BIOGRAPHICAL SKETCH

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NAME: Zheng, Hongjin

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

POSITION TITLE: Associate Professor of Biochemistry & Molecular Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, including 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 & Technology of China	B.S.	06/2004	Biological Sciences
University of Washington, Seattle	Ph.D.	08/2009	Biochemistry, Biomolecular Structure & Design
University of Washington, Seattle	Postdoctoral	11/2011	Biochemistry & Biophysics
Janelia Research Campus, Howard Hughes Medical Institute	Postdoctoral	07/2015	Biochemistry & Biophysics

A. Personal Statement

My role in this proposal is that of PD/PI. My research aims to understand the molecular mechanisms of various essential membrane proteins by studying their structure-function relationship. Such research has implications for many human diseases and could ultimately facilitate corresponding drug development. I use multidisciplinary tools toward this goal, including protein biochemistry, biophysics, structural biology, and computational biology. My extensive interdisciplinary training in these approaches has prepared me well for this pursuit.

I started my career as a cryo-electron microscopist (cryo-EM), working on the structural characterization of a bacteriophage DNA portal by single particle reconstruction. As a postdoctoral fellow, I initiated structural and functional studies of several bacterial membrane transporters using interdisciplinary approaches involving cryo-EM electron diffraction and X-ray crystallography. In my laboratory at the University of Colorado, I have created an independent research program focusing on disease-related membrane proteins. For example, we have discovered an unusual protein receptor for the mitochondrial accumulation of amyloid beta peptides, which may lead to a better understanding of the mitochondrial dysfunction in Alzheimer's. For the first time, we have revealed the intact sensor domain of an MscS-like mechanosensitive channel YnaI. Recently, we have determined high-resolution structures of multiple siderophore-Fe^{3+} importers by Cryo-EM, contributing novel structural/functional information to the scientific understanding of ABC transporters. Last but not least, our work on the human solute carriers has provided a better understanding of why specific pathogenic mutations cause genetic disorders.

I have also contributed significantly to the scientific community by providing my service. Besides regular mentoring and committee duties, I served on the School of Medicine Faculty Senate in the university for three years, promoting efficient communications between faculty members and school leadership. I am heavily involved in local outreach programs, providing research opportunities to local high school and undergraduate students. I served as a peer reviewer for many prestigious scientific journals. In addition, I served on multiple regional, national, and international grant peer review panels, including the Cancer League of Colorado, Alzheimer's Association, NIH study sections, and Agence Nationale De La Recherche (France).

Ongoing and recently completed projects that I would like to highlight include the following:

R01 HL168686
Zheng (PI)
02/01/2024 - 01/31/2028
Mechanistic studies of human transporter Sialin
Brief description: The grant aims to study the detailed molecular mechanisms of the sialic acid transporter sialin and its physiological roles in cardio biology.

R01 AI177445
Zheng (PI)
07/17/2024 - 05/31/2029
Molecular Mechanism of an Exporter-like ABC Importer YbtPQ
Brief description: This project studies the detailed structure-function relationship of a yersiniabactin importer from uropathogenic *E.coli*, which is the main cause of human urinary tract infections.

R35 GM151970
Zheng (PI)
09/01/2024 - 08/31/2029
Mechanistic studies of essential membrane transporters
Brief description: This project is to study the structure-function relationship of various membrane transporters related to human health.

B. Positions, Scientific Appointments, and Honors
Positions and Scientific Appointments

2022-	Associate Professor, Department of Biochemistry & Molecular Genetics University of Colorado, Anschutz Medical Campus, School of Medicine, Aurora, CO
2015-2022	Assistant Professor, Department of Biochemistry & Molecular Genetics University of Colorado, Anschutz Medical Campus, School of Medicine, Aurora, CO
2016-2019	Boettcher Investigator, Boettcher Foundation, Denver, CO
2011-2015	Research Specialist, Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA
2009-2011	Senior Fellow, University of Washington, Seattle, WA

Honors and Awards

2016	Webb-Waring Biomedical Research Award, Boettcher Foundation, Denver, CO
2008	Schultz Graduate Fellowship, University of Washington, Seattle, WA

C. Contributions to Science

1. **Unexpected receptor for mitochondrial uptake of amyloid beta peptides.** The mitochondrial accumulation of intracellular amyloid-β(Aβ) peptides in the brains of individuals with Alzheimer's disease is highly toxic because Aβ disrupts the normal functions of many mitochondrial proteins, resulting in significant mitochondrial dysfunction. However, little is known about how this accumulation happens. We have discovered that a noncanonical receptor specifically recognizes Aβ within the mitochondrial inner membrane, named Tom22 in yeast or TOMM22 in humans. This recognition is critical for the Aβ accumulation in mitochondria. This work confirms that yeast mitochondria can be used as a model to study mitochondrial dysfunction caused by Aβ in Alzheimer's and paves the way for future studies of the molecular mechanism of mitochondrial Aβ accumulation.

- Hu W, Wang Z and **Zheng H***. Mitochondrial accumulation of amyloid beta (Aβ) peptides requires TOMM22 as a main Aβ receptor in yeast. *J Biol Chem. 2018 Aug 17;293(33):12681-12689*

2. **Unique characterizations of siderophore ABC importers.** To fight for essential metal ions, human pathogens secrete virulent siderophores and reuptake the metal-chelated siderophores through a subfamily of

ATP-binding cassette (ABC) importers, whose molecular mechanisms are mostly unknown. We have determined multiple structures of the yersiniabactin-Fe^{3+} importer YbtPQ from uropathogenic *E. coli* in the inward-facing conformation in both apo and substrate-bound states by cryo-EM. Surprisingly, YbtPQ adopts the fold of type IV ABC exporters, the first example of exporter-like importers ever documented for ABC transporters. The structures also suggest that, after import, the substrate is released by unwinding a transmembrane helix in YbtP, which is also unique in ABC transporters. Furthermore, we have studied the ferrichrome importer FhuCDB (type II ABC importer) from the same pathogenic strain. FhuCDB structure reveals an exciting arrangement of residues in the substrate translocation pathway, including a continuous ladder of Met residues that might be responsible for the substrate translocation. This feature might be expected in other siderophore ABC importers.

- Wang Z, Hu W, and **Zheng H***. Pathogenic siderophore ABC importer YbtPQ adopts a surprising fold of exporter. *Sci Adv. 2020 Feb 5;6(6): eaay7997.*
- Thomas C, Aller SG, …, **Zheng H**, Zimmer J, and Tampé R. Structural and functional diversity calls for a new classification of ABC transporters. *FEBS Lett. 2020 Dec;594(23):3767-3775.*
- Hu W and **Zheng H***. Cryo-EM Structure of a Ferrichrome Importer FhuCDB. *Commun Biol. 2021 Dec 9;4(1):1383.*
- Hu W, Parkinson C, Zheng H. Mechanistic Insights Revealed by YbtPQ in the Occluded State. *Biomolecules. 2024 Mar 8;14(3).*

3. **Inhibitory mechanism revealed by IgA1 protease structures.** Pathogenic bacteria, including *Streptococcus pneumoniae* and *Gemella Haemolysans,* secrete a giant metalloprotease called IgA1 protease to cleave the host IgA1. Yet, the molecular mechanism remains unknown for nearly 30 years despite the potential for developing vaccines that target these enzymes to block the infection. We determined multiple cryo-EM structures of the IgA1 proteases to understand how they facilitate IgA1 substrate binding and how antibodies can inhibit it. These structures explain decades of biological and biochemical studies and provide a general strategy to potentially block the IgA1 protease activity to prevent related bacterial infections.

- Wang Z, Rahkola J, Redzic JS, Chi YC, Tran N, Holyoak T, **Zheng H***, Janoff E*, and Eisenmesser E*. Mechanism and inhibition of Streptococcus pneumoniae IgA1 protease. *Nat Commun. 2020 Nov 27;11(1):6063.*
- Redzic JS, Rahkola J, Tran N, Holyoak T, Lee E, Martin-Galiano AJ, Meyer N, **Zheng H***, and Eisenmesser E*. A substrate-induced gating mechanism is conserved among gram-positive IgA1 metalloproteases. *Commun Biol. 2022 Nov; 5: 1190.*

4. **Lipid-bound extended sensor paddle in YnaI.** Extensive studies on a small conductance channel MscS from *E. coli* have characterized the general mechanism of bacterial mechanosensitive channels. However, recent structural studies have revealed controversial roles of surrounding lipids in MscS channel gating depending on their specific locations. To shed light on that, we have determined the high-resolution structure of an MscS-like channel called YnaI from *E. coli*, which exhibits an extended paddle domain in the membrane with apparent lipid densities buried in the pockets. Together with biochemical data, our results support that the lipids in paddle pockets are functionally crucial for mechanosensitive channels.

- Hu W, Wang Z, and **Zheng H***. Mechanosensitive channel YnaI has lipid-bound extended sensor paddles. *Commun Biol*. *2021 May 20;4(1):602.*

5. **SLC structures provide plausible explanations for pathogenic mutations.** Although the human solute carrier (SLC) superfamily is the second largest superfamily among membrane proteins, it is the most under-studied group in the literature, highlighting a significant knowledge gap. How pathogenic mutations of SLC cause severe diseases has yet to be well understood because of the lack of structural information. We have determined the high-resolution structures of SLC17A5 and SLC26A2 for the first time, both in the inward-facing state. These structures explain why specific pathogenic mutations lead to dysfunctional substrate transport. Our work represents a significant conceptual advance in the field of human transporters. The results could shed light on potential pharmaceutical development to restore the function of these transporters in patients.

- Hu W and **Zheng H***. The molecular mechanism of sialic acid transport mediated by Sialin. *Sci Adv 9, eade8346 (2023)*
- Hu W, Song A, and **Zheng H***. Substrate binding plasticity revealed by cryo-EM structures of SLC26A2. *Nat Commun. 2024 Apr 29;15(1):3616*

***** Corresponding Author

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/hongjin.zheng.1/bibliography/public/