BIOGRAPHICAL SKETCH

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NAME: James Z. Chen

eRA COMMONS USER NAME (credential, e.g., agency login): CHENZHI

POSITION TITLE: Assistant Professor of Biochemistry and Molecular Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Jilin University, China	B.S.	06/1994	Physics
Florida State University	Ph.D.	12/2000	Physics
University of North Carolina, Chapel Hill	M.S.	10/2002	Computer Science
Brandeis University	Postdoctoral	10/2010	Biophysics
Massachusetts Institute of Technology	Research Scientist	10/2013	Biology

A. Personal Statement

My research focuses on molecular electron microscopy (EM), and high-resolution single-particle EM in particular. My research goal is to advance molecular EM imaging towards higher resolution and apply EM to molecular and cellular structure elucidation. The research topics in my lab comprise three mutually connected components:

High-Quality EM Data Acquisition Obtaining high-quality EM images is the starting point to achieve better resolution in 3D reconstruction. We have been developing novel imaging techniques to reduce beam-induced specimen damage and movement, to expedite the RCT data collection, and to enable "big data" (terabytes) acquisition and management.

High-Resolution EM Structural Analysis Intrinsically, molecular EM images contain very high noise. In order to retrieve the maximal amount of information from "an ocean of noise" we have been developing novel statistical algorithms for single-particle EM data analysis, from high-throughput particle screening, image CTF determination, to particle 2D classification and high-resolution 3D model reconstruction.

EM Structural Biology "Seeing is believing." Utilizing high-resolution molecular EM imaging, my lab has been investigating the structural detail of macromolecular assemblies of biological significance that include the DNA mismatch repair machinery and the membrane protein CFTR.

B. Positions and Honors

2010 – 2013 Research Scientist, Biology, Massachusetts Institute of Technology.
2013 – Present Assistant Professor, Department of Biochemistry and Molecular Biology, OHSU.

C. Contribution to Science

My multidisciplinary training in physics, biology and computer science has enabled me to embark on a career in EM structural biology. During my postdoctoral research in Dr. Nikolaus Grigorieff's lab at HHMI-Brandeis University, I investigated the structure of the rotavirus virion in collaboration with Dr. Stephen Harrison. Rotavirus is a non-enveloped, triple-layered dsRNA virus that is the major cause of

gastroenteritis in children. An electron-density map of the complete virus particle reconstructed at ~4Å resolution revealed detailed interactions between the capsid proteins and enabled de novo modeling of the virion spikes that interact with cellular receptors during cell entry. Moreover, the near-atomic structure has indicated a sophisticated conformational transition of the virion spike during the virus-cell interaction that resembles the rearrangement of membrane-fusion proteins of enveloped viruses.

JZ Chen*, EC Settembre*, ST Aoki, X Zhang, AR Bellamy, P Dormitzer, SC Harrison and N Grigorieff (2009). "Molecular interactions in rotavirus assembly and uncoating seen by high-resolution cryo-EM." PNAS 106: 10644-10648. (* Co-first authors)

EC Settembre*, JZ Chen*, PR Dormitzer, N Grigorieff and SC Harrison (2010). "Atomic model of an infectious rotavirus particle." EMBO J. 30(2): 408-416. (* Co-first authors)

My lab has recently determined the structure of inactive and active states of a thermally stabilized CFTR. These structures have revealed a unique repositioning of the transmembrane helices and regulatory domain density that provide insights into the structural transition between active and inactive functional states of CFTR. Moreover, we observe an extracellular vestibule that may provide anion access to the pore due to the conformation of transmembrane helices that differs from the previous orthologue CFTR structures. Our work contributes detailed structural information on an active, open state of the CFTR anion channel.

JF Fay, LA Aleksandrov, TJ Jensen, LL Cui, JN Kousouros, L He, AA Aleksandrov, DS Gingerich, JR Riordan and JZ Chen (2018). "Cryo-EM Visualization of an Active High Open Probability CFTR Anion Channel." Biochemistry, **57**(43):6234-6246.

In collaboration with Dr. Show-Ling Shyng's lab at Oregon Health & Science University, we have used single-particle cryo-EM to obtain the first sub-nanometer structure of the KATP channel. The structure has revealed a closed Kir6.2 tetrameric core with four peripheral SUR1s each anchored to a Kir6.2 by its N-terminal transmembrane domain (TMD0). This work lays the foundation for the ongoing research on the detailed mechanism of the channel activation and regulation.

Martin, G.M., C. Yoshioka, E.A. Rex, J. F. Fay, Q. Xie, M.R. Whorton, J.Z. Chen, and S.-L. Shyng (2017). "Cryo-EM structure of the ATP-sensitive potassium channel illuminates mechanisms of assembly and gating." eLife 2017;6:e24149. (DOI: 10.7554/eLife.24149)

As single-particle cryo-EM advances towards higher resolution, ever-increasing numbers of particles are needed for 3D model reconstruction. To overcome subjective bias in the time consuming process of manual annotation, I designed and implemented the program SIGNATURE to expedite the task of particle screening. This open-source program has been released to the research community and is being extensively used in the field. Also, by extending my graduate research in Dr. Michael Chapman's lab on real-space protein structural refinement in X-ray crystallography, I transported the methodology to the nanometer and sub-nanometer resolution realm typical of EM structures. This force-field-based, flexible-docking method has been successfully applied to EM structural analysis of large molecular machines, e.g., the arrangement of the protein FlgE in the flagellar hook, and a novel conformation in the core of Tobacco Mosaic Virus.

JZ Chen and N Grigorieff (2006). "SIGNATURE: A single-particle selection system for molecular electron microscopy." Journal of Structural Biology 157: 168-173.

JZ Chen, E Blanc and MS Chapman (1999). "*Real Space Molecular Dynamics Structural Refinement.*" Acta Crystallographica D55: 464-468.

JZ Chen, J Furst, MS Chapman and N Grigorieff (2003). "Low-Resolution Structure Refinement in Electron Microscopy." Journal of Structural Biology 144: 144-151.

To improve the quality of cryo-EM imaging for single-particle reconstruction to reach higher resolution, I

have also investigated the dose-rate effect and developed a low dose-rate imaging protocol, LINDA. This new method can reduce beam-induced specimen movement and secondary radiation damage from radiolysis of the embedding ice. LINDA is an integral component of the toolset for my current research in utilizing sparse tilt series and tomography to analyze heterogeneous molecular structures.

JZ Chen, C Sachse, C Xu, T Mielke, C Spahn and N Grigorieff (2007). "A Dose-Rate Effect in Single-Particle Electron Microscopy." Journal of Structural Biology 161: 92-100.

Complete List of Published Work in MyBibliography

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/46676690/?sort=date&direction=decending

D. Research Support

Ongoing Research Support

CHEN1710 (Chen) 07/01/2017-06/30/19
Cystic Fibrosis Foundation
Structural Elucidation of CFTR by High-Resolution Single Particle EM
Major Goal: CFTR is a unique member of the large ABC transporter family of membrane proteins that functions primarily as an epithelial anion channel, the dysfunction of which causes cystic fibrosis (CF) in humans. We propose to employ high-resolution single-particle EM to elucidate the structure basis of CFTR gating mechanism. Insights from such understanding will greatly facilitate structure-based drug design in developing effective CF therapeutics.
Role: PI

R01 DE014711 (Spatafora) 09/01/2017-08/31/22
NIH / Middlebury College
Investigating SloR Virulence Gene Metalloregulation in *Streptococcus Mutans*
Major Goal: *Streptococcus Mutans* is the causative agent of dental caries, for which the protein SloR is an important regulator of cariogenesis. We propose to elucidate the structure of SloR-DNA binding complex by single-particle cryo-EM.
Role: Site PI

Completed Research Support

R21 DA043001 (Farrens) 04/01/2017-03/31/2019
NIH / OHSU
Crystallization and Structural Analysis of the Human Cannabinoid Receptor CB1
Major Goal: The structure of CB1, the G-protein coupled receptor (GPCR) activated by marijuana, is still not known. Here we propose to generate CB1 crystals that can be used to solve the structure of CB1 by X-ray crystallography, and to study the interaction of purified CB1 with other proteins at a structural level using single particle electron microscopy (EM)
Role: Co-I

None (Chen) 10/01/2015-01/31/2017
Collins Medical Trust Award
Structure Elucidation of MRP1 by Single-Particle Electron Microscopy
Major Goal: To investigate the structural detail of MRP1 using high-resolution single particle electron cryo-microscopy.
Role: PI

None (Chen) 01/01/2016-12/31/2016
KCI – Albert and Elaine Borchard Foundation Early Investigator Award.
Structure Elucidation of MRP1 by Single-Particle Electron Microscopy
Major Goal: To investigate the structural detail of MRP1 using high-resolution single-particle electron cryo-microscopy.
Role: PI

None (Chen) 08/15/14-08/14/15
OCSSB Developmental Pilot Grant, OHSU
Advance Single-Particle Electron Microscopy to Atomic Resolution
Major Goal: To investigate super-resolution EM imaging technique and integrate the direct detector, phase plate and LINDA imaging technologies to advance single-particle EM to atomic resolution.
Role: PI