Tsinghua-*Science* Workshops

Spliceosome and RNA

Session 2: Spliceosome and RNA Function

20:00-20:45
Xiaohua Shen, Tsinghua University, China
A glimpse of the noncoding portions of the genome in chromatin and transcription regulation
20:45-21:00 Q&A

21:00-21:45
Adrian R. Krainer, Cold Spring Harbor Laboratory, USA
From Base Pairs to Bedside: Antisense Modulation of RNA Splicing
21:45-22:00 Q&A

Host

Prof. Yigong Shi

Born in Zhengzhou, Henan Province in 1967, professor Yigong Shi is an Academician of the Chinese Academy of Sciences, a Foreign Associate of the US National Academy of Sciences and an Honorary Foreign Member of the American Academy of Arts and Sciences. As a structural biologist, he is also a recipient of Cheung Kong Scholar, National Distinguished Scholar and Outstanding Youth Talent of National Science Foundation for China. In 1985, he was recommended for admission to Tsinghua University. In 1989, he graduated one year ahead of schedule with a bachelor's degree. In 1995, he received his Ph.D. in molecular biophysics from Johns Hopkins University School of Medicine, and later did postdoctoral research at Memorial Sloan-Kettering Cancer Center. From 1998 to 2008, he was Assistant Professor, Associate Professor, Professor and Warner-Lambert/Parke-Davis Professor in the Department of Molecular Biology, Princeton University, USA. In 2008, he declined the invitation of a researcher from Howard Hughes Medical Center (HHMI) and returned to Tsinghua University full-time. He served as the Dean of the School of Life Sciences of Tsinghua University until 2016 and is now the President of Westlake University. His research group is devoted to combining structural biology and biochemistry to elucidate the molecular mechanisms of fundamental cellular events, with a focus on apoptosis, regulated intramembrane proteolysis related to Alzheimer's disease, and pre-mRNA splicing.

Speakers

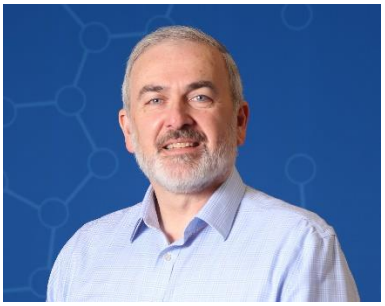
Prof. Xiaohua Shen

Xiaohua Shen received her Ph.D. at the University of Michigan and did the postdoctoral training with Stuart Orkin at Harvard Medical School. Xiaohua is now a professor and a Cheung Kong Scholar at Tsinghua University and an associate investigator in the Tsinghua-Peking Joint Center for Life Sciences. Her major research interest is to understand how the noncoding portions of the genome influence chromatin structure, gene expression, and stem-cell fate in development. Her work facilitates the functional inference of noncoding RNA genes, and brings about a paradigm shift in our understanding of RNA and the noncoding genomes in transcription and chromatin regulation.

A glimpse of the noncoding portions of the genome in chromatin and transcription regulation

Much of the developmental complexity of higher eukaryotes is thought to arise from gene regulation. RNA represents a hidden layer of regulatory information in complex organisms. I will discuss our recent progress in exploring novel functions of genomic repeats, noncoding RNA, and RNA-binding protein in the regulation of transcription and genome organization.

Prof. Adrian Krainer



Adrian R. Krainer, Ph.D. is the St Giles Foundation Professor at Cold Spring Harbor Laboratory (Long Island, NY), and Deputy Director of Research of the CSHL Cancer Center. He was born in Montevideo, Uruguay, and received BA and PhD degrees in Biochemistry from Columbia University and Harvard University, respectively, before joining CSHL in 1986. His laboratory studies the mechanisms and regulation of human pre-mRNA splicing, and is also engaged in the development of mechanism-based targeted therapies to correct or modulate alternative splicing in genetic diseases and cancer. In collaboration with Ionis Pharmaceuticals and Biogen, Dr. Krainer's lab developed nusinersen (Spinraza), which corrects the splicing defect in the SMN2 gene and became the first approved drug to treat the neurodegenerative disease spinal muscular atrophy. He is a co-founder, Director, and Chair of the SAB of Stoke Therapeutics. He was the recipient of the Life Sciences Breakthrough Prize, the RNA Society Lifetime Achievement Award, the International Prize for Translational Neuroscience, the Speiser Award in Pharmaceutical Sciences, the Bermuda Principles Award, the Brandwein Award in Genetic Research, the Bennett Award of the American Neurological Association, the Ross Prize in Molecular Medicine, the Takeda Pharmaceuticals & NY Academy of Sciences Innovators in Science Senior Scientist Award in Rare Diseases, and an honorary doctorate from Tel Aviv University. Prof. Krainer is a member of the US National Academy of Sciences, the National Academy of Medicine, the National Academy of Inventors, the American Academy of Arts & Sciences, and the Royal Society of Medicine (UK).

From Base Pairs to Bedside: Antisense Modulation of RNA Splicing

We have developed antisense approaches for targeted splicing modulation, exploiting the natural mechanisms of alternative splicing regulation. Nusinersen (Spinraza), the first approved drug for spinal muscular atrophy (SMA), exemplifies a successful path from basic studies of pre-mRNA splicing to an effective treatment for a devastating disease. Nusinersen is a splice-switching antisense oligonucleotide (ASO) that efficiently promotes SMN2 exon 7 inclusion and increases the level of SMN protein, which is limiting in SMA-patient motor neurons. Clinical trials of CSF-administered nusinersen in SMA patients, sponsored by Ionis and Biogen, began at the end of 2011.

Based on the striking results of two phase-3 trials in infants with the most severe form of SMA, and in children with an intermediate form of SMA, respectively, Spinraza was approved by the FDA in December 2016, for all SMA types. It became the first therapy that corrects defective splicing, and the first disease-modifying therapy for neurodegeneration. We have also explored prenatal ASO treatment in SMA mouse models, considering that early intervention maximizes the clinical benefit. Using a similar approach as for SMA, we also developed an ASO that corrects defective splicing of ELP1 pre-mRNA, due to a 5' splice site mutation that causes familial dysautonomia. The long duration of action of CNS-administered ASOs allows infrequent dosing, providing a feasible and effective approach to treat neurological disorders.