BIOGRAPHICAL SKETCH

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NAME: Zhou, Ming

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

POSITION TITLE: Professor

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
Fudan University, Shanghai, China	B.S.	07/1990	Biochemistry
State University of New York at Buffalo, New York	Ph.D.	07/1999	Biophysics
Rockefeller University, New York	Postdoctoral	07/2004	Biophysics

A. Personal Statement

My research focuses on structure and function of membrane-embedded proteins with the goals of visualizing these proteins in their different functional states and elucidating their mechanisms in terms of physical and chemical basis of protein functions. Since the target proteins that we study are involved in important physiological or pathophysiological processes, my work also helps establish structural frameworks for analyzing their functions in the cell and for developing new therapeutic reagents that target these proteins.

a. Levin, E.J., Quick, M., Zhou, M. (2009). Crystal structure of a bacterial homologue of the kidney urea transporter. ***Nature;*** 462(7274): 757-761. PMC2871279.
b. Cao Y., Pan Y., Huang H., Jin X., Levin EJ, Kloss B., and Zhou M. (2013). Gating of the TrkH ion channel by its associated RCK protein, TrkA. ***Nature;*** 496 (7445):317-321. PMC3726529
c. Zhou X., Levin E.J., Pan Y., McCoy, J.G., Sharma R., Kloss B., Bruni R., Quick M., Zhou M. (2014). Structural basis of the alternating-access mechanism in a bile acid transporter. ***Nature****;* Vol 505: 569-573. PMC4142352
d. Bai, Y., McCoy, J.G., Levin, E.J., Sobrado, P., Rajashankar, K.R., Fox, B.G., Zhou, M. (2015) X-ray structure of a mammalian stearoyl-CoA desaturase. ***Nature;*** Vol 524: 252-256. PMC4689147

B. Positions and Honors

Positions and Employment

Aug 2004 – Aug 2012: Assistant Professor and then Associate Professor, Department of Physiology & Cellular Biophysics, Columbia University, New York, NY

Jan 2014 – Dec 2018: Senior Investigator, Kunming Institute of Zoology, Kunming, China. This was an honorary position for teaching and mentoring graduate students. The position does not require FTE commitment.

Jun 2012 - now: Associate Professor and then Professor, Ruth McLean Bowman Bower Endowed Chair, Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

Other Experience and Professional Memberships

2006-09 Member, American Heart Association Cardiac Electrophysiology Peer Review Study Group
2010-14 Member, Swiss National Science Foundation, Danish Council for Independent Research
2014-17 Member, Proposal Review Panel at SLAC National Accelerator Laboratory

2015-19 Member, NIH BBM study section

Honors

2006 Pew Scholar in Biomedical Science
2006 Alfred P. Sloan Fellow
2006 Basil O'Connor Starter Scholar Award

C. Contribution to Science

My work as an independent investigator has centered on membrane proteins, starting with ion channels and expanding into transporters and membrane embedded enzymes. I start a project with expressing and purifying the target proteins for structure determination, and once a structure is obtained, I then proceed to conduct mechanistic studies by testing structure-based hypotheses.

1. Structure and mechanism of PEP group translocation: The phosphoenolpyruvate-dependent phosphotransferase system (PTS or PEP group translocation) is unique to bacteria and required for sugar uptake. PTS has multiple components and the membrane-embedded EIIC component eluded structural determination. Since the EIIC component is responsible for sugar transport and participates in sugar phosphorylation, the lack of EIIC structure hampered our understanding of PTS. We solved crystal structures of EIIC in different conformations and then combined functional studies with single-molecule FRET and molecular dynamics simulations to elucidate how sugar substrate is recognized and how conformational changes in EIIC transport sugar across the cell membrane. These results also build a foundation for understanding the mechanism of sugar phosphorylation.
   a. Cao, Y., Jin, X., Levin, E.J., Huang, H., Zong, Y., Quick, M., Weng, J., Pan, Y., Love, J., Punta, M., Rost, B., Hendrickson, W., Javitch, J., Rajashankar, K., & Zhou, M. (2011). Crystal structure of a phosphorylation-coupled saccharide transporter. ***Nature;*** Vol 473 (7345): 50-54. PMC3201810.
   b. McCoy JG, Ren Z, Stanevich V., Lee J., Mitra S., Levin EJ, Poget S., Quick M., Im W., Zhou M. (2016) The structure of a sugar transporter of the glucose EIIC superfamily provides insight into the elevator mechanism of membrane transport. ***Structure;*** Vol 24(6):956-64. PMC4899283.
   c. Lee J, Ren Z, Zhou M, Im W (2017) Molecular Simulation and Biochemical Studies Support an Elevator-type Transport Mechanism in EIIC. ***Biophys J.;*** 112(11):2249-2252. PMCID: PMC5474738.
   d. Ren Z, Lee J, Moosa MM, Nian Y, Hu L, Xu Z, McCoy JG, Ferreon ACM, Im W, Zhou M. (2018). Structure of an EIIC sugar transporter trapped in an inward-facing conformation. ***Proc Natl Acad Sci U S A.*** Vol 115(23):5962-5967. PMID: 29784777

2. Regulation of Kv1 channel by cellular redox state: The Kv1 family of voltage-dependent potassium ion channels are important for controlling the timing and frequency of action potentials. Kv1 channels assemble with a cytosolic beta subunit (Kvβ) to form a stable complex but the physiological role of beta subunit was not clear. My lab demonstrated that Kvβ is an oxidoreductase that uses NADPH as a cofactor, and that oxidation of the Kvβ-bound NADPH increases channel current. We then showed that potentiation of channel current is achieved by interaction of Kvβ with a stretch of amino acid sequence and that the interaction eliminates channel inactivation. These studies established a pathway by which cellular redox state can regulate its membrane potential.
   a. Weng J, Cao Y, Moss N, Zhou M. (2006). Modulation of voltage-dependent *Shaker* family K channel by an aldo-keto reductase. ***Journal of Biological Chemistry****;* Vol 281 (22): 15194-15200. PMCID: PMC2862575.
   b. Pan Y, Weng J, Cao Y, Bhosle R, Zhou M. (2008). Functional coupling between the Kv1.1 channel and an aldo-keto reductase Kvbeta1. ***Journal of Biological Chemistry****;* Vol. 283 (13): 8634-8642. PMCID: PMC2417172.
   c. Pan Y Weng J, Kabaleeswaran V, Li H, Cao Y, Bhosle R, Zhou M. (2008). Cortisone dissociates *Shaker* family K^+ channels from their β subunits. ***Nature Chemical Biology***; Vol 4 (11): 708-714. PMCID: PMC2633621.
   d. Pan Y, Weng J Levin EJ**,** Zhou M. (2011). Oxidation of NADPH on Kvβ1 inhibits the ball-and-chain type inactivation by restraining the chain. ***Proc. Natl. Acad. Sci. USA***.; Vol. 108 (14): 5885-5890. PMCID: PMC3078402.

3. Structure and mechanism of an ATP-gated ion channel in bacteria: The superfamily of K^+ transporters (SKT) is found in bacteria, fungi, plants and protists, and implicated in K^+ uptake, osmoregulation and salt balance. However, the precise function of SKT in cell remains unresolved. In bacteria, SKT has a membrane embedded component (TrkH) and a cytosolic component (TrkA). My lab expressed and purified the TrkH-TrkA complex, and reconstituted the complex into proteoliposomes. We then demonstrated that TrkH is an ion channel by recording its single channel activities, and we showed that ATP binds to TrkA and increases TrkH open probability. These results established coupling between metabolic state of a cell and its membrane potential, and will guide further analysis to understand SKT function. We also solved crystal structures of TrkH and TrkH in complex with TrkA, and the structures provide a starting point for understanding the mechanism of how ATP induces a conformational change in TrkA and how changes in TrkA opens the TrkH channel.
    a. Cao, Y., Jin, X., Huang, H., Derebe, M., Levin, E.J., Kabaleeswaran, V., Pan, Y., Punta, M., Love, J., Weng, J., Quick, M., Ye, S., Kloss, B., Bruni, R., Martinez-Hackert, E., Hendrickson, W., Rost, B., Javitch, J., Rajashankar, K., Jiang, Y., & Zhou, M. (2011). Crystal structure of a potassium ion transporter TrkH. ***Nature;*** 471(7338):336-340. PMC3077569.
    b. Cao Y., Pan Y., Huang H., Jin X., Levin EJ, Kloss B., and Zhou M. (2013). Gating of the TrkH ion channel by its associated RCK protein, TrkA. ***Nature;*** 496 (7445):317-321. PMC3726529
    c. Zhang H, Pan Y, Hu L, Hudson MA, Hofstetter KS, Xu Z, Rong M, Wang Z, Prasad BVV, Lockless SW, Chiu W, Zhou M. TrkA undergoes a tetramer-to-dimer conversion to open TrkH which enables changes in membrane potential. **Nat Commun.** 2020 Jan 28;11(1):547. PMCID: PMC6987127

Complete List of Published Work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/ming.zhou.2/bibliography/public/

D. Research Support

Ongoing Research Support

1R01DK122784 (Zhou)
NIH 07/01/2019-05/31/2024
Structure and mechanism of mammalian stearoyl-CoA desaturases
The goal of the project is to reveal the mechanism of substrate recognition and the redox reaction catalyzed by a novel diiron center.

Subaward from R01GM119396 (Quick, Columbia Univ.) 6/01/2016-03/31/2021
NIH
Molecular mechanism of nucleobase/vitamin C transporters
The goal of the project is to solve structures of an ascorbic acid transporter in different conformations.

Subaward from R01DK061425 (Swaan, Univ. Maryland) 07/01/2016-06/30/2021
Structural biology of the apical bile acid transporter
The goal of the project is to express and purify a eukaryotic homolog of human apical sodium dependent bile acid transporter, and solve its structure by x-ray crystallography.

Subaward from R01CA217333 (Nijhawan, Univ. Texas) 04/01/2018-03/31/2023
Tumor-targeted inhibitors of stearoyl-CoA desaturase for the treatment of cancer
The goal of the project is to solve crystal structures of human stearoyl-CoA desaturase in complex with anti-tumor reagents.

Subaward from R01GM132436 (Lockless, Texas A&M) 07/01/2019-06/30/2023
Physiological role for cation channels in bacteria
The goal of the project to express and purify Kch ion channel from E. coli, and to examine its function and structure.