Tsinghua-*Science* Workshops

Structural Biology and Drug Design

Session 5: Structural Biology and Drug Design – Ion Channels

Thursday, April 15th, 2021 9-11 am (GMT +08:00, Beijing)

09:00am-09:45am

Nieng Yan, Princeton University, USA

How is electrical signal generated? Structural and mechanistic investigations of Na_v channels

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

10:00am-10:45am

David Julius, University of California, San Francisco, USA

Natural Products as Probes of the Pain Pathway: From Physiology to Atomic Structure

10:45am-11:00am Q&A

Host

Prof. Hongwei Wang

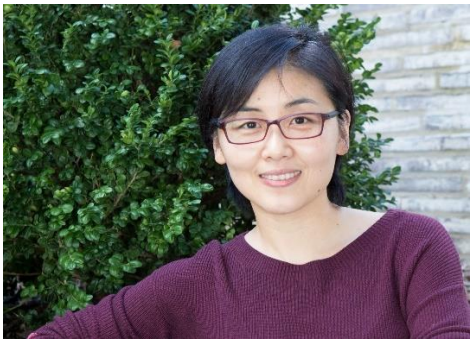
Dr. Hong-Wei Wang is currently Professor of School of Life Sciences at Tsinghua University, Deputy Director of Tsinghua-Peking Joint Center for Life Sciences, and Executive Director of Beijing Advanced Innovation Center for Structural Biology at Tsinghua University. Dr. Wang received his B.S. degree 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. Nieng Yan



Dr. Nieng Yan received her B.S. degree from the Department of Biological Sciences & Biotechnology, Tsinghua University, Beijing, China, in 2000. She then pursued her PhD in the Department of Molecular Biology at Princeton University under the supervision of Prof. Yigong Shi between 2000 and 2004. She was the regional winner of the Young Scientist Award (North America) co-sponsored by Science/AAAS and GE Healthcare in 2005 for her thesis on the structural and mechanistic study of programmed cell death. She continued her postdoctoral training at Princeton University, focusing on the structural characterization of intramembrane proteases. In 2007, she joined the faculty of School of Medicine, Tsinghua University. Her lab has been mainly focusing on the structural and functional study of membrane transport proteins exemplified by the glucose transporters and Na_V/Ca_V channels. In 2012 and 2013, she was promoted to tenured professor and Bayer Endowed Chair Professor, respectively. She returned to Princeton University as the founding Shirley M. Tilghman Professor of Molecular Biology in 2017. Dr. Yan was an HHMI international early career scientist in 2012-2017, the recipient of the 2015 Protein Society Young Investigator Award, the 2015 Beverley & Raymond Sackler International Prize in Biophysics, the Alexander M. Cruickshank Award at the GRC on membrane transport proteins in 2016, the 2018 FAOBMB Award for Research Excellence, and the 2019 Weizmann Women & Science Award. She was elected as a Foreign Associate of the US National Academy of Sciences in 2019. (https://molbio.princeton.edu/people/nieng-yan)

How is electrical signal generated?
Structural and mechanistic investigations of Na_v channels

The voltage-gated sodium (Na_v) channels are responsible for the initiation and propagation of action potentials. Being associated with a variety of channelopathies, they are targeted by multiple pharmaceutical drugs and natural toxins. Employing the modern methods of cryo-EM, we determined the near atomic resolution structures of a Na_v channel from American cockroach (designated Na_vPaS) and then the one from electric eel (designated $EeNa_v1.4$)**.** Recently, we have determined the cryo-EM structures of the human Na_v channels that function in different tissues, including $Na_v1.1/1.2/1.4/1.5/1.7$, in complex with distinct auxiliary subunits, toxins, and FDA-approved drugs. These structures provide the 3D template to study hundreds of disease mutations, and will facilitate drug discovery for the treatment of various diseases, such as pain syndrome. Structural comparison of the conformationally distinct Na_v channels reveals the molecular basis for ion selectivity, voltage sensing, and electromechanical coupling of Na_v channels. The most striking conformational difference occurs to the III-IV linker, which is essential for fast inactivation. Based on the structural findings, we suggest a “door wedge” model, or the allosteric blocking mechanism, for the fast inactivation of Na_v channels.

Prof. David Julius

David Julius hails from Brighton Beach, Brooklyn, where he attended public elementary and high schools. David received his undergraduate degree from MIT (1973-77), gaining his first research experience in the laboratory of Alexander Rich studying mechanisms of tRNA aminoacylation. He then moved to the University of California at Berkeley for graduate studies (1977-84), where he worked with Jeremy Thorner and Randy Schekman to elucidate mechanisms of peptide hormone processing and secretion in *Saccharomyces* yeast, culminating in characterization of KEX2 as the first identified prohormone convertase. For postdoctoral studies (1984-1989), David joined Richard Axel's group at Columbia University, where his focus turned to neuropharmacology and receptor function. During this time, David developed novel expression cloning methods that enabled him to identify genes encoding members of the serotonin receptor family. David then joined the faculty at the University of California, San Francisco (1990), where he is currently the Morris Herzstein Chair in Molecular Biology and Medicine and Chair of the Department of Physiology.

A major focus of David's work is to elucidate molecular mechanisms of somatosensation and pain, and sensory adaptation. His group has exploited the properties of natural products to discover a family of thermo- and chemo-sensitive ion channels that enable sensory nerve fibers to detect hot or cold temperatures and other noxious stimuli. With the aid of genetic, electrophysiological, and behavioral methods, they have determined how these ion channels contribute to pain sensation, and how channel activity is modulated in response to tumor growth, infection, or other forms of injury that produce inflammation and pain hypersensitivity.

David is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, the Hungarian Academy of Sciences (Honorary), and the Norwegian Academy of Science and Letters (Foreign Member). His work has been recognized with numerous awards, including the Shaw Prize in Life Sciences and Medicine, the Paul Janssen Prize for Biomedical Research, the Canada Gairdner International Award, the Rosenstiel Basic Medical Sciences Award, the Breakthrough Prize in Life Sciences, the Kavli Prize in Neuroscience, and the BBVA Frontiers of Knowledge Award.

Natural Products as Probes of the Pain Pathway: From Physiology to Atomic Structure

We are interested in determining the molecular basis of somatosensation - the process whereby we experience touch and temperature - with an emphasis on identifying molecules that detect noxious (pain-producing) stimuli. We are also interested in understanding how somatosensation is altered in response to tissue or nerve injury. Our approach has been to identify molecular targets for natural products that mimic the psychophysical effects of commonly encountered somatosensory stimuli, such as heat or cold, and to then ask how these molecules are activated or modulated by noxious stimuli or injury.

We have focused on three members of the TRP channel family (TRPV1, TRPM8, and TRPA1) that are expressed by subpopulations of primary afferent sensory neurons and which have been implicated in the detection of thermal stimuli and/or inflammatory agents. Genetic studies support the idea that the capsaicin receptor (TRPV1) and the menthol receptor (TRPM8) function as detectors of heat and cold, respectively, whereas the wasabi receptor (TRPA1) functions as a detector of environmental and endogenous chemical irritants.

From a signal transduction and therapeutics perspective, there is great interest in understanding how these channels are activated (gated) by physical and/or chemical stimuli. We use a combination of molecular genetics, natural product biochemistry, and biophysics to address these issues and probe mechanisms of stimulus detection, channel activation, and coding logic of the somatosensory system.