BIOGRAPHICAL SKETCH

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NAME: Wang, Longfei

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

POSITION TITLE: Research Fellow

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
Huazhong Agricultural University, Wuhan, China	B.S.	07/2005	Biology
Institute of Biophysics, Beijing, China	Ph.D.	07/2011	Biochemistry and Molecular Biology
Harvard Medical School, Boston, MA	Postdoctoral	09/2011-04/2017	Biochemistry and Pharmacology

A. Personal Statement

My long-term research interests are the mechanism of macromolecular machineries that play crucial roles in living organisms and mechanism-based development of therapies for related human diseases. I gained expertise in membrane protein biochemistry in Dr. Wenrui Chang's laboratory, where my Ph.D. work focused on light-harvesting complexes in plants and my team determined the crystal structure of the light-harvesting antenna protein CP29. I then briefly worked in Dr. Zhenfeng Liu's laboratory and solved the crystal structure of a trimeric intracellular cation (TRIC) channel. At Harvard Medical School, I extended my research skills by screening small-molecule drugs for an oncogene and pluripotency factor called LIN28. The screening assay I developed as well as the lead compounds were licensed to Twenty-eight-seven Therapeutics as one of their core pipelines. Under Dr. Hao Wu's mentorship at Boston Children's Hospital, I focused on the structure and function of the human TRPM2 cation channel. By optimization of purification procedures, I obtained full-length human TRPM2, determined its cryo-EM structures in three distinct states, and revealed that the opening mechanism of human TRPM2 is quite different from that of zebrafish TRPM2. With Ph.D. and postdoctoral training under world-class scientists and challenging studies that have answered important questions in biology, I am fully confident to lead the proposed project.

1. **Wang, L.**, Fu, T. M., Zhou, Y., Xia, S., Greka, A., & Wu, H. 2018. Structures and gating mechanism of human TRPM2. ***Science***, eaav4809.
2. **Wang, L.**, Sliz, P. Small-molecule Inhibitors of the Lin28/Let-7 Complex. US Patent Application No. 62/332,512. (licensed to Twentyeight-Seven Therapeutics).
3. **Wang, L.**, Nam, Y., Lee, A.K., Yu, C., Roth, K., Chen, C., Ransey, E.M. and Sliz, P., 2017. LIN28 zinc knuckle domain is required and sufficient to induce let-7 oligouridylation. ***Cell reports***, 18(11), pp.2664-2675.
4. **Wang, L.**, Rowe, R.G., Jaimes, A., Yu, C., Nam, Y., Pearson, D.S., Zhang, J., Xie, X., Marion, W., Heffron, G.J. and Daley, G.Q., 2018. Small-Molecule Inhibitors Disrupt let-7 Oligouridylation and Release the Selective Blockade of let-7 Processing by LIN28. ***Cell reports***, 23(10), pp.3091-3101.

B. Positions and Honors

Positions and Employment

2011-2011 Research Associate, Institute of Biophysics, Beijing, China

2011-2017 Postdoctoral research Fellow, Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, MA
2017- Postdoctoral research Fellow, Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, MA

Other Experience and Professional Memberships
2011-2012 Software Curator, SBGrid Consortium
2015-2016 Data Science, Harvard Extension School

Honors
2001-2004 Outstanding Student, Huazhong Agricultural University
2002 Honghua Scholarship, Huazhong Agricultural University

C. Contributions to Science

1. **Structures and gating mechanism of human TRPM2.** Transient receptor potential (TRP) melastatin 2 (TRPM2) is a cation channel associated with numerous diseases. It has a C-terminal NUDT9 homology (NUDT9H) domain responsible for binding adenosine diphosphate (ADP)-ribose (ADPR), and both ADPR and calcium (Ca^{2+}) are required for TRPM2 activation. We determined cryo-EM structures of human TRPM2 in Apo state, with ADPR, and with ADPR and Ca^{2+}. NUDT9H forms both intra- and inter-subunit interactions with the N-terminal TRPM homology region (MHR1/2/3) in the Apo state but undergoes conformational changes upon ADPR binding, resulting in rotation of MHR1/2 and disruption of the inter-subunit interaction. The binding of Ca^{2+} further engages transmembrane helices and the conserved TRP helix to cause conformational changes at the MHR arm and the lower gating pore to potentiate channel opening. These findings explain the molecular mechanism of concerted TRPM2 gating by ADPR and Ca^{2+} and provide insights into the gating mechanism of other TRP channels.

   a. **Wang, L.**, Fu, T. M., Zhou, Y., Xia, S., Greka, A., & Wu, H. 2018. Structures and gating mechanism of human TRPM2. ***Science***, eaav4809. PMC in progress.

2. **LIN28-mediated regulation in stem cell and cancers and LIN28-targeting cancer therapies.** LIN28 is an RNA binding protein that plays crucial roles in embryonic development, pluripotency, glucose metabolism, tissue regeneration, and tumorigenesis. I identified that ZKD domain of LIN28 recruits TUTase and initiate let-7 degradation pathway by oligouridylation. I then determined the human LIN28/let-7 complex structure. Based on the structure, I developed a sensitive screening assay and performed drug screening targeting LIN28. Several lead compounds were identified from the screening that inhibits LIN28 with micromolar potency in cells.

   a. **Wang, L.**, Nam, Y., Lee, A.K., Yu, C., Roth, K., Chen, C., Ransey, E.M. and Sliz, P., 2017. LIN28 zinc knuckle domain is required and sufficient to induce let-7 oligouridylation. ***Cell reports***, 18(11), pp.2664-2675. PMC in progress.
   b. **Wang, L.**, Rowe, R.G., Jaimes, A., Yu, C., Nam, Y., Pearson, D.S., Zhang, J., Xie, X., Marion, W., Heffron, G.J. and Daley, G.Q., 2018. Small-Molecule Inhibitors Disrupt let-7 Oligouridylation and Release the Selective Blockade of let-7 Processing by LIN28. ***Cell reports***, 23(10), pp.3091-3101. PMC in progress.
   c. **Wang, L.**, Yang, Q., Jaimes, A., Wang, T., Strobelt, H., Chen, J. and Sliz, P., 2018. MightyScreen: an open-source visualization application for screening data analysis. ***SLAS DISCOVERY: Advancing Life Sciences R&D***, 23(2), pp.218-223. PMC in progress.
   d. Zhang, J., Ratanasirintrawoot, S., Chandrasekaran, S., Wu, Z., Ficarro, S.B., Yu, C., Ross, C.A., Cacchiarelli, D., Xia, Q., Seligson, M. and Shinoda, G., Xie W.,Cahan P., **Wang L.**, …, 2016. LIN28 regulates stem cell metabolism and conversion to primed pluripotency. ***Cell Stem Cell***, 19(1), pp.66-80. PMC in progress.

3. **Structure of anti-tumor peptide rBTI.** BWI-1 (buckwheat trypsin inhibitor), a member of the potato inhibitor I family, suppresses the growth of T-acute lymphoblastic leukemia cells and induces apoptosis in human solid

tumor cell lines. I determined the crystal structures of rBTI alone and rBTI in complex with trypsin. The structures reveal a novel conformation change of P8 position residue.

a. **Wang, L.**, Zhao, F., Li, M., Zhang, H., Gao, Y., Cao, P., Pan, X., Wang, Z. and Chang, W., 2011. Conformational changes of rBTI from buckwheat upon binding to trypsin: implications for the role of the P8′ residue in the potato inhibitor I family. ***PloS one***, 6(6), p.e20950. PMCID: PMC3115953.

4. **The crystal structure of a trimeric intracellular cation (TRIC) channel.** Trimeric intracellular cation (TRIC) channels are crucial for Ca2+ handling in eukaryotes and are involved in K+ uptake in prokaryotes. I determined the crystal structure of *Sulfolobus solfataricus* (*ss*TRIC) channel in the presence of potassium. The structure revealed a Velcro-like plug-pore interacting model which serves as a unified framework for the gating mechanisms of prokaryotic and eukaryotic TRIC channels.

a. Ou, X., Guo, J., **Wang, L.**, Yang, H., Liu, X., Sun, J. and Liu, Z., 2017. Ion-and water-binding sites inside an occluded hourglass pore of a trimeric intracellular cation (TRIC) channel. ***BMC biology***, 15(1), p.31. PMCID: PMC5401562.

Complete list of published work in MyBibliography
https://www.ncbi.nlm.nih.gov/labs/bibliography/1Lkpw4Jce-GkCd/bibliography/public/

D. Research Support:

Ongoing: None

Completed: None