BIOGRAPHICAL SKETCH

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NAME: Ji Sun

eRA COMMONS USER NAME (credential, e.g., agency login): jisun2016

POSITION TITLE: Assistant member

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
University of Science and Technology of China	BS	07/2007	Life Science
Insititute of Biophysics, CAS	N/A	08/2008	Structure biology
University of Washington, Seattle	PHD	12/2013	Pharmacology
University of Washington, Seattle	N/A	06/2014	Structure Biology
The Rockefeller University	N/A	08/2019	Structure Biology

A. Personal Statement

My long-term career goal is to lead a research group that aims to dissect the cell signaling events at the molecular level, hoping that our research discovery could help understand human physiology and pathology and provide novel strategies for drug development. I started my training in structural biology since 2006 and my first project was to study the mitochondira uncoupling protein 1 (UCP1) in Dr. Dr. Fei Sun's laboratory, Institute of Biophysics, CAS. Dr. Fei Sun not only mentored me on how to design and carry out scientific research but also largely inspired my interests in the structural study of membrane proteins. After obtaining my B.S. degree, I continued to pursue my scientific career as a graduate student under the mentorship of Dr. Ning Zheng, University of Washington. My thesis research focused on a eukaryotic nitrate transporter protein, NRT1.1. I determined the first crystal structure of a nitrate transporter in higher organisms and revealed key residues that were important for substrate recognition and energy coupling for its transport activity. Most importantly, based on the structure discovery, I proposed a potential mechanism that could explain the dual-affinity activity of NRT1.1 regulated by a phosphorylation modification. This research further motivated me to continue my study on membrane protein functional modulation in Dr. MacKinnon's laboratory as a postdoctoral associate. My research focused on the molecular basis of the activation and modulation of the KCNQ1 channel. KCNQ1 plays a key role in cardiac function, and mutations of *kcnq1* can cause cardiac arrhythmias such as long-QT syndromes, short-QT syndromes, familial atrial fibrillation and even sudden death. As an important ion channel, the function of KCNQ1 is regulated by multiple factors such as calcium signaling (Ca^{2+}/CaM), lipids (PIP_2), posttranslational modifications (phosphorylation, ubiquitination, *etc.*), KCNE family of beta subunits and small molecules. My work revealed the cryoEM structures of KCNQ1 in different states: KCNQ1-CaM, KCNQ1-CaM-KCNE3, and KCNQ1-CaM-KCNE3 in the presence of PIP_2. In combination with biochemical, biophysical, and cell-based analyses, my work set the structural foundation for the interpretation of KCNQ1 function and disease mutations. It provided the framework needed for structure-based drug development.

As an independent investigator in St Jude Children's Research Hospital, I expand my research interest to understanding cell signaling events at the membrane interface. My lab strives to understand how signaling events are tuned spatially and temporally and how we can develop pharmacological tools to manipulate these signaling events to treat human diseases.

a. Zhou Q, **Sun J**, Zhai Y, and Sun F. Prokaryotic expression of active mitochondrial uncoupling protein 1. ***Progress in Biochemistry and Biophysics*.** 37(1): 56-62. 2010

b. **Sun J**, Bankston JR, Hinds TR, Payandeh J, Zagotta WN, and Zheng N. Crystal structure of the plant dual-affinity transporter NRT1.1. ***Nature***. 507(7490): 73-77. 2014 PMCID: PMC3968801

c. **Sun J** and MacKinnon R. Cryo-EM Structure of a KCNQ1/CaM Complex Reveals Insights into Congenital Long QT Syndrome. ***Cell***. 169(6):1042-1050. 2017. PMCID: PMC5562354

d. **Sun J** and MacKinnon R. Structural basis of human KCNQ1 modulation and gating. ***Cell.*** 180(2):340-347. 2020. PMCID: PMC7083075

e. **Sun J**. Structures of mouse DUOX1–DUOXA1 provide mechanistic insights into enzyme activation and regulation. ***Nature Structural & Molecular Biology*** 27:1086–1093, 2020. PMCID: PMC7644671

f. Myasnikov A, Zhu H, Hixson, P, Xie B, Yu K, Pitre A, Peng J, **Sun J**. Structural analysis of the full-length human LRRK2. ***Cell*** 184:3519–3527, 2021.

B. Positions and Honors

Positions and Employment

09/2006 – 07/2008	Research Assistant, Institute of Biophysics, CAS
09/2008 – 12/2013	Graduate Fellow, University of Washington
01/2014 – 06/2014	Postdoctoral Fellow, University of Washington
08/2014 – 08/2019	Postdoctoral Associate, The Rockefeller University
09/2019 – present	Assistant Member, St. Jude Children's Research Hospital

Honors and Awards

2003 – 2007	Outstanding Student Award, University of Science and Technology of China
01/2017 – 07/2018	Postdoctoral Fellowship, American Heart Association
2018	Rockefeller University PDA Career Development Award

C. Contributions to Science

Undergraduate Career

1. Recombinant expression and purification of the mitochondria uncoupling protein 1.

a. Zhou Q, **Sun J**, Zhai Y, and Sun F. Prokaryotic expression of active mitochondrial uncoupling protein 1. ***Progress in Biochemistry and Biophysics***. 37(1): 56-62. 2010

Graduate Career

1. Structure and function study of the plant dual-affinity transporter. My Ph.D. study focuses on the structural and functional study of a plant dual-affinity nitrate transporter that enables plants to absorb nitrate at various environmental concentrations. My work by determining the first crystal structure of the plant nitrate transporter, NRT1.1, reveals key residues that are important in nitrate recognition and energy coupling. NRT1.1 is captured as a homodimer in the crystal, which represents the first oligomer structure in the Major Facilitator Superfamily. More importantly, my structural and functional study on NRT1.1 reveals a potential mechanism on how posttranslational modifications and transporter oligomerization could be synchronized to modulate the transporter function.

a. **Sun J**, Bankston JR, Hinds TR, Payandeh J, Zagotta WN, and Zheng N. Crystal structure of the plant dual-affinity transporter NRT1.1. ***Nature***. 507(7490): 73-77. 2014 PMCID: PMC3968801

b. **Sun J** and Zheng N. Molecular Mechanism Underlying the Plant NRT1.1 Dual-Affinity Nitrate Transporter. ***Frontiers in Physiology***: 6(386) 2015 PMCID: PMC4683204

2. Recombinant expression and purification of a deubiquitinase complex for structural study.

a. Li H, Lim KS, Kim H, Hinds TR, Jo U, Mao H, Weller CE, **Sun J**, Chatterjee C, D'Andrea AD and Zheng N. Allosteric Activation of Ubiquitin-Specific Proteases by β-Propeller Proteins UAF1 and WDR20. ***Molecular Cell***. 63(2):249-260. PMCID: PMC4958508.

Postdoctoral Career

1. **Structure and function study of the pore-forming subunit of the slow delayed rectifier potassium channel complex.** My postdoctoral research aims to elucidate the molecular basis underlying the slow delayed rectifier current, whose molecular constitution is a channel complex formed by KCNQ1 and KCNE1. I have determined the high-resolution structure of KCNQ1 in complex with CaM by single-particle cryo-EM. The structure captured KCNQ1 in a "decoupled" conformation, which corresponds to the physiological PIP_2-free state. The structure also reveals a novel interface between KCNQ1 and CaM that holds mutations associated with long-QT syndromes. My study suggests that mutations in this novel interface could lead to change in the channel function and therefore cause cardiac arrhythmias.

   a. **Sun J** and MacKinnon R. Cryo-EM Structure of a KCNQ1/CaM Complex Reveals Insights into Congenital Long QT Syndrome. ***Cell***. 169(6):1042-1050. 2017. PMCID: PMC5562354

2. **Molecular mechanisms underlying human KCNQ1 modulation and gating.** KCNQ1 is modulated by KCNEs (KCNE1-5), a family of single transmembrane proteins that function as beta subunits of potassium channels. KCNQ1 and KCNQ1-KCNE complexes are also gated by a key signaling lipid, PIP2. By determining the cryo-EM structure of human KCNQ1-KCNE3 both in the presence and absence of PIP2, my work reveals the gating mechanism of KCNQ1 and provides a structural framework for understanding KCNQ1 modulation by KCNEs.

   a. **Sun J** and MacKinnon R. Structural basis of human KCNQ1 modulation and gating. ***Cell***. 180(2):340-347. 2020. PMCID: PMC7083075

Independent Career

1. **Structural analysis of NADPH oxidases.** NADPH oxidases, which produce ROS, are key players in ROS homeostasis. My lab determined the first eukaryotic NADPH oxidase, providing molecular basis for understanding the catalytic nature and regulation mechanisms of this vital enzyme family.

   a. **Sun J.** Structures of mouse DUOX1–DUOXA1 provide mechanistic insights into enzyme activation and regulation. ***Nature Structural & Molecular Biology*** 27:1086–1093, 2020. PMCID: PMC7644671

2. **Structural analysis of the full-length human LRRK2.** LRRK2 is a large multidomain protein kinase, whose mutation is the leading cause of genetic and sporadic Parkinson's disease. Most of PD mutations in LRRK2 show increased kinase activity, and therefore, LRRK2 inhibitors are of great pharmaceutical significance. My lab determined the first full-length LRRK2 structure in an inactive state, providing a structural framework for drug discovery.

   a. Myasnikov A, Zhu H, Hixson, P, Xie B, Yu K, Pitre A, Peng J, **Sun J**. Structural analysis of the full-length human LRRK2. ***Cell*** 184:3519–3527, 2021.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIH: R00HL143037 (PI: Sun, Ji) 07/12/2018-12/31/2022

"Structural and pharmacological study of the KCNQ1/KCNE1 potassium channel complex."

NIH: R01GM141357 (PI: Sun, Ji) 04/01/21 – 03/31/2026

Molecular Mechanisms Underlying Mammalian NADPH Oxidase Activation and Regulation

BIOGRAPHICAL SKETCH

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NAME: Chenxi Cui

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

POSITION TITLE: Postdoc Associate

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
Shanxi Agricultural University, Jinzhong, China	BS	07/2014	Animal Quarantine
China Agricultural University, Beijing, China	MS	07/2017	Preventive veterinary medicine
University of Chinese Academy of Sciences, Beijing, China	PHD	07/2021	Structure Biology

A. Personal Statement

My research experience and academic training provided me with a good background in multiple biological disciplines including biochemistry, biophysics, virology, and molecular biology. As an Ph.D. candidate, I conducted research under supervision of Dr. Xinzheng Zhang on the cryo-EM studies of virus structure, virus entry and virus neutralizing. My research focused on the structural assembly and the mechanism of nucleic acids release of a rare T4 virus, LSV. I was the co-first author to determine the cryo-EM structures of native virion and empty particle of LSV. In the meanwhile, I also elucidated the alphavirus assembly mechanism by the cryo-EM structure of Getah Virus. The resolving of the GETV structure provided new insights into the structure and assembly of alphaviruses and lays a basis for studying the differences of biology and pathogenicity between arthritogenic and encephalitic alphaviruses. Also, we developed a new, fast and quantifiable method to analyze the stability of purified FCV virions with the application of cryo-EM. Finally, I participated in a project to indicate the rapid and divergent evolution of mycoplasma enolase and mycoplasmas. Through these projects, I gained expertise in the single particle analysis (SPA) of cryo-EM. Structural information shed light on molecular interaction details that can guide drug target and antibodies design.

1. Wang, M., Sun, Z., **Cui, C**., Wang, S., Yang, D., Shi, Z., ... & Wang, J. (2022). Structural Insights into Alphavirus Assembly Revealed by the Cryo-EM Structure of Getah Virus. *Viruses*, *14*(2), 327.
2. Qu, Z., Kang, H., Cui, C., Meng, K., Zhang, X., Qu, L., ... & Meng, G. (2022). Purification-induced damage to calicivirus particles at near-atomic resolution. Journal of General Virology, 103(5), 001742.
3. Chen, R., Zhao, L., Gan, R., Feng, Z., Cui, C., Xie, X., ... & Shao, G. (2021). Evidence for the Rapid and Divergent Evolution of Mycoplasmas: Structural and Phylogenetic Analysis of Enolases. Frontiers in molecular biosciences, 8.

B. Positions and Honors

Positions and Employment

2021- Postdoc Associate, St Jude Children's Research Hospital

C. Contributions to Science

My graduate research contributions focused on the cryo-EM studies of virus structure, virus entry and virus neutralizing. The application of different purification processes may affect the quality of the virus particles, such as structural integrity and homogeneity, which may further influence the infectivity and immunogenicity of the purified virus. Results from our research showed that molecular sieving purification will impact the stability of protrude domains through increasing flexibility as determined by cryo-EM SPA. The purification of virus particles is an essential process for the manufacture of vaccines. In a subsequent publication, we succeeded in purifying the Getah Virus. As a large family, alphaviruses show great diversities in host tropism, genetics, pathogenicity, and other biological characteristics, and the structure of GETV has not yet been determined. Finally, we resolve the cryo-EM structure of an arthritogenic alphavirus GETV to a resolution of 3.5 Å. This study provides a structural basis for further exploring the biological differences among alphaviruses. My main role was to determine the structure and process data. All these research results showed clear structural maps for viruses, which could guide the target for drug or epitope for antibodies.

1. Wang, M., Sun, Z., **Cui, C**., Wang, S., Yang, D., Shi, Z., ... & Wang, J. (2022). Structural Insights into Alphavirus Assembly Revealed by the Cryo-EM Structure of Getah Virus. *Viruses*, *14*(2), 327.
2. Qu, Z., Kang, H., **Cui, C**., Meng, K., Zhang, X., Qu, L., ... & Meng, G. (2022). Purification-induced damage to calicivirus particles at near-atomic resolution. *Journal of General Virology*, *103*(5), 001742.