BIOGRAPHICAL SKETCH

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NAME: Zhao, Minglei

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

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)	END DATE MM/YYYY	FIELD OF STUDY
Fudan University, Shanghai	BS	06/2005	Biological Sciences
University of California Los Angeles, Los Angeles, California	PHD	06/2011	Molecular Biology
Stanford University, Stanford, California	Postdoctoral Fellow	12/2016	Structural Biology / Biophysics

A. Personal Statement

As a structural biology lab, we are interested in understanding the mechanism of molecular machines and their roles in human diseases. Currently we focus on two systems, p97 / ubiquitination system, and vault. p97 is a central hub in cellular protein homeostasis. It is involved in several neurodegenerative diseases, and is also a cancer drug target. We want to gain insights into the molecular architectures of p97 in complex with various adaptor proteins and poly-ubiquitinated substrates. We are investigating the preference of p97 towards specific ubiquitin chains. Our findings will nurture new approaches to tackle the diseases. Vault is the largest ribonuclear protein in many eukaryotes including human. It can be regarded as a membraneless organelle. Despite the fact that vault has been studied for thirty years, the function of vault remains elusive. Overexpression of major vault protein (MVP) correlates with drug resistance in cancer cells. However, the mechanism is completely unknown at the molecular level. We are investigating the structures of vault components and using proteomic and imaging techniques to address the molecular function of vault. There are two major techniques used in the lab: X-ray crystallography and cryo-electron microscopy. Throughout my graduate and postdoc research, I have got extensive training in both techniques. Combining the two techniques will enable us to elucidate the molecular mechanism of p97 and vault.

1. Zhou Q, Zhou P, Wang AL, Wu D, Zhao M, Südhof TC, Brunger AT. The primed SNARE-complexin-synaptotagmin complex for neuronal exocytosis. Nature. 2017 Aug 24;548(7668):420-425. PubMed PMID: 28813412; PubMed Central PMCID: PMC5757840.
2. Zhou Q, Lai Y, Bacaj T, Zhao M, Lyubimov AY, Uervirojnangkoorn M, Zeldin OB, Brewster AS, Sauter NK, Cohen AE, Soltis SM, Alonso-Mori R, Chollet M, Lemke HT, Pfuetzner RA, Choi UB, Weis WI, Diao J, Südhof TC, Brunger AT. Architecture of the synaptotagmin-SNARE machinery for neuronal exocytosis. Nature. 2015 Sep 3;525(7567):62-7. PubMed PMID: 26280336; PubMed Central PMCID: PMC4607316.
3. Diao J, Liu R, Rong Y, Zhao M, Zhang J, Lai Y, Zhou Q, Wilz LM, Li J, Vivona S, Pfuetzner RA, Brunger AT, Zhong Q. ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes. Nature. 2015 Apr 23;520(7548):563-6. PubMed PMID: 25686604; PubMed Central PMCID: PMC4442024.
4. Zhao M, Wu S, Zhou Q, Vivona S, Cipriano DJ, Cheng Y, Brunger AT. Mechanistic insights into the recycling machine of the SNARE complex. Nature. 2015 Feb 5;518(7537):61-7. PubMed PMID: 25581794; PubMed Central PMCID: PMC4320033.

B. Positions and Honors

Positions and Employment

2012 - 2014	Postdoctoral Associate, Stanford University, Stanford, CA
2014 - 2016	Research Associate, Howard Hughes Medical Institute, Stanford, CA
2017 -	Assistant Professor of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL

Other Experience and Professional Memberships

2010 -	Member, American Crystallographic Association
2014 -	Member, Biophysical Society

Honors

2009	Philip J. Whitcome Fellowship, University of California Los Angeles
2010	Dissertation Year Fellowship, University of California Los Angeles

C. Contribution to Science

1. Structural studies of amyloid-forming proteins and peptides

   I studied structures of amyloid proteins and peptides using X-ray crystallography as a major technique for my graduate research. Many neurodegenerative diseases are associated with deposition of insoluble plaques of amyloid proteins including the well-known Alzheimer's disease and Parkinson's disease. Elucidating the structures of these plaques is of central importance to understand the etiology of the diseases and to develop drugs for treatment. Insoluble fibrils and soluble oligomers had both been proposed to be the toxic species, but the structural information at atomic level was elusive. The publications listed below provide atomic-resolution models of fibrils and oligomers, revealing structural relationship between the two species and possible pathways of conversion.

   a. Luo F, Gui X, Zhou H, Gu J, Li Y, Liu X, Zhao M, Li D, Li X, Liu C. Atomic structures of FUS LC domain segments reveal bases for reversible amyloid fibril formation. Nat Struct Mol Biol. 2018 Apr;25(4):341-346. PubMed PMID: 29610493.
   b. Liu C, Zhao M, Jiang L, Cheng PN, Park J, Sawaya MR, Pensalfini A, Gou D, Berk AJ, Glabe CG, Nowick J, Eisenberg D. Out-of-register β-sheets suggest a pathway to toxic amyloid aggregates. Proc Natl Acad Sci U S A. 2012 Dec 18;109(51):20913-8. PubMed PMID: 23213214; PubMed Central PMCID: PMC3529048.
   c. Colletier JP, Laganowsky A, Landau M, Zhao M, Soriaga AB, Goldschmidt L, Flot D, Cascio D, Sawaya MR, Eisenberg D. Molecular basis for amyloid-beta polymorphism. Proc Natl Acad Sci U S A. 2011 Oct 11;108(41):16938-43. PubMed PMID: 21949245; PubMed Central PMCID: PMC3193189.
   d. Zhao M, Cascio D, Sawaya MR, Eisenberg D. Structures of segments of α-synuclein fused to maltose-binding protein suggest intermediate states during amyloid formation. Protein Sci. 2011 Jun;20(6):996-1004. PubMed PMID: 21462277; PubMed Central PMCID: PMC3104229.

2. Structural studies of protein complexes involved in vesicle and membrane fusion

   I studied structures of protein complexes involved in vesicle and membrane fusion for my postdoctoral research. Vesicle and membrane fusion are essential for many physiological processes in eukaryotic cells, including protein trafficking, hormone secretion, and neurotransmitter release. The publications represent the efforts to elucidate the mechanisms of these intricate machineries using either X-ray crystallography or single-particle cryo-EM as the major technique. The structures of full-length NSF (N-ethylmaleimide sensitive factor) and its complex with adaptor and substrate proteins (20S supercomplex) are considered as a milestone in a long history of structural studies in this field. It is actually the first time that a protein-disassembling machine has been visualized with its substrate at near-atomic to sub-nanometer resolutions. It also demonstrated a striking molecular asymmetry of AAA+ ATPases which are regarded as homohexamer and are usually modeled as six-fold symmetric. Besides NSF and 20S supercomplex, I also

made key contributions to the studies of synaptotagmin-SNARE complex and autophagic SNARE complex, which are important protein machinery involved in neurotransmission and autophagy.

a. Zhou Q, Zhou P, Wang AL, Wu D, Zhao M, Südhof TC, Brunger AT. The primed SNARE-complexin-synaptotagmin complex for neuronal exocytosis. Nature. 2017 Aug 24;548(7668):420-425. PubMed PMID: 28813412; PubMed Central PMCID: PMC5757840.
b. Zhou Q, Lai Y, Bacaj T, Zhao M, Lyubimov AY, Uervirojnangkoorn M, Zeldin OB, Brewster AS, Sauter NK, Cohen AE, Soltis SM, Alonso-Mori R, Chollet M, Lemke HT, Pfuetzner RA, Choi UB, Weis WI, Diao J, Südhof TC, Brunger AT. Architecture of the synaptotagmin-SNARE machinery for neuronal exocytosis. Nature. 2015 Sep 3;525(7567):62-7. PubMed PMID: 26280336; PubMed Central PMCID: PMC4607316.
c. Diao J, Liu R, Rong Y, Zhao M, Zhang J, Lai Y, Zhou Q, Wilz LM, Li J, Vivona S, Pfuetzner RA, Brunger AT, Zhong Q. ATG14 promotes membrane tethering and fusion of autophagosomes to endolysosomes. Nature. 2015 Apr 23;520(7548):563-6. PubMed PMID: 25686604; PubMed Central PMCID: PMC4442024.
d. Zhao M, Wu S, Zhou Q, Vivona S, Cipriano DJ, Cheng Y, Brunger AT. Mechanistic insights into the recycling machine of the SNARE complex. Nature. 2015 Feb 5;518(7537):61-7. PubMed PMID: 25581794; PubMed Central PMCID: PMC4320033.

3. Elucidating the mechanism of synaptic vesicle fusion

I contributed to the mechanistic study of synaptic vesicle fusion using single-molecule fluorescence microscopy techniques.

a. Lai Y, Choi UB, Leitz J, Rhee HJ, Lee C, Altas B, Zhao M, Pfuetzner RA, Wang AL, Brose N, Rhee J, Brunger AT. Molecular Mechanisms of Synaptic Vesicle Priming by Munc13 and Munc18. Neuron. 2017 Aug 2;95(3):591-607.e10. PubMed PMID: 28772123; PubMed Central PMCID: PMC5747255.
b. Lai Y, Choi UB, Zhang Y, Zhao M, Pfuetzner RA, Wang AL, Diao J, Brunger AT. N-terminal domain of complexin independently activates calcium-triggered fusion. Proc Natl Acad Sci U S A. 2016 Aug 9;113(32):E4698-707. PubMed PMID: 27444020; PubMed Central PMCID: PMC4987820.
c. Choi UB, Zhao M, Zhang Y, Lai Y, Brunger AT. Complexin induces a conformational change at the membrane-proximal C-terminal end of the SNARE complex. Elife. 2016 Jun 2;5PubMed PMID: 27253060; PubMed Central PMCID: PMC4927292.
d. Diao J, Cipriano DJ, Zhao M, Zhang Y, Shah S, Padolina MS, Pfuetzner RA, Brunger AT. Complexin-1 enhances the on-rate of vesicle docking via simultaneous SNARE and membrane interactions. J Am Chem Soc. 2013 Oct 16;135(41):15274-7. PubMed PMID: 24083833; PubMed Central PMCID: PMC3854000.

4. Methods development for crystallography

I contributed to the methods development for crystallography. In particular, I developed new approaches to crystalize proteins and new data processing tools for serial crystallography.

a. Lyubimov AY, Uervirojnangkoorn M, Zeldin OB, Zhou Q, Zhao M, Brewster AS, Michels-Clark T, Holton JM, Sauter NK, Weis WI, Brunger AT. Advances in X-ray free electron laser (XFEL) diffraction data processing applied to the crystal structure of the synaptotagmin-1 / SNARE complex. Elife. 2016 Oct 12;5PubMed PMID: 27731796; PubMed Central PMCID: PMC5094853.
b. Zeldin OB, Brewster AS, Hattne J, Uervirojnangkoorn M, Lyubimov AY, Zhou Q, Zhao M, Weis WI, Sauter NK, Brunger AT. Data Exploration Toolkit for serial diffraction experiments. Acta Crystallogr D Biol Crystallogr. 2015 Feb;71(Pt 2):352-6. PubMed PMID: 25664746; PubMed Central PMCID: PMC4321488.
c. Laganowsky A, Zhao M, Soriaga AB, Sawaya MR, Cascio D, Yeates TO. An approach to crystallizing proteins by metal-mediated synthetic symmetrization. Protein Sci. 2011 Nov;20(11):1876-90. PubMed PMID: 21898649; PubMed Central PMCID: PMC3267952.

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

Ongoing Research Support

C-086, Chicago Biomedical Consortium
Zhao, Minglei (Co-PI)
03/01/18-02/29/20
Observing Protein Allostery Dynamics By Single-Particle Imaging
Role: Co-PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Chang Liu

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

POSITION TITLE: Graduate Student Research Assistant

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
Wuhan University	B.S.	06/2016	Chemistry
The University of Chicago	M.S.	12/2017	Chemistry
The University of Chicago	Ph.D	06/2022	Chemistry

A. Personal Statement

My long term research interests involve the structural determination of the proteins associated with human diseases. I have joined Prof. Minglei Zhao's Lab for three years to learn the techniques of X-ray crystallography and single-particle cryogenic-electron microscopy (cryo-EM). In the first two years, I was devoted to the structural determination and functional study of Eled, which can serve as a drug target for *Schistosomiasis*. I co-authored a paper about Eled published on eLife with Dr. Bo Wang's lab in Stanford University. The findings are of central importance to develop new drugs for *Schistosomiasis* and reduce parasite burdens. Currently, I focus on METTL3-METTL14 complex, which is an enzyme specifically catalyzing methylation to form N^6-methyladenosine (m^6A). Disruption of METTL3-METTL14 methylation process is a highly attractive target for drug development in diseases like cancers and HIV. My goal is to use single particle cryo-EM as the major technique to determine the structure of METTL3-METTL14 complex, and the supercomplex of METTL3-METTL14 containing mRNA and the co-factor *S*-(5'-adenosyl)-L-methionine (AdoMet). These structures will elucidate the molecular mechanism of how METTL3-METTL14 catalyzes m^6A transfer. My academic training and research experience have provided me with knowledge and skills in biochemistry and structural biology, such as protein purification, X-ray crystallography, negative staining electron microscopy, cryogenic-electron microscopy, etc. With these techniques, I will be able to elucidate the molecular mechanism of METTL3-METTL14.

B. Positions and Honors

Positions and Employment

2016 - 2017 Teaching Assistant, The University of Chicago
2017 - Graduate Student Research Assistant, The University of Chicago

Honors

2014 Principle Wang Xinggong Scholarship, Wuhan University
2014 First-class scholarship for Hongyi Class, Wuhan University
2015 Scholarship of Dalian Institute of Chemical Physics, Wuhan University

2015 The first prize for “Chemistry Seminar of Undergraduates from Key Universities” , Wuhan University

C. Contributions to Science

1. Eled

I studied structure and function of Eled, a putative nuclear receptor involved in the development of *Schistosomiasis*, during the first two years. Schistosomes, the pathogen of *Schistosomiasis*, are able to infect and reproduce in human beings, and thus, cause severe damage to human health. Although treatments of *Schistosomiasis* have been developed for centuries, there are still some problems with the currently most common drug, praziquantel. Praziquantel only works on adult worms, not juveniles, whose migration process can cause organ lesions, especially in lungs. Therefore, identification of a new drug target for juveniles is urgent for *Schistosomiasis* treatment. The paper which I co-authored with Dr. Bo Wang’s lab indicates that Eled is specific to juvenile/adult schistosomes, and it is highly expressed in productive organs in juveniles, including primordial testes, ovaries, and vitellaria. Structurally, small-angle X-ray scattering indicated that Eled is a protein with elongated shape. Functionally, Eled is found to inhibit germ cell differentiation of schistosomes, and it is identified as the earliest marker for the schistosome germline. In conclusion, considered its specificity to juveniles and its function in schistosomes, Eled is of great importance for the development of schistosomes and can serve as a drug target for *Schistosomiasis*.

Wang, B., Lee, J., Li, P., Saberi, A., Yang, H., **Liu, C.,** Zhao, M., Newmark, P. A. (2018). Stem cell heterogeneity drives the parasitic life cycle of Schistosoma mansoni. *ELife*, *7*. https://doi.org/10.7554/eLife.35449

2. METTL3-METTL14

My ongoing project is to determine the structure of an RNA methyltransferase complex, METTL3-METTL14, by cryo-EM. METTL3-METTL14 is associated with many diseases, including type 2 diabetes, cardiovascular disease, cancers, and HIV. Elucidating the structure of METTL3-METTL14 is critical to understand its role in these diseases and how it can serve as a drug target. Although the catalytic methyltransferase domain of METTL3-METTL14 bound with AdoMet has been crystallized, it still cannot explain how METTL3-METTL14 catalyzes m^6A transfer. Currently, I am working on the full-length structure of METTL3-METTL14 bound with AdoMet and RNA, which will elucidate how METTL3-METTL14 binds and modifies mRNA. For now, I have developed a protocol for the purification for METTL3-METTL14, and have collected a dataset on Talos™ transmission electron microscope of this complex.

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

Scholastic Performance

Year	Course Title	Grade
	Wuhan University	
2012	Advanced Mathematics E1	A
2012	Inorganic Chemistry 1	A
2013	College Physics B1	A
2013	Analytical Chemistry 1	A
2013	Analytical Chemistry Seminar 1	A
2013	Advanced Mathematics J2	A
2013	Inorganic Chemistry Seminar 2	B+
2013	College Physics B2	A

2013	Introduction to Life Science	B+
2013	Physical Chemistry 1	B+
2013	Physical Chemistry Seminar 1	A
2013	Organic Chemistry Seminar 1	A
2014	Structural Chemistry	A
2014	Physical Chemistry 2	A
2014	Physical Chemistry Seminar 2	A
2014	Organic Chemistry 2	A
2014	Organic Chemistry Seminar 2	A
2014	Analytical Chemistry 2	A
2014	Analytical Chemistry Seminar 2	A
2014	Structural Chemistry Seminar	A
2014	Molecular Simulation Experiment	A
2014	Organic Spectrum Analysis	B+
2014	Organic Synthesis Chemistry	B+
2014	Biochemistry	A
2014	Bioinorganic chemistry	A
2014	Organic Chemistry 1	B+
2015	Introduction to Polymer Science	A
2015	Inorganic Chemistry 2	A
	The University of Chicago	
2016	Materials Chemistry 1	A-
2016	Wave Mechanics/ Spectroscopy	B+
2016	Chemical Biology 1	B-
2016	Advanced Training for Teachers and Researchers in Chemistry	P
2017	Quantum Mechanics	A
2017	Synthesis & Physical Methods in Inorganic Chemistry	B+
2017	Materials Chemistry 2	B+
2017	Protein Fundamentals	B+