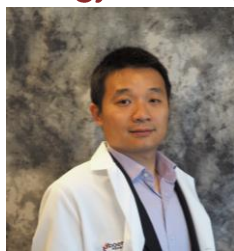


2016 Webb-Waring Biomedical Research Awards Investigator Research Profile



Hongjin Zheng, Ph.D.



University of Colorado Anschutz Medical Campus

Dr. Zheng is currently an assistant professor in the biochemistry & molecular genetics department at the University of Colorado School of Medicine. Dr. Zheng previously completed postdoctoral training in biochemistry and biophysics at the Janelia Research Campus of the Howard Hughes Medical Institute and at the University of Washington, Seattle. He earned his Ph.D. in biochemistry, biomolecular structure & design at the University of Washington,

Seattle.

Select Honors

Dr. Zheng has been the recipient of a Schultz Graduate Fellowship from the University of Washington, Seattle and the Chinese Government Award for Outstanding Self-Financed Students Abroad.

Medical Focus

Mitochondria are specialized subcellular organelles that are essential for metabolism and energy generation. Dysfunctional mitochondria are thought to play a significant role in conditions such as Alzheimer's, Parkinson's and Huntington's diseases and autism. There is an urgent need to develop drugs to improve mitochondrial function in order to help those patients with dysfunctional mitochondria. However, such drug development has made little progress because knowledge about the mechanism of mitochondrial failure in these disorders is largely unclear. One subclass of mitochondrial dysfunction is caused by the malfunction in the cellular machinery that transports proteins from the cytosol into the mitochondria. By understanding the protein import process in molecular detail, there is the potential to develop novel drugs that could regulate mitochondrial protein import, improve mitochondrial function and thereby help patients with damaged mitochondria.

Research Proposal

It has been well documented that mitochondrial malfunction is often associated with specific disease-related proteins (e.g. PINK1 in Parkinson's disease and APP/A β in Alzheimer's disease), which interact with the mitochondrial membrane proteins that make up the protein transport machinery, known as TOM-TIM. In the first part of his research program, Dr. Zheng will use biochemical and biophysical structural biology methods, including pull-down experiments, cross-linking, isothermal titration calorimetry (ITC), surface plasmon resonance (SPR) and X-ray crystallography to perform a detailed structural analysis of how TOM recognizes, interacts with and transports disease-related pre-proteins.

In the second aim of his proposal, Dr. Zheng proposes to perform a higher-level analysis designed to understand the structure and function of the TOM machinery as a whole. To do that, he will first investigate the interactions between the Tom components and understand how they assemble together. Next, he will study the entire complex by using cryo electron microscopy single particle reconstruction (cryo-EM SPR). Cryo-EM SPR is a powerful structural tool for studying the structure-function relationship of very large protein complexes, and is capable of revealing both the overall conformational dynamics and the atomic-level details inside the complex. The TOM complex is extremely dynamic and complicated, so Dr. Zheng's team will use specific substrates to arrest the complex in a series of stable states for such structural characterization. It is Dr. Zheng's expectation that determination of the three-dimensional structures of TOM, with or without substrates, will aid in understanding how TOM contributes to various disease conditions. The outcome of Dr. Zheng's proposal is expected to elucidate TOM-

TIM's unique architecture and structural rearrangements during substrate transport, and thereby suggest therapeutic targets for future drug development.