BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Zhang, Wei

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

POSITION TITLE: Research 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 25 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 cryo-electron microscopy (cryo-EM), in particular, understanding 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.

The research in my lab has been focused on the studies of the structural biology of retrovirus assembly (in collaboration with Dr. Louis Mansky and Dr. Joachim Mueller) and enveloped virus membrane fusion (in collaboration with Dr. Guichuan Yu from the Informatics Institute and Dr. Chanakha Navaratnarajah from Mayo Clinic). My lab has hardware and software platforms that support single-particle reconstruction, cryo-electron tomography, and sub- tomogram averaging computations. Together with Dr. Louis Mansky and Dr. Joachim Mueller, we study morphogenesis and infection of human immunodeficiency virus type 2 (HIV-2), HIV-1 and human T-cell leukemia virus type 1 (HTLV-1). We are also actively developing new technologies that enhance our understanding about HTLV-1 assembly, budding and maturation. This collaborative work will potentially lead to breakthrough discoveries and deepens our understanding of this important human pathogen.

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. 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.

BIOGRAPHICAL SKETCH

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NAME: Mansky, Louis M.

eRA COMMONS USER NAME (credential, e.g., agency login): mansky03

POSITION TITLE: Professor & Director

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
Purdue University, W. Lafayette, IN	B.S.	05/1984	Biology
Iowa State University, Ames, IA	Ph.D.	07/1990	Molecular Virology
University of Wisconsin, Madison, WI	Postdoc	12/1992	Human Retrovirology
University of Wisconsin, Madison, WI	Res. Asso.	08/1996	Human Retrovirology

A. Personal Statement

I have been engaged in virology research for over 38 years. My training in retrovirology began in the laboratory of Dr. Howard Temin at the McArdle Laboratory for Cancer Research, University of Wisconsin-Madison. As an independent investigator, my research group has had intense research interests on human retrovirus (i.e., HIV, HTLV) replication (reverse transcription, virus assembly), pathogensis, evolution and antiretroviral therapy (drug target identification, drug resistance). Our research has been extended to address related questions with hepadnaviruses (i.e., hepatitis B virus, HBV). Key recent findings from my research group have led to 1) the discovery of the interrelationship between the HIV-1 mutation rate and viral fitness, 2) discovery that G-to-A hypermutation susceptibilities are different between HIV-1 and HIV-2 but that these viruses otherwise have comparable mutation rates, 3) the discovery of drugs that harness and elevate the ability of HIV-1 to mutate and induce lethal mutagenesis, 4) the preclinical evaluation of HIV-1 lethal mutagenesis as a novel anti-HIV-1 therapy in an AIDS mouse model, 5) the discovery of novel ribonucleoside analogs that intriguingly possess anti-HIV-1 activity, 6) the analysis of the potential for APOBEC3G to contribute to HIV-1 genetic variation and evolution through sublethal mutagenesis, 7) first cryo-electron tomography characterization of authentic HTLV-1 particles, 8) discovery of distinct modes of Gag oligomerization between HIV-1 and HTLV-1, 8) discovery of a role of the actin cortex as a physical barrier to HIV particle assembly, 9) discovery of novel structural environments that help explain morphological differences between HIV-1 and HIV-2 and influence Gag lattice stability and virus maturation.

I have mentored over 37 undergraduate students, 21 predoctoral students and 13 postdoctoral fellows, and I have acted as a mentor for 7 faculty during their time as junior faculty (e.g., Reuben Harris, Fang Li, Shelley Grimes, Paul Jardine, Wei Zhang, Christine Clouser, José Maldonado-Ortiz, Luiza Mendonça). Most all of my trainees have been successful in securing federal/foundation support during the time of their training as part of their career development. Former predoctoral and postdoctoral students have secured faculty positions at major research universities (e.g., Casey Dorr, Huating Wang, Lauren Beach, José Maldonado-Ortiz, Luiza Mendonça) and liberal arts colleges (e.g., Richard Heineman, Keir Fogarty), as well as research positions in private and federal research laboratories (e.g., Renxiang Chen, Nancy Jewell, Iwen Grigsby, Azah Tabah). Others are still in training. I have been particularly dedicated to the training of underrepresented minority predoctoral (Raquel Raices, Casey Dorr, Lauren Beach, José Maldonado-Ortiz, Makky Mousa-Makky) and postdoctoral (Willie Greggs, Azah Tabah, Luiza Mendonça) students.

I am the founding Director of the Institute for Molecular Virology (IMV), which is a campus-wide institute that unites all UMN researchers conducting research on viruses – a major focus of which is retrovirology, and have served in this role since 2003. I have twice served as a Principal Investigator for our

BIOGRAPHICAL SKETCH

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NAME: William Arndt

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

POSITION TITLE: PhD Candidate Research Assistant

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
University of Minnesota- Twin Cities, Minneapolis, MN	B.S.	09/2016	12/2019	Biochemistry
University of Minnesota - Twin Cities, Minneapolis, MN	Ph.D.	08/2021	In progress	Molecular, Cellular, and Structural Biology

A. Personal Statement

My research interests are focused on understanding human retrovirus particle assembly and morphology and its relationship to pathogenicity by using structural and biochemical techniques. My education and research experience has provided me with a strong foundation in biochemistry and molecular biology.

During my undergraduate studies, I began working in the Dr. Louis Mansky lab, where I decided to change career paths after becoming interested in HIV molecular and structural biology. I gained experience in protein purification and mammalian cell culture. Following my undergraduate studies, I joined the Dr. Mansky lab as a research assistant before applying to graduate school. I continued to gain knowledge and expertise in HIV particle assembly and began learning the experimental workflow in cryo-electron microscopy (cryo-EM). These experiences have solidified my interest in using structural techniques to better understand HIV particle assembly and morphology. I am particularly interested in gaining strong expertise in cell culture-based HIV molecular biology as well as harnessing the latest technological advancements in HIV structural biology, such as cryo-electron tomography (cryo-ET) and cryo-correlative light and electron microscopy (cryo-CLEM), which together will allow me to help address knowledge gaps in the field of HIV assembly.

I wanted to continue my training and education at the University of Minnesota – Twin Cities due to the diverse subset of researchers focused on virology and the strong sense of collaboration. Furthermore, I also wanted to continue my training in the lab of Dr. Mansky due to his extensive experience in mentoring highly productive and successful Ph.D. students and because of having the opportunity to expand my skills and expertise in cryo-EM by working collaboratively with Dr. Wei Zhang. Outside of gaining expertise in structural retrovirology, I knew I would continue to advance my skills in molecular retrovirology. Further, Dr. Mansky is a champion of collaborative research, which will allow me to engage with researchers here at the University of Minnesota as well as other institutions for enhancing my research and career development. I have completed my coursework, including 3 graduate virology courses and a biostatistics course.

B. Positions, Scientific Appointments and Honors

Positions:

2018-2019	Undergraduate Research Assistant, University of Minnesota – Twin Cities, MN
2020-2021	Researcher 1, University of Minnesota – Twin Cities, MN
2021-Present	Graduate Research Assistant, University of Minnesota

Honors:

2016-2019	University of Minnesota Dean's List
2021-Present	Institute for Molecular Virology T32 Training Program Fellowship

C. Contributions to Science

Research Assistant:

As a research assistant in the Mansky lab, I was able to work on the development of sensitive sequencing approaches for more accurate estimation and characterization of mutations occurring during HIV-1 and HIV-2 infection. My work on these projects included generating high quality DNA samples for mutation analysis, fine-tuning the mutational analysis workflow, and analyzing complex datasets.

1. Meissner, M.E.; Julik, E.J.; Badalamenti, J.P.; **Arndt, W.G**.; Mills, L.J.; Mansky, L.M. *Development of a User-Friendly Pipeline for Mutational Analyses of HIV Using Ultra-Accurate Maximum-Depth Sequencing*. Viruses, 2021. **13**(7):1338. doi: 10.3390/v13071338. PMID: 34372543; PMCID: PMC8310143.

   Contribution: My role for this work was to prepare and optimize the generation of high-quality DNA to be used for the sequencing approach. I also contributed to some of the complex data analysis from the sequencing data.

2. Meissner, M.E., Willkomm, N.A., Lucas, J., **Arndt, W.G**., Aitken, S.F., Julik, E.J., Baliga, S., Mansky, L.M. *Differential Activity of APOBEC3F, APOBEC3G, and APOBEC3H in the Restriction of HIV-2*. 2022. J Mol Biol*,* 2022*.* **434**(2): p. 167355. doi: 10.1016/j.jmb.2021.167355. Epub 2021 Nov 10. PMID: 34774569; PMCID: PMC8752514.

   Contribution: I aided in optimizing and preforming infectivity assays with virus produced in the presence of different APOBECS. I also aided in generating and analyzing mutational data from the above infections.

Graduate Research:

My current research is focused on understanding how unique capsid interactions results in differential retroviral particle morphologies. This work has focused on using *in vitro* systems to purify and assemble regions of the Gag polyprotein. These studies will benefit the field of retrovirology by deepening the knowledge surrounding capsid assembly mechanisms and particle maturation. I am a co-author on the below manuscript, which is centered around understanding the unique morphology of HIV-2 capsid, as described in my proposal.

3. Yang, H., Talledge N., **Arndt, W.G.,** Zhang W., Mansky L.M. *Human Immunodeficiency Virus Type 2 Capsid Protein Mutagenesis Reveals Amino Acid Residues Important for Virus Particle Assembly.* J Mol Biol, 2022. **434**(19): p.167753. doi: 10.1016/j.jmb.2022.167753. Epub ahead of print. PMID: 35868362.

   Contribution: I designed and optimized the purification and *in vitro* assembly assay for the HIV-2 CA-NC protein. I also generated negative stain images for the final manuscript.

4. Talledge, N., Yang, H., Shi, K., Yu, G., **Arndt, W.G**., Mendonca, L.M., Aihara, H., Mansky, L.M., Zhang, W., *HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. Revised manuscript submitted for publication*; *bioRxiv* DOI: 10.1101/2022.02.01.478508

Contribution: I aided with the design and implementation of the mutational studies for Gag assemlby and the maturation, which provided insights into helix 10 and helix 12 interations in the capsid protein.

Scientific Presentations (Abstracts)

Wisc-e-sota Collaborative UMN-UW Virology Training Grant Symposium – Poster Presentation, October 2022. Arndt WG**,** Talledge N, Zhang W, Mansky LM. *High-resolution structural analysis of capsid-capsid interactions reveals novel insights into human retrovirus particle morphology.*

Institute for Molecular Virology Symposium – Oral Presentation, Minneapolis, MN, May 2022 Arndt WG**,** Talledge N, Zhang W, Mansky LM. *Cryo-EM Analysis of Human Retrovirus Capsid Protein Assemblies: Insights into Immature and Mature Particle Morohpology.*

International Conference on Human Retrovirology: HTLV and Related Viruses (HTLV22) – Poster Presentation, March 2022. Arndt WG**,** Talledge N, Zhang W, Mansky LM. *High-resolution structural analysis of capsid-capsid interactions reveals novel insights into human retrovirus particle morphology.*

Wisc-e-sota Collaborative UMN-UW Virology Training Grant Symposium – Oral Presentation, La Crosee, WI. October 2021. Arndt WG**,** Talledge N, Zhang W, Mansky LM . *Cryo-EM Analysis of Human Retrovirus Capsid Protein Assemblies.*

Institute for Molecular Virology Symposium – Poster Presentation, Minneapolis MN, June 2021 Meissner ME, Arndt WG, Julik E, Badalamenti JP, Mills LJ, Mansky LM, *Investigation of SAMHD1 and its role in enhancing HIV mutagenesis.*

D. Scholastic Performance

YEAR	COURSE TITLE	GRADE
	University of Minnesota – Twin Cities Undergraduate Coursework	
2016	The Future Physician I	A
2016	Chemical Principles I	A-
2016	Chemical Principles I Lab	C+
2016	Linear Algebra and Differential Equations	A
2016	Physics for Science and Engineering I	A
2016	Intro to Sociology	A
2017	Art & the Environment	B
2017	Chemical Principles II	A
2017	Chemical Principles II Lab	B
2017	Physics for Science and Engineering II	A-
2017	University Writing	A-
2017	Foundation of Biology I	A
2017	Foundation of Biology Lab I	A
2017	Organic Chemistry I	A
2017	Rhetorical Fiction & 20th Century Conflict	A
2017	Principles of Microeconomics	A
2018	Intro to Financial Reporting	A
2018	Foundation of Biology II	A
2018	Foundation of Biology Lab II	A
2018	Molecular Biology and Society	S
2018	Organic Chemistry II	A

YEAR	COURSE TITLE	GRADE
2018	Intro to Management Accounting	A
2018	Structure/Catalysis/Metabolism	A
2018	Genetics	A
2018	Organic lab	A-
2018	Intro to Entrepreneurship	A
2019	Laboratory in Biochemistry	A
2019	Signal Transduction and Gene Expression	A
2019	Intro to Physical Biochemistry	A
2019	Directed Research	S
2019	Biotechnology and Bioengineering	A
2019	Finance Fundamentals	A
2019	Cell Biology	A
2019	Ecology	A
2019	Molecular Biology of Cancer	A
2019	Fundamentals of Management	A
	University of Minnesota – Twin Cities Graduate Coursework	
2021	Biochemistry: Structure and Catalysis	A
2021	Introduction to Modern Structural Biology - Diffraction	B
2021	Molecular Biology of DNA	A-
2021	Research & Literature Reports	S
2021	MCDG Special Topics	S
2021	Virology Research Presentations	S
2021	Evolution of Emerging Viruses	A
2022	Evaluation of Biochemical Research	S
2022	Ethics and Policy in Molecular and Cellular Biology	S
2022	Computational Genomics	A
2022	Molecular Virology	A
2022	Virus Pathogenesis	A
2022	Immunology and Immunopathology	A-
2022	Biostatistics I	A
2022	Graduate Seminar	S

At the University of Minnesota, various classes are offered on a S/N grading scale. On this scale, S is equivalent to a C- or better.

Undergraduate Cumulative GPA: 3.901
Graduate Cumulative GPA: 3.826

Research Support

Award: NIH T32, Institute for Molecular Virology NIH T32 Training Program
Type: Predoctoral T32 Fellow
Funding Period: September 1, 2021-August 31, 2022. Renewed September 1, 2022-August 31, 2023.

institution's first NIH T32 training program dedicated to virology research, as well as succeeding in attracting to the UMN in 2009 the 7th International Retrovirus Nucleocapsid Symposium as well as the 30th American Society for Virology (ASV) Annual Meeting in 2011. My leadership as IMV Director has helped to increased national and international recognition of the UMN's virology research community. The recognition has led to our institution being selected host a return visit of the ASV Annual Meeting in 2019 (Local Host: Reuben Harris), and now slated to host ASV 2026.

I am highly enthusiastic to continue my longstanding collaboration with Dr. Joachim Mueller and Dr. Wei Zhang to address fundamental knowledge gaps in the field of HIV particle assembly in this multi-PI grant.

Ongoing research projects include the following:

"HTLV-1 Particle Analysis and Gag Interactions"
Principal Investigator: Louis M. Mansky, Ph.D.; Joachim Mueller & Wei Zhang (Co-I's)
Agency: National Institutes for Health
Type: R01 (GM098550) Period: July 1, 2012-Apr 30, 2023* (In 2nd no-cost extension)

Project goal: The goal of this project is to investigate the HTLV-1 Gag protein trafficking virus particle structure and assembly.

"HIV Gag Lattice Morphology and Particle Biogenesis"
Principal Investigator: Louis M. Mansky, Ph.D. (Contact PI); Joachim Mueller (PI) & Wei Zhang (Co-I)
Agency: National Institutes for Health
Type: R01 AI150468 Period: September 30, 2017-August 31, 2023* (In 2nd no-cost extension)

Project goal: The goal of this project is to investigate the HIV Gag lattice morphology and particle biogenesis.

"Cryo-ET Guided Single Particle Reconstruction of HIV"
Principal Investigator: Wei Zhang, Ph.D. (Contact PI); Louis M. Mansky, Ph.D. (PI)
Agency: National Institutes for Health
Type: R21 AI148328 Period: August 21, 2020-July 31, 2023* (In no cost ext.)

Project goal: The goal of this project is to develop novel approaches for conducting cryo-electron microscopy approaches that are guided by single particle reconstruction of HIV.

"Minnesota Training Program in Virology"
Principal Investigator: Louis M. Mansky, Ph.D.
Agency: National Institutes for Health
Type: T32AI83196 Period: July 1, 2010-June 30, 2025

Project goal: The goal of this training program is to support the career development of young scientists who will help develop new antiviral drugs and vaccines for viral diseases.

Highlighted publications from the past decade:

1. Rawson JMO, Gohl DM, Landman SR, Roth ME, Meissner ME, Peterson TS, Hodges JS, Beckman KB, **Mansky LM**. 2017. Single-strand consensus sequencing reveals that HIV type but not subtype significantly impacts viral mutant frequencies and spectra. Journal of Molecular Biology 429:2290-2307.

   Significance: Discovery that HIV-2 reverse transcription occurs with higher fidelity than that of HIV-1.

2. Eichorst JE, Chen Y, Mueller JD, **Mansky LM**. 2018. Distinct pathway of human T-cell leukemia virus type 1 Gag punctum biogenesis provides new insights into enveloped virus assembly. mBio 9(5). pii: e00758-18. doi: 10.1128/mBio.00758-18.

   Significance: First demonstration of a distinct pathway for virus particle assembly for HTLV-1.

3. Angert, I, Karuka SD, **Mansky LM**, Mueller, J.D., 2022. Partitioning of ribonucleoprotein complexes from the cellular actin cortex. Sciences Advances 8(33):eabj3236; doi: 10.1126/sciadv.abj3236

   Significance: This research provides evidence that the actin cortex meshwork can play a role in regulating retroviral genome RNA in complex with Gag protein at the plasma membrane.

4. Talledge N, Yang H, Shi K, Coray R, Yu G, Arndt WG, Mendonça LM, Castaño-Díez, Aihara H, **Mansky LM**., Zhang W. 2022. HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. Journal of Molecular Biology *In revision.* bioRxiv, DOI: 10.1101/2022.02.01.478508

   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.

* Co-corresponding author

B. Positions. Scientific Appointments, and Honors

Positions

2007-present	Professor, University of Minnesota, Minneapolis, MN
2003-present	Director, Institute for Molecular Virology, University of Minnesota, Minneapolis, MN
2003-2007	Associate Professor, University of Minnesota, Minneapolis, MN
2002-2003	Associate Professor, Ohio State University, Columbus, OH
1997-2002	Assistant Professor, Ohio State University, Columbus, OH
1996-1997	Assistant Professor, Creighton University School of Medicine, Omaha, NE
1993-1996	Research Associate, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison
1990-1992	Postdoctoral Fellow, McArdle Laboratory, University of Wisconsin-Madison, Madison, WI

Service

2016	Organizer, Retroviruses Satellite Meeting, American Society for Virology Annual Mtg
2016	Co-Organizer, 2016 Cold Spring Harbor Laboratory Retroviruses Meeting
2011	Local Faculty Host, 30th Annual American Society for Virology (ASV) Meeting
2009	Local Organizer, 7th International Retrovirus Nucleocaspid Symposium
2007-present	Member, External Advisory Cmte, School of Science, Purdue University
2013-present	Member, Editorial Board, Virology
2010-present	Member, Editorial Board, PLoS One
2010-present	Member, Editorial Board, *Current HIV Research*
2006-2010	Member, AIDS Molecular and Cell Biology (AMCB) study section, NIH
2004-present	Adhoc Member, Virology B study section, NIH
2003-2008	Member, Editorial Board, *Retrovirology*
2002-2006	Adhoc Member, AIDS Molecular and Cell Biology (AMCB) study section, NIH
1997-present	Ad hoc Reviewer, > 20 scientific journals, including *J. Virol., Virology, PNAS, & J. Biol. Chem.*

Honors/Awards

2007	Distinguished Alumni Award in Biological Sciences, Purdue University
2004	NRSA Career Development Award
1990	Postdoctoral Fellowship, NRSA
1989	Gamma Sigma Delta Honor Society (Plant Molecular Virology/Agriculture)
1988	Sigma Xi Grant-in-Aid for Research
1988	American Society for Microbiology President's Fellowship

C. Contributions to Science

Cell and molecular biology of human cancer virus assembly and virus particle structure, and applications

Central steps in the retrovirus life cycle include the trafficking of Gag, Env and the viral RNA to the plasma membrane, Gag oligomerization, RNA genome recognition by Gag, Env incorporation, and ultimately the biogenesis of virus particles. The details behind how Gag trafficking as well as virus particle biogenesis occurs is currently being investigated via interdisciplinary collaboration by employing highly sophisticated cell biology and imaging approaches - including fluorescence spectroscopy methodologies that have single molecule resolution, total internal reflection fluorescence (TIRF) microscopy, photoactivated localization microscopy (PALM), as well as cryoelectron microscopy/tomography. A long-term goal of these studies is to develop a better understanding of the detailed steps of Gag oligomerization and virus biogenesis/virus

structure for better understanding the basis for cell-to-cell transmission of HTLV-1 infectivity – a crucial aspect of HTLV-1 pathogenesis required to establish new infections. Such studies are amendable towards the use of virus-like particles for many different types of nanoparticle applications. Key discoveries made from this research include 1) discovery of distinct modes of Gag oligomerization between HIV-1 and HTLV-1 and 2) first cryo-electron tomography characterization of authentic HTLV-1 particles. These are collaborative studies with Drs. Joachim Mueller and Wei Zhang, who are both members of the Institute for Molecular Virology, University of Minnesota. Ongoing collaborative studies are being extended to 1) HIV-1 envelope protein stoichiometry on virus particles, and 2) identifying the location of virus particle assembly/budding sites in various biologically relevant cell types.

1. Fogarty, KH, Grigsby, IF, Chen, Y, **Mansky, LM***, Mueller, JD.* 2014. Interrelationship between cytoplasmic retroviral Gag concentration and Gag-membrane association. Journal of Molecular Biology426:1611-1624. PMCID: PMC3951590

   Significance: Discovery that HIV-1 Gag reaches a critical cytoplasmic concentration before dimers form and traffic to the plasma membrane, while HTLV-1 Gag trafficks as a monomer to the plasma membrane.

2. Martin JL, Cao S, Maldonado JO, Zhang W, **Mansky LM**. 2016. Distinct particle morphologies revealed through comparative parallel analyses of retrovirus-like particles. Journal of Virology 90:8074-84.

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

3. Eichorst JE, Chen Y, Mueller JD, **Mansky LM**. 2018. Distinct pathway of human T-cell leukemia virus type 1 Gag punctum biogenesis provides new insights into enveloped virus assembly. mBio 9(5). pii: e00758-18. doi: 10.1128/mBio.00758-18.

   Significance: First demonstration of a distinct pathway for virus particle assembly for HTLV-1.

4. Angert, I, Karuka SD, **Mansky LM**, Mueller, J.D., 2022. Partitioning of ribonucleoprotein complexes from the cellular actin cortex. Sciences Advances 8(33):eabj3236; doi: 10.1126/sciadv.abj3236

   Significance: This research provides evidence that the actin cortex meshwork can play a role in regulating retroviral genome RNA in complex with Gag protein at the plasma membrane.

* Co-corresponding author

HIV-1 Genetic Diversity and Evolution, Mechanisms of HIV-1 Mutagenesis

My research in this area had led to several important recent findings, including 1) the discovery of the interrelationship between the HIV-1 mutation rate and viral fitness, 2) discovery that HIV-1 and HIV-2 have different mutation rates, in part due to susceptibility to G-to-A mediated hypermutagenesis, 3) the discovery of viral mutagens that can extinguish HIV-1 infectivity through lethal levels of mutations, 4) the discovery of novel ribonucleoside analogs that intriguingly possess anti-HIV-1 activity, 5) the analysis of the potential for APOBEC3G to contribute to HIV-1 genetic variation and evolution through sublethal mutagenesis.

1. Dapp, MJ, Heineman, R, **Mansky LM**. 2013. Interrelationship between HIV-1 fitness and mutation rate. Journal of Molecular Biology 425:41-53. PMCID: PMC3534800

   Significance: Discovery of the interrelationship between HIV-1 fitness and mutation (i.e., increases or decreases in mutation rate result in a reduction in viral fitness).

2. Rawson JMO, Gohl DM, Landman SR, Roth ME, Meissner ME, Peterson TS, Hodges JS, Beckman KB, **Mansky LM**. 2017. Single-strand consensus sequencing reveals that HIV type but not subtype significantly impacts viral mutant frequencies and spectra. Journal of Molecular Biology 429:2290-2307.

   Significance: Discovery that HIV-2 reverse transcription occurs with higher fidelity than that of HIV-1.

3. Meissner ME, Julik EJ, Badalamenti JP, Arndt WG, Mills LJ, **Mansky LM**. 2021. Development of a User-Friendly Pipeline for Mutational Analyses of HIV Using Ultra-Accurate Maximum-Depth Sequencing. Viruses. 2021 Jul 11;13(7):1338. doi: 10.3390/v13071338. PMID: 34372543; PMCID: PMC8310143.

   Significance: Development of ultrasensitive workflow to investigate sources of HIV mutagenesis.

4. Meissner ME, Willkomm NA, Lucas J, Arndt WG, Aitken SF, Julik EJ, Baliga S, **Mansky LM**. 2022. Differential Activity of APOBEC3F, APOBEC3G, and APOBEC3H in the Restriction of HIV-2. J Mol Biol. 2022 Jan 30;434(2):167355. doi: 10.1016/j.jmb.2021.167355. Epub 2021 Nov 10. PMID: 34774569; PMCID: PMC8752514.

   Significance: Discovery of differential activities of APOBEC3 proteins among HIV-1 and HIV-2.

Complete list of publications in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/louis.mansky.1/bibliography/41159407/public/?sort=date&direction=ascending

Ongoing research projects include the following:

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

R01GM098550, NIH Mansky, Louis (PI); Joachim Mueller & Wei Zhang (Co-I's)
07/ 01/12-04/30/23 (In 2nd no-cost extension)
HTLV-1 Particle Analysis and Gag Interactions
This project is to investigate the HTLV-1 Gag protein trafficking, virus particle structure and assembly.

R01AI150468, NIH Mansky, Louis (contact PI) and Mueller, Joachim (PI); Wei Zhang (Co-I)
09/30/17-08/31/23 (In 2nd no-cost extension)
HIV Gag Lattice Morphology and Particle Biogenesis
This project is to investigate the HIV-2 Gag protein trafficking, virus particle structure and assembly.

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

U24 GM116789, NIH Contact PI: Jiang, Wen, Purdue University 06/01/17-05/31/23
Midwest Consortium for High Resolution Cryoelectron Microscopy
Role: PI

Citations:

1. Talledge N, Yang H, Shi K, Coray R, Yu G, Arndt WG, Mendonça LM, Castaño-Díez, Aihara H, Mansky LM* and **Zhang W***. 2022. HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. J Mol Biol; In revision; bioRxiv DOI: 10.1101/2022.02.01.478508

   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

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, Mendonça LM, Castaño-Díez D. Aihara H, Mansky LM***** and **Zhang W***. 2022. HIV-2 Immature Particle Morphology Provides Insights into Gag Lattice Stability and Virus Maturation. J Mol Biol; In revision; bioRxiv DOI: 10.1101/2022.02.01.478508

   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. Meissner ME, Mendonça LM, **Zhang W***, Mansky LM*. Polymorphic Nature of Human T-Cell Leukemia Virus Type 1 Particle Cores as Revealed through Characterization of a Chronically Infected Cell Line. J Virol. 2017 Aug 15; 91(16):e00369-17. PMID: 28615198; PMCID: PMC5533927.

Significance: First cryo-EM examination of HTLV-1 core morphology in chronically infected cell lines

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

2. **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.

3. **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/