different ligands are able to elicit unique intracellular responses and functional outcomes, and to exploit this information to engineer receptor-specific ligands Dr. Garcia has founded or co-founded several biotech companies that are attempting to clinically develop technologies from his lab, including ALXO (SIRP/CD7 antagonist), Synthekine (cytokine engineering), Surrozen (Wnt agonists), 3T (TCR antigen discovery), and Mozart (immune modulation by regulatory T cells).

**Exploiting T cell and cytokine receptor structural principles to engineer immunotherapeutics**

Many activities of the immune system are controlled by cell surface receptors through their interactions with either soluble or membrane-bound ligands. My lab has determined and exploited structural information on a wide variety of immune receptor complexes to both probe signaling mechanisms and engineer therapeutics. In particular I will highly recent studies on T cell receptor/peptide-MHC and cytokine receptor systems as examples where structural information can open doors to powerful strategies to manipulate biology and develop immunotherapeutics.