BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Fu, Tianmin

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

POSITION TITLE: Assistant Professor of Biological Chemistry & Pharmacology

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
Shandong University, Jinan, China	B.S.	07/2005	Biology
Peking University, Beijing, China	Ph.D.	07/2011	Biochemistry and Molecular Biology
Weill Cornell Medical College, New York, NY	Postdoc Fellow	07/2012	Biochemistry and Immunology
Boston Children's Hospital, Boston, MA	Research Fellow	02/2017	Biochemistry and Immunology
Boston Children's Hospital, Boston, MA	Research Associate	06/2020	Biochemistry and Immunology

A. Personal Statement

As an assistant professor, I am focusing on elucidation the logic of lysosomal signaling, in particular, the assembly and regulation of membrane proteins on lysosome including ion channels, transporters, and V-ATPases. As a postdoc with Dr. Hao Wu, I have made numerous contributions to the study of death receptor signaling and inflammasome signaling. Then I initiated my own projects on lysosomal signaling in Wu lab and my supervisor is very generous to allow me to bring them with me. I have made a few breakthroughs in lysosomal signaling. In 2018, I revealed the molecular mechanism of TRPM2 gating, a lysosomal cation channel that is regulated by calcium and ADP-ribose in response to oxidative stress. After I started my own lab, I determined cryo-EM structures of human V-ATPase and crystal structures of CRISPR-Cas proteins, and have published 3 peer reviewed research articles as leading corresponding author or co-corresponding author in *Molecular Cell*, *STAR Protocols*, and *Nucleic Acid Research*. More recently, I laid the groundwork for the proposed research by purifying and determining the cryo-EM structures of human TMEM175, a non-canonical potassium channel, in open and closed conformations at different pH, revealing the molecular mechanism of gating, ion selectivity, and regulation of human TMEM175. The current application builds logically on my prior work. My expertise and experience have prepared me to further conduct the proposed project.

The PI is experienced in many aspects of structural and cellular biology, including cryo-EM, protein crystallography, membrane protein biology, cellular imaging, biochemistry, and biophysics.

B. Positions and Honors

Positions and Employment

2020- Assistant Professor, Department of Biological Chemistry and Pharmacology, The Ohio State University, Columbus, OH

Other Experience and Professional Memberships

2005-2011 Member, Chinese Crystallography Society
2012-2013 Associate Faculty Member, F1000 Prime
2016- Member of Editorial Board, Journal of Pharmaceutical and Pharmacological Sciences
2017- Member, American Association for the Advancement of Science
2019- Member, American Society for Biochemistry and Molecular Biology

2019- Member, American Biophysical Society

Honors

2001 University-Admission Scholarship, Shandong University
2002 Zhonghaiyou Scholarship, Shandong University
2003 Merit Scholarship, Shandong University
2004 Merit Scholarship, Shandong University
2006 Gu Wenyu Fellowship, Peking University
2008 Yu Caifan Fellowship, Peking University
2009 Merit student of Peking University, Peking University
2018 Harvard Digestive Disease Center Grant
2019 Distinguished Research Award, Chinese Scientists and Scholars Association, Harvard Medical School

C. Contributions to Science

1. **Elucidating the assembly and regulation of human V-ATPase.** V-ATPases play important roles in many physiological processes by pumping protons for the acidification of numerous cellular organelles. Our group determined the cryo-EM structures of human V-ATPases in three rotational states, revealing the mechanisms of proton transfer. Moreover, we identified many lipids, sugars, and glycolipids as bone fide components of human V-ATPase, opening the door for further understanding the regulation of V-ATPase by these molecules.

    a. Wang, L., Wu, D., Robinson C.V., Wu, H., **Fu, T.M. 2020.** Structures of a complete human V-ATPase reveal mechanisms of its assembly. ***Mol. Cell***, 80 (3): 501-511. PMID:33065002, PMCID: PMC7655608.
    b. Wang, L., Chen, L., Wu, H., **Fu, T.M. 2021.** Purification and cryoelectron microscopy structure determination of human V-ATPase. ***STAR Protocols***, 2(1): 100350. PMID: 33665630, PMCID: PMC7902551.

2. **Revealing the gating mechanism of human TRPM2.** TRPM2 is a non-selective cation channel that is co-activated by calcium and ADP-ribose. The activation of TRPM2 regulates many important physiological processes including insulin secretion, body temperature maintenance, immune response. I recently determined the cryo-EM structures of the full-length human TRPM2 channel in apo, primed, and open states. Together, these structures provide a full picture of TRPM2 gating and also suggest a general principle of TRP channel gating, which may apply to many other TRP families.

    a. Wang, L.*, **Fu, T.M.**$^{*\#}$, Zhou, Y., Xia, S., Greka, A., Wu, H.$^{\#}$ **2018.** Structures and gating mechanism of human TRPM2. ***Science***, 362, eaav4809 (*co-first author; $^{\#}$co-corresponding author) PMID:30467180, PMCID: PMC6459600.
    b. Xia, S., Wang, L., **Fu, T.M.** $^{\#}$, Wu, H.$^{\#}$ **2019.** Mechanism of TRPM2 channel gating revealed by cryo-EM. ***FEBS J.***, 286, 3333-39 ($^{\#}$co-corresponding author) PMID:31144442, PMCID: PMC7151886.

3. **Elucidation of the molecular mechanism of death receptor signaling.** Fas or DR5 signaling pathway mediates extrinsic signal induced cell death and plays an important role in physiology and pathology. In collaboration with Chou lab, I determined the transmembrane domain structure of Fas, revealing a trimeric assembly mediated activation mechanism. In contrast, we found that the transmembrane domain of DR5 forms higher-order cluster to drive cell signaling. I also determined crystal and Cryo-EM structures of tDED domain of caspase-8, the downstream effector protein of Fas signaling pathway. I further showed the helical assembly of caspase-8 is critical for signal transduction. I also showed that the helical assembly of caspase-8 could be regulated by cFLIP and vFLIP through comingling and capping mechanism, respectively. These studies established a new paradigm of signal transduction mediated by protein oligomerization.

    a. Pan, L.*, **Fu, T.M.***, Zhao, W.*, Zhao, L.*, Chen, W., Qiu, C., Liu, W., Liu, Z., Piai, A., Fu, Q., Chen, S., Wu, H., Zhou, J. 2019. Higher-order clustering of the transmembrane anchor of DR5 drives signaling. ***Cell***, 176: 1477-89. (*co-first author) PMID: 30827683, PMCID: PMC6529188.
    b. **Fu, T.M**., Li, Y., Lu, A., Li, Z., Vajjhala, P.R., Cruz, A.C., Srivastava, D.B., DiMiao, F., Penczek, P.A., Siegel, R.M., Stacey, K.J., Egelman, E.H., Wu, H. **2016.** Cryo-EM structure of Caspase-8 tandem DED

filament reveals assembly and regulation mechanisms of the death-inducing signaling complex. ***Mol. Cell***, 64:236-250 (Feature Article of the Issue) PMID:27746017, PMCID: PMC5089849.

c. Fu, Q.*, **Fu, T.M**.*, Cruze, A., Richardson, T., Wu, H., Zhou, J. **2016**. Proline mediated trimerization of Fas transmembrane region is critical for signaling. ***Mol. Cell***, 61: 602-613 (*co-first author) PMID:26853147, PMCID: PMC4761300.

4. **Revealing the molecular mechanism of inflammasome assembly and activation.** Inflammasomes are large protein complexes that trigger host defense in cells by activating inflammatory caspases for cytokine maturation and pyroptosis. My study reveals that the pyrin domain in sensor protein of NLRP6 or CARD domain in adaptor proteins of ASC or NLRC4 assembles into filament for signal initiation and amplification.

   a. Li, Y. *, **Fu, T.M.** *#, Lu, A, Witt, K., Ruan, J., Shen, C., Wu, H.# **2018.** Cryo-EM structures of ASC and NLRC4 CARD filaments reveal a unified mechanism of nucleation and activation of caspase-1. ***Proc. Natl. Acad. Sci. USA*** 115:10845-52 (*co-first author; #co-corresponding author) PMID:30279182, PMCID: PMC6205419.

   b. Shen, C., Lu, A., Xie, WJ., Ruan, J., Negro, R., Egelman, E.H., **Fu, T.M.** #, Wu, H.# **2019.** Molecular mechanism for NLRP6 inflammasome assembly and activation. ***Proc. Natl. Acad. Sci. USA*** 116:2052-57 (#co-corresponding author) PMID:30674671, PMCID: PMC6369754.

Complete list of published work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/16OSr3OybrLQc/bibliography/public/

D. Research Support

Ongoing Support: None

Completed Support:

07/01/2017-06/30/2018 Harvard Digestive Disease Center Pilot Feasibility Grant (Role: PI)

Molecular Mechanism of NLRP6 Inflammasome Assembly and Activation.

The major goal of this project is to elucidate the molecular mechanism of NLRP6 inflammasome activation and to identify its ligand.