BIOGRAPHICAL SKETCH

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NAME: Zhang, Wei

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

POSITION TITLE: Associate 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
Nankai University, Tianjin	BS	07/1989	Biophysics
Institute of Biophysics, Chinese Academy of Science, Beijing	MS	07/1992	Biophysics
Purdue University, West Lafayette, Indiana	PHD	05/2001	Structural Biology
Purdue University, West Lafayette, Indiana	MS	05/2002	Computer Science
Purdue University, West Lafayette, Indiana	Postdoctoral Fellow	07/2002	Structural Biology

A. Personal Statement

I have been doing fundamental research on structural virology for 28 years and will continue to work vigorously on mechanistic studies of enveloped virus assembly and infection, two important stages of the virus life cycle. I have a deep interest in using cryo-electron microscopy (cryo-EM) to understand how structural information of macromolecules is preserved, transformed, detected, verified, reconstituted via computation, and how the structural information is used in deciphering the cellular functions of macromolecules and their roles in biological processes. My research expertise and interest were grounded in my training in physical science as an undergraduate student, the training in computer science as a graduate student, and my Ph.D. training from several key scientists in the world-renowned structural biology group at Purdue University, including Drs. Timothy Baker (Ph.D. mentor), Michael Rossmann, Richard Kuhn and Jue Chen.

One research direction in my lab is to study the dynamic structural changes when the viral membrane fuses with the cellular membrane. We use alphaviruses, as a model system for studying membrane fusion driving by the class II viral fusion proteins. My lab has established reliable and reproducible virus-liposome fusion assays that reveal the alphavirus pre-fusion intermediate and the post- fusion state on the TEM grids. We have hardware and software platforms that support single-particle reconstruction, cryo-electron tomography, and sub-tomogram averaging computations. Through collaboration with Dr. Guichuan Yu, we actively develop computation methods to achieve innovative image processing solutions to challenging problems. We aim to determine the structures of the critical viral proteins at several discernable steps of the membrane fusion. In addition, we propose to further investigate the significance and impact of the specific structure properties of these proteins to the success of the membrane fusion in both *in vitro* and *in vivo* assays. Dr. Chanakha Navaratnarajah from Mayo Clinic is a molecular virologist who has extensive experience in studying the fusion mechanism in several virus systems. This collaborative work will potentially lead to breakthrough discoveries and deepens our understanding of this important biological process.

I have a strong commitment to instrumentation and mentoring graduate students and post-doctoral scientists. I am the PI of several NIH- or university-funded instrumentation grants that upgraded cryo-EM technology on campus. I have mentored and co-mentored five post-doc scientists and several graduate students. Two of the post-doc scientists I mentored and co-mentored have started their independent research positions, as principal investigators. I believe that an effective graduate and post-doctoral training program should not only teach knowledge and methodology relevant to the specific research field but also coach the students' critical scientific skills that include identifying significant research questions, utilizing various theoretical or experimental modalities, integrating information obtained from different sources, critical reasoning, effective communication, and good work ethics. I will cultivate these skills and positive work habits when I mentor graduate students and post-doctoral scientists.

Ongoing research projects include the following:

R21 DE032878, NIH Mansky, Louis (PI); Joachim Mueller & Wei Zhang (Co-I's)
05/01/23-04/30/25

Imaging of HTLV-1 by cryo-CLEM
The goal of this project is to analyze HTLV-1 assembly at cell-cell contact by using cryo-CLEM and cell micropatterning technologies.

R01 AI177264, NIH Mansky, Louis (contact PI) and Mueller, Joachim (PI); Wei Zhang (Co-I)
07/01/23-06/30/28

HIV Gag Lattice Morphology and Particle Biogenesis
This project is to investigate the HIV-2 Gag protein trafficking, virus particle structure and assembly.

R01AI162699-01, NIH Zhang, Wei (PI), Navaratnarajah, Chanakha (Co-I) 04/22/22-03/30/27
Structural Mechanisms of Alphavirus Membrane Fusion
This project studies the conformational changes of Alphavirus structural proteins during membrane fusion

U19AI171954, NIH Harris, Reuben (PI), Li, Fang (Co-I) 05/16/22-04/30/25
Midwest AViDD Center
This center grant conducts the basic and translational research on small molecules against emerging viruses.
Role: Co-Investigator in the Structural Biology Core

Recently completed projects:

R21 AI148328, NIH Zhang, Wei Zhang (contact) and Mansky, Louis (PI)
08/21/20-07/31/23 (in no-cost extension)

Cryo-ET Guided Single Particle Reconstruction of HIV
This project aims to develop an imaging and computation method to study HIV immature particle structure

Citations:

1. Talledge N, Yang H, Shi K, Coray R, Yu G, Arndt WG, Meng S, Baxter GC, Mendonça LM, Castaño-Díez D, Aihara H, Mansky LM*, **Zhang W***. HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. J Mol Biol. 2023 Aug 1;435(15):168143. PMID: 37150290.

   Significance: This study presents the first evidence for a novel stabilization interface mediated by the HIV-2 CA-CTD and provides important clues for explaining differences between HIV-1 and HIV-2 immature particle morphology, as well as insights into Gag lattice stabilization and virus maturation.

2. Shang J, Zheng Y, Yang Y, Liu C, Geng Q, Tai W, Du L, Zhou Y, **Zhang W***, Li F*. Cryo-Electron Microscopy Structure of Porcine Deltacoronavirus Spike Protein in the Prefusion State. J Virol. 2018 Feb 15;92(4) PubMed Central PMCID: PMC5790952.

   Significance: Cryo-EM reconstruction of Deltacoronavirus spike protein at 3.3Å resolution.

3. Cao S, Maldonado JO, Grigsby IF, Mansky LM*, **Zhang W*.** Analysis of human T-cell leukemia virus type 1 particles by using cryo-electron tomography. J Virol. 2015 Feb;89(4):2430-5. PubMed Central PMCID: PMC4338869.

   Significance: First cryo-tomographic study of authentic HTLV-1 particles.

4. Cao S, **Zhang W.** Characterization of an early-stage fusion intermediate of Sindbis virus using cryo-electron microscopy. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13362-7. PubMed Central PMCID: PMC3746934.

   Significance: Discovery that at the initial stage of membrane fusion, Sindbis virus E2 stays as a trimer conformation when E1 attaches to a target membrane.

B. Positions and Honors

Positions and Employment

2023 -	Associate Professor, Department of Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN
2020 -	Research Professor, Department of Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN
2016 - 2020	Research Associate Professor, Department of Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN
2008 -	Scientist, Characterization Facility, University of Minnesota, Minneapolis, MN
2008 - 2016	Research Assistant Professor, Department of Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN
2004 - 2008	Associate Research Scientist, Department of Biological Scientist, Purdue University, West Lafayette, MN
2002 - 2004	Assistant Research Scientist, Department of Biological Sciences, Purdue University, West Lafayette, IN
2001 - 2002	Postdoctoral Research Scientist, Department of Biological Sciences, Purdue University, West Lafayette, IN
1996 - 2001	Graduate Research Assistant, Department of Biological Sciences, Purdue University, West Lafayette, IN
1994 - 1996	Graduate Teaching Assistant, Department of Psychology, Purdue University, West Lafayette, IN
1992 - 1994	Research Associate, Department of Neurobiology, Institute of Biophysics, Chinese Academy of Science, Beijing

Other Experience and Professional Memberships

1997 -	Member, Microscopy Society of America
2002 -	Member, Biophysical Society of America
2003 -	Member, American Society for Virology

Honors

1988	Shen Shou-Chun Experimental Physics 1st Prize, Nankai University, China
1994	Neuroscience Program Graduate Fellowship, Purdue University
1999	Presidential Student Award, Microscopy Society of America
2000	Purdue Research Foundation Grant, Purdue University
2001	Elected as a member, ΤΠΕ - Honor Society in the Computing Sciences
2002	Postdoctoral Travel Award, American Society for Virology 22nd Annual Meeting, Davis, CA
2002	Young Investigator Travel Award, FASEB Summer Research Conference on Virus Assembly, Saxtons River, VT

C. Contribution to Science

1. **Retrovirus assembly and morphogenesis**: This study was done in collaboration with Drs. Joachim Mueller (quantitative super-resolution fluorescence microscopy) and Louis Mansky (virology) at the University of Minnesota. Our interdisciplinary research team employs coordinated biochemical, biophysical and virology approaches to address fundamental questions in retrovirus assembly. We determined the first cryo-ET reconstruction of authentic HTLV-1 particles (ref. d). We also characterized the morphology of retrovirus virus-like particles by cryo-EM, including HTLV-1, HIV-1, HIV-2, Rous sarcoma virus, Mason- Pfizer monkey virus, bovine leukemia virus, walleye dermal sarcoma virus, murine leukemia virus, and human foamy virus (ref. b and c). The following papers are selected from 14 peer-reviewed publications:

    a. Talledge N, Yang H, Shi K, Coray R, Yu G, Arndt WG, Meng S, Baxter GC, Mendonça LM, Castaño-Díez D, Aihara H, Mansky LM*, **Zhang W***. HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. J Mol Biol. 2023 Aug 1;435(15):168143. PMID: 37150290.

Significance: This study presents the first evidence for a novel stabilization interface mediated by the HIV-2 CA_{CTD} and provides important clues for explaining differences between HIV-1 and HIV-2 immature particle morphology, as well as insights into Gag lattice stabilization and virus maturation

b. Yang H, Arndt WG, **Zhang W***, Mansky LM*. Determinants in the HTLV-1 Capsid Major Homology Region that are Critical for Virus Particle Assembly. J Mol Biol. 2024 Dec 15;436(24):168851. PubMed Central PMCID: PMC11637902.

Significance: First comprehensive analysis about the MHR region of the HTLV-1 capsid.

c. Martin JL, Mendonça LM, **Zhang W***, Mansky LM*. Distinct particle morphologies revealed through comparative parallel analyses of retrovirus-like particles. J Virol. 2016 Sep15; 90(18): 8074-84. PMID: 27356903; PMCID: PMC5008088.

Significance: Cryo-EM description of the distinct morphological features that exist among retrovirus-like particles in a comparative, parallel analysis.

d. Cao S, Maldonado JO, Grigsby IF, Mansky LM*, **Zhang W***. Analysis of human T-cell leukemia virus type 1 particles by using cryo-electron tomography. J Virol. 2015 Feb;89(4):2430-5. PubMed Central PMCID: PMC4338869.

Significance: First cryo-ET study of authentic HTLV-1 particles

* co-corresponding author

4. **Structure studies on alphavirus and flavivirus assemblies:** my research in this area has led to several influential discoveries: (1) The first cryo-EM structure of Sindbis virus that resolved the shape of both E1 and E2 protein densities on the viral membrane (ref. a); (2) The first flavivirus (dengue virus) structure that revealed the molecular arrangement of the surface E proteins and densities of M proteins illustrating the tetramer organization of E and M (ref. b and c). This result and method developed in this paper paved the way for the structural studies on other prominent flaviviruses including West Nile virus and Zika virus. (3) The membrane fusion intermediate structure of Sindbis virus when attaching to a target membrane at the low pH condition (ref. d). The following papers are chosen from 15 peer-reviewed research papers:

a. **Zhang W**, Mukhopadhyay S, Pletnev SV, Baker TS, Kuhn RJ, Rossmann MG. Placement of the structural proteins in Sindbis virus. J Virol. 2002 Nov;76(22):11645-58. PubMed Central PMCID: PMC136788.

b. **Zhang W**, Chipman PR, Corver J, Johnson PR, Zhang Y, Mukhopadhyay S, Baker TS, Strauss JH, Rossmann MG, Kuhn RJ. Visualization of membrane protein domains by cryo-electron microscopy of dengue virus. Nat Struct Biol. 2003 Nov;10(11):907-12. PubMed Central PMCID: PMC4148076.

Significance: 9Å resolution reconstruction map that confirmed the fitted atomic model of Dengue virus

c. Yu IM, **Zhang W**, Holdaway HA, Li L, Kostyuchenko VA, Chipman PR, Kuhn RJ, Rossmann MG, Chen J. Structure of the immature dengue virus at low pH primes proteolytic maturation. Science. 2008 Mar 28;319(5871):1834-7. PubMed PMID: 18369148.

Significance: Deciphering the structural changes during Dengue virus maturation

d. Cao S, **Zhang W**. Characterization of an early-stage fusion intermediate of Sindbis virus using cryoelectron microscopy. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13362-7. PubMed Central PMCID: PMC3746934.

4. **Technique development:** I have a great interest in developing novel methods to expedite cryo-EM image processing and to solve challenging problems. Some of the computation tools are disseminated after publication and used by others in the field. Technology development will be one of the principal research themes in my lab. My original computation work includes: (1) Using microscope contrast transfer function as a weighting function in resolving 3D reconstruction maps: this approach significantly improved the resolution of the reconstruction map from data sets with limited variation of under-focus conditions; (2) Particle orientation determination for elongated Geminivirus particles (ref. a): this approach led to the first reconstruction map of a geminate virus particle. (3) Analyzing the curvature of the viral membrane in flavivirus and alphavirus (ref. c): this work demonstrates an algorithm that computes curvature, a property derived from the differential equation in positions of pixelated cryo-EM maps. (4) Determining the liposome- binding site on the surface of an icosahedral particle at low pH (ref. d): this work led to characterization of an early-state fusion intermediate of Sindbis

virus. The following papers are selected from 7 peer-reviewed research papers that reported these image processing methods:

a. **Zhang W**, Olson NH, Baker TS, Faulkner L, Agbandje-McKenna M, Boulton MI, Davies JW, McKenna R. Structure of the Maize streak virus geminate particle. Virology. 2001 Jan 20;279(2):471-7. PMID: 11162803.

   Significance: Establishing an orientation determination method that led to the first reconstruction map of a Geminivirus

b. Ji Y, Marinescu DC, **Zhang W**, Zhang X, Yan X, Baker TS. A model-based parallel origin and orientation refinement algorithm for cryoTEM and its application to the study of virus structures. J Struct Biol. 2006 Apr;154(1):1-19. PMID: 16459100; PMCID: PMC4147871.

   Significance: Reporting a parallel origin orientation determination and refinement software package

c. **Zhang W**, Kaufmann B, Chipman PR, Kuhn RJ, Rossmann MG. Membrane curvature in flaviviruses. J Struct Biol. 2013 Jul;183(1):86-94. PMID: 23602814; PMCID: PMC4091808.

   Significance: Implementing an algorithm that determines the membrane curvature from pixelated cryo-EM reconstruction density maps

d. Cao S, **Zhang W**. Characterization of an early-stage fusion intermediate of Sindbis virus using cryoelectron microscopy. Proc Natl Acad Sci U S A. 2013 Aug 13;110(33):13362-7. PMID: 23898184; PMCID: PMC3746934.

   Significance: Elucidating an algorithm that determines the unique liposome-binding site on an icosahedral Sindbis virus particle

Complete List of PubMed Cited Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/wei.zhang.11/bibliography/public/