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 CryoEM/CryoET 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. I specifically emphasize transcriptional regulation and have discovered numerous important structures. In a number of landmark publications through collaborating with Dr. O'Malley, I have revealed the first complete functional receptor-coactivator complex structures for both estrogen receptor and androgen receptor. Our work details the mechanisms of nuclear receptor assembly and action, serve as exciting proof-of-principles highlighting coactivators and corresponding interacting regions in the nuclear receptor as a new type of drug target that not previously predicted. My training and background make me well suited to determine 3-dimensional structures of androgen receptor/coactivators complexes by electron cryo-microscopy, computer reconstruction, and relate the structures in hormonally promoted diseases including Prostate cancers.

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 Sep 3;79(5):812-823.e4. PubMed PMID: 32668201.
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 Apr;6(16):eaay6410. PubMed PMID: 32494598; PubMed Central PMCID: PMC7159914.
3. 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 PMID: 31201302; PubMed Central PMCID: PMC6570770.
4. 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 Mar 19;57(6):1047-1058. PubMed PMID: 25728767; PubMed Central PMCID: PMC4369429.

*** corresponding author**

B. Positions and Honors

Positions and Employment

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

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

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

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

2017 - Co-director, CryoEM Core, Baylor college of medicine, Houston, TX

2018 - Assistant Professor (tenure track), Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

2018 - Assistant Professor (tenure track), Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX

Other Experience and Professional Memberships

2008 - 2012 Member, Chinese Biophysical Society

2013 - Member, American Biophysical Society

2017 - Member, American Endocrine Society

2019 - Member, Microscopy society of America

Honors

2005 The First Prize Scholarship, Wuhan University, China

2005 - 2006 Pacemaker to Merit Student , Wuhan University, China

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

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

2015 First Place Poster Presentation Award, Multiscale Cancer System Biology Symposium, Houston Methodist Research Insitute

C. Contribution to Science

1. My group first uses 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 assembly 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 receptor and the active androgen receptor-coactivator complex binding with the same core activators (SRC-3 and p300). Our work highlights the N-terminal direct involvement in the coactivator recruitment and provide a structural basis on the understanding 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 Sep 3;79(5):812-823.e4. PubMed PMID: 32668201.

    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 Sep 7;67(5):733-743.e4. PubMed PMID: 28844863; PubMed Central PMCID: PMC5657569.

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 Mar 19;57(6):1047-1058. PubMed PMID: 25728767; PubMed Central PMCID: PMC4369429.

2. Research on assembling and working mechanisms of multidrug efflux pump from bacteria is the most enduring project in my research, spanning the last decade. Expression of the efflux pump is one the major reason causes antibiotic resistance in pathogenic bacteria and it is known as an important drug target. Utilizing recent technological advances in direct electron detection and advances in image processing algorithms, we have solved the first in-vitro structure of the entire efflux pump reveal the assembly architecture of the complex in substrate-free to at 16 Å by single-particle cryo-EM, into which crystallographic structures of individual components could be docked. We have now improved the resolution of this pump to 3.9 Å resolution and solved a number of functional states with substrate binding by single-particle cryo-EM. This new view of the detailed interactions of the components confirms some past proposals and adds fascinating new information for the first time. My laboratory is a pioneer in investigating the in-vivo structure of the efflux pump directly solve in living bacteria using cryoET and our current research efforts are focused on technical development to push higher resolution beyond the current limit. Our newly published in-situ structures resolve key questions concerning stoichiometry in the complete structure and offer new insights into the assembly and operation of important determinants of drug resistance that are conserved in a wide range of pathogens.

   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 Nov;16(11):1161-1168. PubMed PMID: 31611690; PubMed Central PMCID: PMC6858567.
   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 Jun 14;10(1):2635. PubMed PMID: 31201302; PubMed Central PMCID: PMC6570770.
   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 Mar 29;6PubMed PMID: 28355133; PubMed Central PMCID: PMC5404916.
   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 PMID: 24747401; PubMed Central PMCID: PMC4361902.

3. I participated in solving the first near-atomic resolution structures of a number of cation ion channels, including IP3R and full-length Trpv2 by single-particle cryo-EM. Specifically, we discovered a unique architecture in the IP3R C-terminal domain suggests a distinctive allosteric mechanism underlying activation of IP3R gating. Our TRPV2 structures resolve the full-length pore turret and reveal fully open and partially open states of TRPV2, suggest channel regulate the lower gate and couple to the upper gate through a pore-turret-facilitated mechanism.

   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 Jan;26(1):40-49. PubMed PMID: 30598551; PubMed Central PMCID: PMC6458597.
   b. Fan G, Baker MR, **Wang Z**, Seryshev AB, Ludtke SJ, Baker ML, Serysheva II. Cryo-EM reveals ligand induced allostery underlying InsP$_3$R channel gating. Cell Res. 2018 Dec;28(12):1158-1170. PubMed PMID: 30470765; PubMed Central PMCID: PMC6274648.
   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 Nov 19;527(7578):336-41. PubMed PMID: 26458101; PubMed Central PMCID: PMC4804758.
   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 Feb 10;5:8370. PubMed PMID: 25667046; PubMed Central PMCID: PMC4322351.

4. I have been an investigator in the development of experimental methodologies for structural determination of biological assemblies by single-particle cryo-electron microscopy (cryo-EM) towards atomic resolution.

My research including developing experimental methodologies of the first-generation direct electron detection device (DDD) and first solve a high-resolution structure use a small plant virus. My strategy, a novel protocol of data collation and processing includes the first development of the "damage compensation" analysis strategy, is now commonly using 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 to the EM experimental technical development of my group is involving in the usage of support films. We spend efforts in specimen optimization with first observed decreased beam-induced movement in the sample with continuous carbon films compare to sample in ice. In the past few years, we have expanded our technics using Graphene-oxide films. We have recently succeeded in determining maps of several protein samples using single-particle cryo-EM ~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 Apr;6(16):eaay6410. PubMed PMID: 32494598; PubMed Central PMCID: PMC7159914.

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 PMID: 30730999; 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 PMID: 28270620; 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 PMID: 25185801; PubMed Central PMCID: PMC4155512.

*** corresponding author**

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Q-1967-20180324, Welch Foundation WANG (PI)
06/01/18-05/31/21
Determining Chemical Interactions Mediating Biological Complex Formation by Cryo-EM
Role: PI

1RP190602 YR , CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS (CPRIT) LUDTKE (PI)
08/31/19-08/30/24
NEW CAPABILITIES FOR CANCER RESEARCH IN THE TMC CRYOEM CORES
Expand the CryoEM ATC with new equipment and capabilities, and supplement center operations for cancer research
Role: Co-Investigator

5 R01 HD07857, National Institutes of Health Bert O'Malley (PI)
05/01/77-02/08/22
Sex Hormone Receptor Components and the Cell Genome
Role: CPI