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)	START DATE MM/YYYY	COMPLETION DATE MM/YYYY	FIELD OF STUDY
Wuhan University, WUHAN, HUBEI	BS	09/2000	06/2004	Applied Physics / Biophysics
Wuhan University, WUHAN, HUBEI	MA	09/2004	06/2006	Biophysics
Peking University, BEIJING	PHD	09/2008	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	12/2013	11/2016	Research Associate

A. Personal Statement

The ultimate goal of my research is to gain a deeper understanding of biological nano-machines by determining their structures using cryo-EM/cryo-ET techniques and computer reconstruction, by using the structures to reveal their structure-based functional mechanisms. Structural study of macromolecular complex structures using cryo-electron microscopy has been the 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 have published numerous important structures, including the first structures of nuclear receptor coactivator complexes, structures of multidrug efflux pumps, and those of 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 type of camera. Our work first developed 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 at Baylor College of Medicine, in 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 involved in many critical functions such as $InsP_3R$ and TRPV2; the resistance-nodulation-cell division (RND)-superfamily of efflux pumps such as the AcrAB-TolC tripartite pump (including its *in vivo* structure by cryo-ET); and integrins. 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 and Nature Com., 2019) for application in current research. My training and background make me well suited to determine 3-dimensional structures of integrins and related *in situ* structures in platelets by cryo-EM and cryo-ET.

<u>Ongoing and recently completed projects that I would like to highlight include:</u>

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

Citations:

1. 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
2. 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
3. Chen M, Shi X, Yu Z, Fan G, Serysheva I, Baker M, Luisi B, Ludtke S, **Wang Z***. *In situ* structure of the AcrAB-TolC efflux pump at subnanometer resolution. Biorxiv, 2020
4. 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

*** Corresponding author.**

B. Positions and Honors

Positions and Scientific Appointments

2018 -	Assistant Professor, Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX
2018 -	Assistant Professor, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX
2017 -	Co-director, 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

2015	First Place Poster Presentation Award, Multiscale Cancer System Biology Symposium, Houston Methodist Research Insitute
2012	Traveling Award, Kuo Symposium on 3D Cryo-EM Molecular Imaging
2008 - 2011	The Second Prize Scholarship, Peking University Health Science Center, China
2005	The First Prize Scholarship, Wuhan University, China
2005 - 2006	Pacemaker to Merit Student, Wuhan University, China

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 assembly, and identified positioning of key interactions in the near-atomic resolution structure 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 structures of the pump in both open and closed states in the cell, first at 10-20 Å and more recently at ~7 Å. The results indicate that the opening of the pump and efflux of antibiotics are transient processes and demonstrate binding sites between the pump and the peptidoglycan layer.

a. 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
b. 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
c. **Wang Z**, Fan G, Hryc CF, Blaza JN, Serysheva II, Schmid MF, Chiu W, Luisi BF, Du D. An allosteric transport mechanism for the AcrAB-TolC multidrug efflux pump. Elife. 2017
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

2. My group first used electron cryo-microscopy (cryo-EM) to determine the structural architecture of a complex of DNA-bound estrogen receptor (Erα) bound to co-regulator SRC-3, and a secondary coactivator, p300. 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 reveals 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. 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
b. 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
c. Yi P, **Wang Z**, Feng Q, Pintilie GD, Foulds CE, Lanz RB, Ludtke SJ, Schmid MF, Chiu W, O'Malley BW. Structure of a biologically active estrogen receptor-coactivator complex on DNA. Mol Cell. 2015

3. I now direct the cryo-EM Core at BCM. I have been working collaboratively with 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 $InsP_3R1$, a ubiquitous Ca^{2+} 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 Ca^{2+} 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. 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
b. Fan G, Baker MR, **Wang Z**, Seryshev AB, Ludtke SJ, Baker ML, Serysheva II. Cryo-EM reveals ligand induced allostery underlying $InsP_3R$ channel gating. Cell Res. 2018
c. 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
d. Hu H, **Wang Z**, Wei R, Fan G, Wang Q, Zhang K, Yin CC. The molecular architecture of dihydropyrindine receptor/L-type Ca2+ channel complex. Sci Rep. 2015

4. I have been a leader 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 innovations include 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 was the first one to push the resolution beyond 4 Å using a DDD camera (DE). My group has pioneered the use of novel 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 alone. In the past few years, we have expanded our techniques 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 to ~2-4 Å resolution.

   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
   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
   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
   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

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