OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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NAME: WANG, ZHAO

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

POSITION TITLE: Assistant 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)	END DATE MM/YYYY	FIELD OF STUDY
Wuhan University, WUHAN, HUBEI	BS	06/2004	Applied Physics / Biophysics
Wuhan University, WUHAN, HUBEI	MA	06/2006	Biophysics
Peking University, BEIJING	PHD	06/2015	Biophysics
National Center for Macromolecular Imaging (NCMI), Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, HOUSTON, TX	Postdoctoral Fellow	11/2016	Research Associate

A. Personal Statement

The ultimate goal of my research is to gain a deeper understanding of biological nano-machines by cryo-EM/cryo-ET techniques and computer reconstruction, and the use of structures to reveal their structure-based functional mechanisms. Electron microscopy has been one of the primary techniques used for my studies. Structural studies of macromolecular complex structures have been a keystone of my scientific career since I joined the National Center for Macromolecular Imaging (Baylor College of Medicine, Houston TX) as a Research Associate. I published numerous important structures, including the first structures of nuclear receptor coactivator complexes, multidrug efflux pumps, and several ion channels. I pioneered using the first direct electron detection device (DDD), a newly designed piece of equipment that enables a ‘resolution revolution’ in single-particle cryo-EM, and I am developing a novel protocol of data collation and processing using this camera. Our work first develops the ‘damage compensation’ analysis strategy, which is now commonly used by the EM community. Having a broad background in biochemistry and structural biology, with specific training and expertise in cryo-EM of membrane proteins, I started as an independent principal investigator (tenure-track assistant professor) at the Department of Biochemistry and Molecular Biology (Baylor College of Medicine, Houston TX) in 2018. I have been trained in experimental & computational biophysics, and my laboratory research involves the development of experimental and computational methodologies for cryo-EM/cryo-ET, and applications for research related to the following biological systems: the structure, and mechanism of several membrane complexes: cation ion channels involving many critical functions such as IP3R and TRPV(in collaborating with Theodore Wensel, BCM); resistance-nodulation-cell division

(RND)-superfamily of efflux pumps AcrAB-TolC tripartite pump(in collaborating with Ben Luisi, Cambridge and Steven Lutdke, BCM); transmembrane receptors integrins(in collaborating with Mehmet Sen, UH); and nuclear receptors(Bert O'Melley, BCM). My laboratory research also focuses on the structural study of platelet cells in hematologic diseases and applying cryo-EM/ET for translational research. Technically, we have established protocols for high throughput cellular tomogram reconstruction and averaging at sub-nanometer resolution (Nature Methods, 2019, Nature Com., 2019, Com. Bio., 2022) for application in current research. My training and background make me well suited to determine 3-dimensional structures of integrin and relate *in situ* structures in platelets by cryo-EM and cryo-ET.
Ongoing and recently completed projects that I would like to highlight include:
R01GM143380, NIH 07/08/2021-04/30/2026 Wang (PI) Molecular mechanism of Androgen Receptor-mediated transcription
R01HL162842, NIH-NILBI 05/05/2022-04/30/2026 Wang (PI) Investigation of the Cellular and Molecular Mechanisms of Thrombocyte Integrin Signaling
Q-1967-20180324, Welch Foundation Wang (PI) 06/01/18-05/31/21 Determining Chemical Interactions Mediating Biological Complex Formation by Cryo-EM
1RP190602 YR, CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS (CPRIT) LUDTKE (PI), Role: co-investigator 08/31/19-08/30/24 Expand the CryoEM ATC with new equipment and capabilities, and supplement center operations for cancer research
5 R01 HD07857, National Institutes of Health O'Malley (PI) Role: co-investigator 05/01/77-02/08/22 Sex Hormone Receptor Components and the Cell Genome

1. Wang Y, Huo T, Tseng YJ, Dang L, Yu Z, Yu W, Foulks Z, Murdaugh RL, Ludtke SJ, Nakada D*, **Wang Z*.** Using Cryo-ET to distinguish platelets during pre-acute myeloid leukemia from steady state hematopoiesis. Commun Biol. 2022
2. Yi P, Yu X, **Wang Z**, O'Malley BW. Steroid receptor-coregulator transcriptional complexes: new insights from CryoEM. Essays Biochem. 2021 Dec
3. Yu X, Yi P, Hamilton RA, Shen H, Chen M, Foulds CE, Mancini MA, Ludtke SJ, **Wang Z***, O'Malley BW*. Structural Insights of Transcriptionally Active, Full-Length Androgen Receptor Coactivator Complexes. Mol Cell. 2020

*** Corresponding author**

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2018 -	Assistant Professor, Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Houston, TX
2018 -	Assistant Professor, Department of Molecular and Cellular Biology, Houston, TX
2018 -	Joint Assistant professor, Department of Molecular and Cellular Oncology, Division of Basic Science, The University of Texas MD Anderson Cancer Center, Houston, TX
2019 -	Assistant Professor, Department of Pharmacology and Chemical Biology at Baylor College of Medicine, Houston, TX
2022 -	Adjunct Professor, Department of Materials Science and NanoEngineering at Rice University, Houston, TX
2017 -	Co-director, CPRIT CryoEM Core, Baylor College of Medicine, Houston, TX
2016 - 2018	Instructor, National Center for Macromolecular Imaging (NCMI), Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

2013 - 2016 Research Associate, National Center for Macromolecular Imaging (NCMI), Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

2009 - 2013 Project Intern, National Center for Macromolecular Imaging (NCMI), Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

2006 - 2009 Research Assistant, Department of Biophysics, Peking University Health Science Center, Beijing

Honors

2008 - 2011 The Second Prize Scholarship, Peking University Health Science Center, China

2015 First Place Poster Presentation Award, Multiscale Cancer System Biology Symposium, Houston Methodist Research Institute, Houston, U.S.

2012 Traveling Award, Kuo Symposium on 3D Cryo-EM Molecular Imaging

C. Contribution to Science

1. I have been working on the structural determination of Gram-negative bacterial Drug Efflux pumps, which actively expel a wide range of toxic substrates across the cell envelope and play a major role in intrinsic and acquired antibiotic resistance. My investigations of both in vitro and in vivo whole-pump assembly have been cutting-edge in the field of cryo-EM/ET studies, as the structures have fundamentally changed the understanding of pump organization and have promoted other related studies. Our in vitro structural studies determined the first three-dimensional structure of the fully assembled pump; defined the quaternary organization; identified a key protein component (AcrA) that bridges full pump assembling, and identified positioning of key interactions in near-atomic resolution of AcrAB-TolC, revealing a quaternary structural switch that allosterically couples and synchronizes initial ligand binding with channel opening. In the past few years, we have expanded our technology development for electron cryo-tomography to visualize the AcrAB-TolC multidrug efflux pump in situ directly in the E. coli cell. We have established an imaging protocol to obtain the best quality images, and we aggressively participate in developing suitable software for reconstructing maps at the highest possible resolution. Our study visualized the first intermediate subcomplex of AcrAB without TolC binding in the cell and first determined a decent resolution structure of the pump in both open and closed states in the cell. In recent, we have determined in situ structure of this pump at 7Å shows 8-degree counterclockwise conformational changes in AcrA and clearly resolved efflux-related N and C terminus of AcrA which was previously absent in other structures. These results demonstrate binding sites between the pump and peptidoglycan layer and indicate that the opening/closing switch in TolC of the pump related to antibiotics/inhibitor binding at AcrB requires allosteric conformational changes bridge through AcrA.
    a. Chen M, Shi X, Yu Z, Fan G, Serysheva II, Baker ML, Luisi BF, Ludtke SJ, **Wang Z***. In situ structure of the AcrAB-TolC efflux pump at subnanometer resolution. Structure. 2022 Jan 6;30(1):107-113.e3. PubMed Central PMCID: PMC8741639.
    b. Chen M, Bell JM, Shi X, Sun SY, **Wang Z**, Ludtke SJ*. A complete data processing workflow for cryo-ET and subtomogram averaging. Nat Methods. 2019 Nov;16(11):1161-1168. PubMed Central PMCID: PMC6858567.
    c. Shi X, Chen M, Yu Z, Bell JM, Wang H, Forrester I, Villarreal H, Jakana J, Du D, Luisi BF, Ludtke SJ, **Wang Z***. In situ structure and assembly of the multidrug efflux pump

AcrAB-TolC. Nat Commun. 2019 Jun 14;10(1):2635. PubMed Central PMCID: PMC6570770.

d. Du D, **Wang Z**, James NR, Voss JE, Klimont E, Ohene-Agyei T, Venter H, Chiu W, Luisi BF. Structure of the AcrAB-TolC multidrug efflux pump. Nature. 2014 May 22;509(7501):512-5. PubMed Central PMCID: PMC4361902.

2. My group first used electron cryo-microscopy (cryo-EM) to determine the structural architecture of DNA-bound ER-alpha, SRC-3, and a secondary coactivator (p300) complex. This work provides a structural basis for understanding the assembly of a transcriptionally active nuclear receptor-coactivator complex. In a continuing study, we developed a computational procedure to classify the images in order to sort out different assemblies of 3D structures. We demonstrated that a late-recruited coactivator alters the structure and function of the pre-existing receptor-coactivator complex to synergistically activate estrogen receptor-mediated transcription and to prepare the complex for the next step of transcription. Our latest study determines the first structure of DNA bound androgen receptors and the active androgen receptor-coactivator complex binding with the same core activators (SRC-3 and p300). This work highlights the N-terminal direct involvement in coactivator recruitment and provides a structural basis for understanding the difference between estrogen receptor-mediated and androgen receptor-mediated transcriptional activation.
   a. Yi P, Yu X, **Wang Z**, O'Malley BW*. Steroid receptor-coregulator transcriptional complexes: new insights from CryoEM. Essays Biochem. 2021 Dec 17;65(6):857-866. PubMed Central PMCID: PMC8845409.
   b. Yu X, Yi P, Hamilton RA, Shen H, Chen M, Foulds CE, Mancini MA, Ludtke SJ, **Wang Z***, O'Malley BW*. Structural Insights of Transcriptionally Active, Full-Length Androgen Receptor Coactivator Complexes. Mol Cell. 2020 Sep 3;79(5):812-823.e4. PubMed Central PMCID: PMC7483370.
   c. Yi P, **Wang Z**, Feng Q, Chou CK, Pintilie GD, Shen H, Foulds CE, Fan G, Serysheva I, Ludtke SJ, Schmid MF, Hung MC, Chiu W, O'Malley BW. Structural and Functional Impacts of ER Coactivator Sequential Recruitment. Mol Cell. 2017 Sep 7;67(5):733-743.e4. PubMed Central PMCID: PMC5657569.

3. I now direct the cryo-EM Core at BCM. I have been working collaboratively with the multiple groups and have solved a number of important ion channel structures by cryo-EM single-particle analysis, including the apo- and ligand-bound states of IP3R1, a ubiquitous Ca2+ channel in the ER involved in a wide range of cellular functions; the first full-length functional TRPV2, a member of the transient receptor potential cation channel that allows the cell to communicate with its extracellular environment through the transfer of ions; the first full-length dihydropyridine (DHPR) receptor/L-type Ca2+ channel complex, an essential component in EC coupling, which is also involved in other critical cell functions; and a potassium channel, TrkH, which mediates K+ uptake in bacteria.
   a. Kumar D, Yu X, Crawford SE, Moreno R, Jakana J, Sankaran B, Anish R, Kaundal S, Hu L, Estes MK, **Wang Z***, Prasad BVV*. 2.7 Å cryo-EM structure of rotavirus core protein VP3, a unique capping machine with a helicase activity. Sci Adv. 2020 Apr;6(16):eaay6410. PubMed Central PMCID: PMC7159914.
   b. 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. PubMed Central PMCID: PMC6987127.

c. Dosey TL, **Wang Z**, Fan G, Zhang Z, Serysheva II, Chiu W*, Wensel TG*. Structures of TRPV2 in distinct conformations provide insight into role of the pore turret. Nat Struct Mol Biol. 2019 Jan;26(1):40-49. PubMed Central PMCID: PMC6458597.
d. Fan G, Baker ML, **Wang Z**, Baker MR, Sinyagovskiy PA, Chiu W, Ludtke SJ, Serysheva II*. Gating machinery of InsP3R channels revealed by electron cryomicroscopy. Nature. 2015 Nov 19;527(7578):336-41. PubMed Central PMCID: PMC4804758.

4. I have been an investigator in the development of experimental methodologies for structural determination of biological assemblies by single-particle electron cryo-microscopy (cryo-EM) towards atomic resolution. My research includes developing experimental methodologies of the first-generation direct electron detection device (DDD) and first solving a high-resolution structure using a small plant virus. My strategy, a novel protocol of data collation and processing, includes the first development of the "damage compensation" analysis strategy, which is now commonly used in the EM community. In the last decade, the achievement of near-atomic resolution (<4 Å) has attracted wide attention to the approach. I am the first one to push the resolution beyond 4Å using a DDD camera (DE). A second contribution my group has made to the field of EM experimentation involves the use of support films for atomic resolution structure determination. We were the first to optimize specimen samples with decreased beam-induced movement using continuous carbon films, and then to compare them to samples in ice. In the past few years, we have expanded our technics using Graphene-oxide films which have a better signal-to-noise ratio. We have recently succeeded in determining maps of several protein samples using single-particle cryo-EM ~2-4 Å resolution.
   a. Wang Y, Huo T, Tseng YJ, Dang L, Yu Z, Yu W, Foulks Z, Murdaugh RL, Ludtke SJ, Nakada D*, **Wang Z***. Using Cryo-ET to distinguish platelets during pre-acute myeloid leukemia from steady state hematopoiesis. Commun Biol. 2022 Jan 20;5(1):72. PubMed Central PMCID: PMC8776871.
   b. Xie Q, **Wang Z**, Ni F, Chen X, Ma J, Patel N, Lu H, Liu Y, Tian JH, Flyer D, Massare MJ, Ellingsworth L, Glenn G, Smith G, Wang Q. Structure basis of neutralization by a novel site II/IV antibody against respiratory syncytial virus fusion protein. PLoS One. 2019;14(2):e0210749. PubMed Central PMCID: PMC6366758.
   c. Hryc CF, Chen DH, Afonine PV, Jakana J, **Wang Z**, Haase-Pettingell C, Jiang W, Adams PD, King JA, Schmid MF, Chiu W*. Accurate model annotation of a near-atomic resolution cryo-EM map. Proc Natl Acad Sci U S A. 2017 Mar 21;114(12):3103-3108. PubMed Central PMCID: PMC5373346.
   d. Wang Z, Hryc CF, Bammes B, Afonine PV, Jakana J, Chen DH, Liu X, Baker ML, Kao C, Ludtke SJ, Schmid MF, Adams PD, Chiu W*. An atomic model of brome mosaic virus using direct electron detection and real-space optimization. Nat Commun. 2014 Sep 4;5:4808. PubMed Central PMCID: PMC4155512.