Lisa Eshun-Wilson, Ph.D.
NSF Postdoctoral Fellow
Department of Integrative Structural
and Computational Biology
10550 North Torrey Pines Road
La Jolla, California 92037 USA
Phone: (858) 248-1198
Email: leshunwilson@scripps.edu

EDUCATION AND TRAINING

2020 Postdoctoral fellowship in Structural and Computational Biology at the **Scripps Research Institute**, La Jolla, CA
2019 **Ph.D.** in Molecular Cell Biology, **University of California, Berkeley**, CA
2015 Postbaccalaureate Intramural Research Training Awardee (IRTA) in Membrane Biology at the Laboratory of Cell Biology, **National Heart, Lung and Blood Institute** (NHLBI/NIH), Bethesda, MD
2014 **B.A.** in Biological Chemistry, **Grinnell College**, Grinnell, IA

RESEARCH EXPERIENCE

2020–Present	Postdoctoral Fellow, Department of Integrative Structural and Computational Biology, La Jolla, CA, Advisor: **Gabe Lander, PhD** *Funding: National Science Foundation Postdoctoral Research Fellowship in Biology (**NSF-PRFB**)*
2015–2019	PhD Candidate, Department of Molecular Cell Biology, Division of Biochemistry, Biophysics, and Structural Biology, University of California, Berkeley, CA, Advisor: **Eva Nogales, PhD** *Funding: National Science Foundation Graduate Research Fellowship Program (**NSF-GRFP**)*
2014–2015	Postbaccalaureate Fellow, Laboratory of Cell Biology, National Heart, Lung and Blood Institute, Bethesda, MD, Advisor: **Julie Donaldson, PhD** *Funding: Intramural Research Training Award (**IRTA**)*

PUBLICATIONS

Eshun-Wilson, L.*, Ferro, L.*, Fang Q.*, Fernandes, J*, Jack A, Gölcük M, Fernandes J, Huijben T, Costa K, Gür M, DiMaio, F., Nogales, E., Yildez, A. Structural and functional insight into regulation of kinesin-1 by microtubule-associated protein MAP7. UCB, Berkeley, CA. ***Science*** (2022) 375 (6578) 326-331. ***Equal contribution**.

Eshun-Wilson L, Zhang R, Portran D, Toso D, Nachury M, Bonomi M, Fraser JS, Nogales E. Structural insights into the effects of α-tubulin acetylation on microtubule structure and properties. ***Proceedings of the National Academy of Sciences*** (2019) 116 (21) 10366-10371. *Cited by 231.*

Eshun-Wilson L*, Torrents de la Peña A*, Sliepen K*, Newby M, Allen J, Koekkoek S, Zon I, Chumbe A, Crispin M, Schinkel J, Sanders R, Lander G, Ward A. Structure of full-length hepatitis C virus E1E2 glycoprotein complex. ***Science*** (2022) 6617 (378) 263-269. ***Equal contribution**.

Martin G, Quintero MLF, Lee WH, Pholcharee T, **Eshun-Wilson L**, Liedl KR, Pancera M, Seder RA, Wilson IA, Ward AB. Structural basis of epitope selectivity and potent protection from malaria by PfCSP antibody L9. ***Nature Communications*** (2023) 14 (2815) 1-11.

FELLOWSHIPS AND AWARDS, AND INVITED SPEAKING ENGAGEMENTS

2023 ***Cryo-EM Grant Award*, Thermo Fisher Scientific, FEI, Inc.**
2023 *Invited Speaker,* Spring Lecture (Přednáška) Series, Prague IOCB, Prague, Czech Republic
2022 *Invited Speaker,* Next Generation in Biomedicine, Broad Institute, Boston, MA
2022 *Invited Speaker,* Rising Stars Symposium, University of Utah, Salt Lake City, UT
2022 ***Awardee,* Scripps Annual Postdoctoral Travel Award for Excellence in Research**
2022 *Awardee,* National Institutes of Health Loan Repayment Program (NIH-LRP)
2022 *Session Chair and Selected Speaker,* American Crystallography Association, Portland, Oregon
2022 *Invited Speaker,* Rockefeller University, New York, NY
2022 *Selected Poster Presenter,* 3DEM Gordon Research Conference, Barcelona, Spain
2022 *Guest Scientist,* Vallee Foundation Symposium, Lisbon, Portugal
2022 *Invited Speaker,* Molecular Foundry Seminar Series, Lawrence Berkeley National Lab
2022 *Invited NSF Fellow,* National Postdoctoral Association, Chicago, IL
2022 *Invited Speaker,* Rising Stars in Biochemistry Series, UMass Chan, Worcester, MA
2022 *Poster Presenter*, The Biophysical Society, San Francisco, CA
2022 *Invited Speaker*, NIA Office of the Scientific Director Seminar Series, NIH, Bethesda, MD
2021 ***Awarded to inclusiveMCB*, Dean's Graduate Diversity Innovation Fund**
2021 *Fellow*, Leading Edge Fellowship Program
2021 **National Science Foundation Postdoc Research Fellowship in Bio (NSF-PRFB), Accepted**
2021 Damon Runyon Postdoctoral Fellowship, Withdrawn
2021 Ford Foundation Postdoctoral Fellowship, Withdrawn
2021 *Invited Speaker*, Molecular Biosciences Seminar Series, Northwestern University, Evanston, IL
2019 *Invited Speaker*, Rising Stars in Cell Biology, University of Utah, Salt Lake City, UT
2019 **Cris Alvarez Memorial Commencement PhD Award, UC Berkeley**
2019 Carl Storm Minority Fellow, 3DEM Gordon Research Conference, Hong Kong, China
2019 Summer Conference Travel Grant, UC Berkeley Graduate Division
2019 Chancellor's Award for Public Service Nominee
2018 Dean of Students Outstanding Leadership Award Nominee
2018 Selected Speaker, Microtubules: From Atoms to Complex Systems, Heidelberg, Germany
2016 RISE Award Winner, Gender Resource Center
2016 MCB Equity & Inclusion Award, UC Berkeley
2016 **National Science Foundation Graduate Fellowship (NSF-GRFP), Accepted**
2015 Ford Foundation Predoctoral Fellowship, National Academy of Sciences, Accepted
2014 Outstanding Poster Award, National Institutes of Health
2014 Intramural Research Training Award, National Institutes of Health
2014 Travel Award, King Abdullah University of Science and Technology, Jeddah, Saudi Arabia
2014 John. Y. Young Service Memorial Scholarship
2014 Harry S. Truman Scholarship Finalist, Grinnell College
2013 Howard Hughes Medical Institute Summer Fellowship, CalTech
2012 POSSE Foundation Summer Leadership Award
2012 Amgen Scholars Summer Fellowship, UCSF
2010 Fulfillment Fund Higher Education Scholarship
2010 POSSE Foundation Undergraduate Full Scholarship

C. Contribution to Science

Graduate Career | Microtubules (MTs) are highly conserved, cytoskeletal polymers that are involved in virtually every cellular process, ranging from cell division to cell growth to intracellular trafficking. How cells "read and write" unique microtubule populations, or decode the "tubulin code", remains mysterious. My graduate work explored the molecular mechanisms cells employ to regulate these vital filaments as well as their implications in disease. While it is known that αK40 acetylation is associated with more stable MTs, it is not clear whether the relationship between this chemical modification and stability is causative. To tackle this controversy, I applied a reductionist approach to tease out the direct effects of this modification on MT structure by using cryo-electron microscopy to visualize acetylated and deacetylated

MTs under the mentorship of my doctoral advisor **Dr. Eva Nogales**. I showed that acetylation changes the conformational ensemble of the intraluminal αK40 loop in α-tubulin and may serve as an evolutionarily conserved 'electrostatic switch' to regulate MT stability[4]. Due to the high flexibility of the loop, unlocking the effects of this modification required an exciting hybrid EM-MD approach, designed in collaboration with Dr. James Fraser at UCSF and Dr. Massiliano Bonomi at the University of Cambridge.

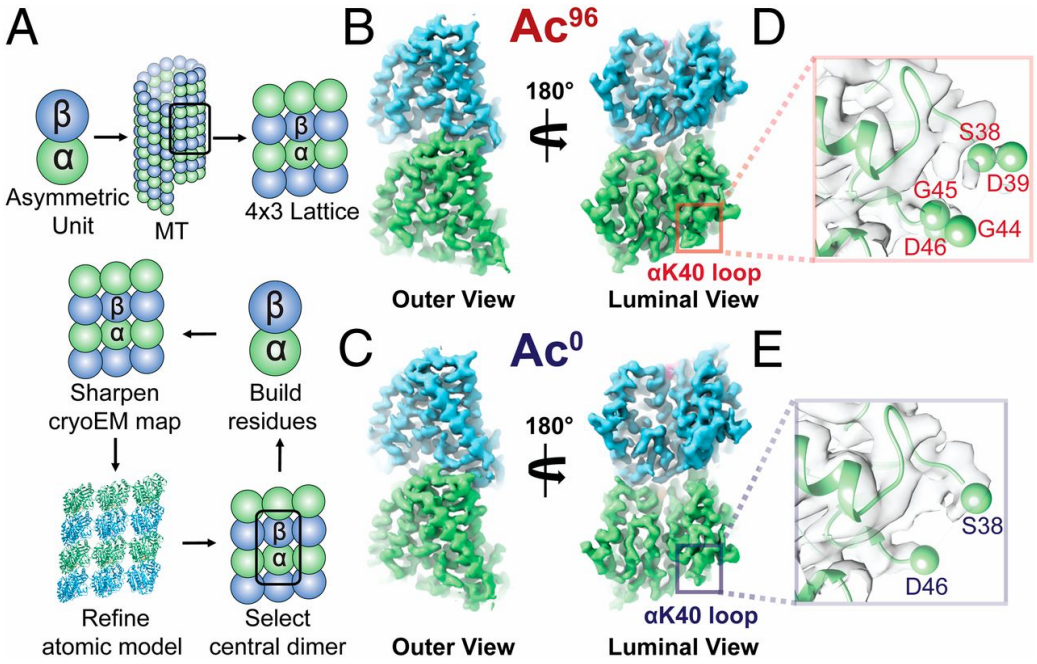

Figure 2. *High-resolution maps of 96% acetylated (Ac^{96}) and <1% acetylated (Ac^{0}) MTs. (A) Schematic of the model-building and refinement process in PHENIX. We sharpened a representative 4 × 3 lattice, refined the corresponding atomic structure (3JAR) into our map, and extracted out the central dimer to build additional residues into the αK40 loop. We performed this process iteratively for both the Ac^{96} and Ac^{0}. The structure of the Ac^{96} (B) and Ac^{0} (C) αβ-tubulin heterodimers, respectively, are shown from the outer and luminal views with close-ups of αK40 loop in each state (D and E).*

1. Eshun-Wilson, L., Zhang R, Portran D, Toso D, Nachury M, Bonomi M, Fraser JS, Nogales E. Structural insights into the effects of α-tubulin acetylation on microtubule structure and properties. UCB, Berkeley, CA. ***Proceedings of the National Academy of Sciences*** (2019) 116 (21) 10366-10371. ***Cited by 218***.

At this point, I became very interested in conformational heterogeneity and plasticity in the MT lattice. For example, the structure and mechanics of the lattice are not only dependent on the modification state of each tubulin, but on the modification states of its neighbors, including the combination of isotypes, interacting drugs or enzymes, local mechanical strain, packing defects and solvent conditions of its neighbors as well. I started to appreciate the MT as an allosteric macromolecular machine that interprets multifaceted inputs and reacts by transforming its conformation, stiffness, and dynamics. This appreciation launched an exploratory project into the complex world of structural microtubule-associated proteins, or MAPs that can remodel MT macromolecular assemblies, from MT bundles to molecular motor interaction sites. These MAPs share a MT-binding domain (MTBD) and a flexible projection domain, that can extend far from the MT surface. However, it is unclear whether the MTBD or the projection domain is responsible for this activity. in collaboration with Dr. Ahmet Yildez, I employed cryo-EM and single-molecule biophysics, I discovered the first structure for MAP7 and provide a framework for how it regulates other MAPs and intracellular molecular motors, such as kinesin and dynein (**Fig. 2**). Foremost, I show how MAP7 regulates tau, an essential MAP for neuronal development and when misregulated forms paired helical filaments, the hallmark of a class of neurological diseases known as tauopathies that includes Alzheimer's.

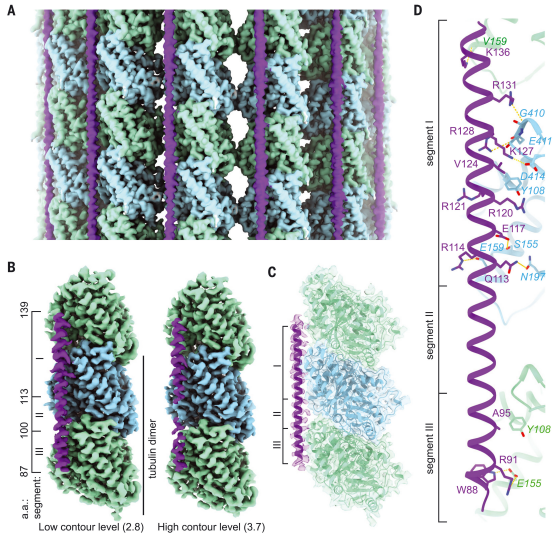

Figure 2. Panels A-D highlight the first structure of MAP7, providing mechanistic and atomic insight into its function for the first time. Published in ***Science*** (2022).

2. Eshun-Wilson, L.*, Ferro, L.*, Fang Q.*, Fernandes, J*, Jack A, Gölcük M, Fernandes J, Huijben T, Costa K, Gür M, DiMaio, F., Nogales, E., Yildez, A. Structural and functional insight into regulation of kinesin-1 by microtubule-associated protein MAP7. UCB, Berkeley, CA. ***Science*** (2022) 375 (6578) 326-331. *Equal contribution.
3. Eshun-Wilson, L. Lander, G. Effects of microtubule-associated protein 7 (MAP7) on MAPs, motors and intracellular trafficking. *Invited Speaker*, Leading Edge Symposium, **Howard Hughes Medical Institute (HHMI)**, Ashburn, VA. June 2021.
4. Eshun-Wilson, L.*, Ferro, L.*, Fang Q.*, Fernandes, J*, Jack A, Gölcük M, Fernandes J, Huijben T, Costa K, Gür M, DiMaio, F., Nogales, E., Yildez, A. Structural and functional insight into regulation of kinesin-1 by microtubule-associated protein MAP7. *Invited Speaker*, **American Crystallographic Association**, Portland, OR. July 2022.

Postdoctoral work: Mitochondrial dysfunction contributes to organismal aging and underlies the pathogenesis of etiologically diverse age-associated diseases, including the most common inherited atrophy: dominant optic nerve atrophy. Imbalances in the activity of inner mitochondrial membrane proteases that acutely manage mitochondrial stress are pathologically implicated in the mitochondrial dysfunction associated with these conditions. Here, we integrate structural biology and cell-based assays to understand the critical decision-making process of YME1L, a quality control inner mitochondrial membrane protease that regulates optic atrophy factor 1 (OPA1), to define the molecular mechanism by which this protease processes OPA1 in response to cellular stress.

During my first year in the Lander lab, I learned and applied cutting edge cryo-electron (cryo-EM) image analysis software and neural-network algorithms to discover new states within functional landscape of yeast YME1 (**Fig**. **3**). Indeed, these conformations have never been observed among any of the members of the structurally conserved family of AAA+ proteins. These conformers profoundly reshape our understanding of the YME1 substrate decision-making and present a new organization of the highly conserved AAA+ module, with far-reaching implications across the AAA+ field.

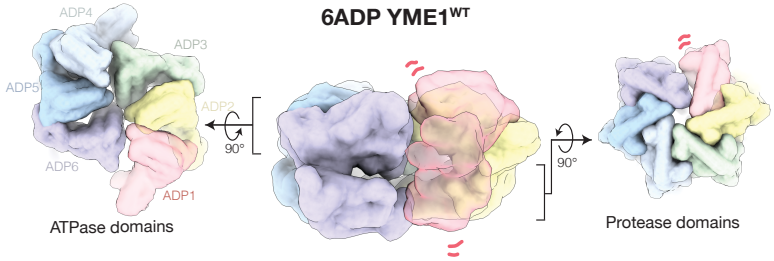

Figure 3. The most dramatic of the yeast YME1 conformers discovered to date: a split open state containing 6 ADP molecules populating each nucleotide binding site. *Could this state represent a glimpse into a well-conserved substrate recognition or release mechanism for AAA+ motors? Or a state utilized under stressful conditions, such as low [ATP]?*

5. Eshun-Wilson, L. Lander, G. Uncovering the molecular mechanisms of stress. *Invited Speaker*, Rising Stars Seminar Series, ***University of Utah***, Salt Lake City, UT. March 2021.
6. Eshun-Wilson, L. Lander, G. Uncovering the molecular mechanisms of stress. *Invited Speaker*, Molecular Biosciences Seminar Series, ***Northwestern University***, Evanston, IL. April 2021.
7. Eshun-Wilson, L. Lander, G. Uncovering the molecular mechanisms of ageing. *Invited Speaker*, National Institute of Aging, ***National Institutes of Health***, Bethesda, MD. February 2022.
8. Eshun-Wilson, L. Lander, G. Using 3D Variability Analysis to resolve some of nature's most mysterious molecular machines. **University of Massachusetts Chan Medical School**. Worcester, MA. March 2022.
9. Eshun-Wilson, L. Lander, G. Using 3D Variability Analysis to resolve some of nature's most mysterious molecular machines. **Rockefeller University**. New York, New York. July 2022.

Building upon my knowledge of 3D visualization software and membrane biology, I collaborated with the Andrew Ward lab at Scripps to tackle one of the most challenging structures I have encountered: the full-length, membrane-extracted ***Hepatitis C virus (HCV) E1E2 glycoprotein complex***. Using cryoEM, we solved the fully assembled E1E2 heterodimer in complex with three broadly neutralizing antibodies: AR4A, AT12009 and IGH505, elucidating how the two glycoprotein subunits interact and providing a molecular description of three key neutralizing epitopes (**Fig. 4**). Our manuscript directly challenges existing controversies regarding stabilization for the E1E2 interface. We find that the E1E2 interface is stabilized by glycans and hydrophobic interaction and AR4A is essential in stabilizing the E1E2 complex in a metastable,

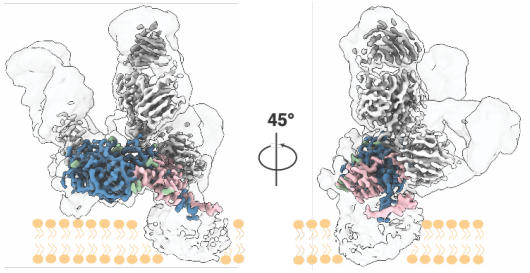

Figure 4. First structure of the membrane extracted, full-length Hepatitis C virus (HCV) E1E2 glycoprotein complex bound to three broadly neutralizing antibodies.

pre-fusion state of the protein. Our cryo-EM structure revealed the distribution of N-linked glycosylation sites only across one side of E1E2 and the presence of a rare N-glycosylation sequon: NXV. Moreover, given that antibodies bind to this side of E1E2, we refer to this as the neutralizing face of the glycoprotein and propose structural evidence that supports the assertion that HCV can form an oligomer. ***Overall, our cryoEM study provides a full molecular description of full-length E1E2, including three novel bNAb epitopes, and provides a long sought-after blueprint for the design of a new generation of HCV glycoprotein immunogens and anti-viral drugs.***

10. **Eshun-Wilson L***, Torrents de la Peña A*, Sliepen K*, Newby M, Allen J, Koekkoek S, Zon I, Chumbe A, Crispin M, Schinkel J, Sanders R, Lander G, Ward A. Structure of full-length hepatitis C virus E1E2 glycoprotein complex. ***Science*** (2022) 6617 (378) 263-269. ***Equal contribution**.
11. Martin G, Quintero MLF, Lee WH, Pholcharee T, **Eshun-Wilson L**, Liedl KR, Pancera M, Seder RA, Wilson IA, Ward AB. Structural basis of epitope selectivity and potent protection from malaria by PfCSP antibody L9. *Accepted in* ***Nature Communications*** (2022) bioRxiv link: https://www.biorxiv.org/content/10.1101/2022.10.07.511358v1.
12. Eshun-Wilson L*, Torrents de la Peña A*, Sliepen K*, Newby M, Allen J, Koekkoek S, Zon I, Chumbe A, Crispin M, Schinkel J, Sanders R, Lander G, Ward A. Structure of full-length hepatitis C virus E1E2 glycoprotein complex. *Poster Presenter*. **The 3D Electron Microscopy (3DEM) Gordon Research Conference**, **Barcelona, Spain.**
13. Eshun-Wilson L*, Torrents de la Peña A*, Sliepen K*, Newby M, Allen J, Koekkoek S, Zon I, Chumbe A, Crispin M, Schinkel J, Sanders R, Lander G, Ward A. Structure of full-length hepatitis C virus E1E2 glycoprotein complex. *Invited Speaker*. **Spring Lecture (Přednáška) Series, Prague Institute of Organic Chemistry and Biochemistry (IOCB), Prague, Czech Republic.**