APPLICANT BIOGRAPHICAL SKETCH

NAME:	Eshun-Wilson, Lisa
eRA COMMONS USERNAME:	lisaeshunwilson
POSITION TITLE:	Principal Investigator
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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Grinnell College	B.A.	05/2014	Biological Chemistry
The National Institutes of Health	Postbaccalaureate	08/2015	Membrane Biology
University of California, Berkeley	Ph.D.	12/2019	Molecular Cell Biology
The Scripps Research Institute	Postdoctoral	04/2024	Integrative Computational and Structural Biology
Profluent Bio, Inc.	Scientist II	08/2025	AI-first protein design
The Genoma Institute	Principal Investigator	Present	Gene Editing

A. Personal Statement

For my doctoral thesis, I tackled a long-standing controversy: whether the relationship between the chemical modification αK40 acetylation and microtubule (MT) stability was causative or correlative. Notably, αK40 acetylation is the only post-translational modification (PTM) known to occur on the inside of MTs, and it marks long-lived, stable MT populations, including those that compose the cytoskeleton of cancerous cells. The misregulation of αK40 acetylation has also been linked to axonal transport defects associated with Huntington's disease, Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis, and Parkinson's disease, as well as to the growth of "microtentacles" that promote metastatic breast cancer. To determine whether this modification directly causes changes in MT structure, I applied a reductionist approach using cryo-electron microscopy (cryo-EM). By visualizing purely acetylated and deacetylated MTs, I showed that acetylation alters the conformational ensemble of the αK40 loop in α-tubulin, changing the dynamics of the modification site and suggesting that it functions as an evolutionarily conserved "electrostatic switch" regulating MT stability. This work was conducted in close collaboration with Drs. James Fraser at **UCSF** and Max Bonomi at the **University of Cambridge**.

Beyond post-translational modifications, microtubule-associated proteins (MAPs) and therapeutic agents also shape MT structure and stability. Building on an interest in intracellular transport developed during my time at the **NIH** with Dr. Julie Donaldson, I investigated the mechanism by which microtubule-associated protein 7 (MAP7) modulates kinesin-1 motility. Using cryo-EM and single-molecule imaging, I showed that the microtubule-binding domain of MAP7 binds as an extended alpha-helix along the protofilament ridge, partially overlapping with the kinesin-1 binding site and directly inhibiting motor motility. Unexpectedly, MAP7 simultaneously promotes transport by tethering kinesin-1 to the microtubule lattice via its projection domain, preventing motor dissociation and facilitating rebinding to adjacent sites. Together, this work revealed a biphasic, concentration-dependent regulatory mechanism in which MAP7 both inhibits and enhances kinesin-1 transport through competitive and cooperative interactions on the microtubule surface, resulting in a co-first author publication in **Science Magazine**.

Small molecules and natural products can also modulate MT dynamics with therapeutic consequence. Taxol, a major breast cancer chemotherapy agent, blocks the cell cycle in its G1 or M phase by stabilizing MTs and limiting their critical dynamics. Lankacidins (LCs), by contrast, were shown to have both in vivo antitumor activity across multiple cancer cell lines and antimicrobial activity against Gram-positive pathogens; because their effects on MTs proved minimal, I focused instead on uncovering the structural basis of their antimicrobial activity and resistance. I resolved a 2.8 Å structure of the LC-ribosome complex and discovered that LC forms an elaborate hydrophobic network within the peptidyl transferase center (PTC) at the exit (E) site of the ribosome, a network essential to its inhibitory effect on translation and common to this class of macrolides, consistent with previous research. I also showed that ring closure is important to LC's inhibitory effect on harmful bacteria; prior evidence indicates that hydrogenation of the macrocyclic ring changes its conformation and reduces its inhibitory effects. These findings suggest that bacteria may develop resistance to LC over time by altering the nucleotides that compose the hydrophobic network, weakening LC binding to the PTC site

without lethally compromising ribosome function. This work was conducted in collaboration with Drs. James Fraser and Ian Seiple at **UCSF**.

I then completed a postdoctoral fellowship at the **Scripps Research Institute** in La Jolla, California, where I resolved the first cryo-EM structure of the Hepatitis C virus (HCV) glycoprotein, a project that resulted in my second co-first author publication in **Science Magazine**. I was subsequently recruited to Profluent Bio, Inc., an AI-first protein design company, where I worked directly at the intersection of machine learning, high-throughput sequencing, and AI-led protein design. There, I helped apply computational and generative models to real biological design problems, gaining hands-on experience with the full pipeline connecting large-scale sequence data, model-driven hypothesis generation, and experimentally testable protein designs. This work deepened my understanding of both the transformative power and the biosecurity implications of generative biological systems, an understanding that now directly informs my approach to responsible, AI-driven biological research. Now, through Genoma, I am building new scientific, organizational, and ethical frameworks for genome engineering research, emphasizing high-risk tool development, interdisciplinary collaboration, and ethical deployment.

Selected Publications (from this biosketch)

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*. **Proceedings of the National Academy of Sciences** (2019) 116(21):10366–10371.
2. **Eshun-Wilson L**, Ferro LS, Fang Q, Fernandes J, Jack A, Farrell DP, Golcuk M, Huijben T, Costa K, Gur M, DiMaio F, Nogales E, Yildiz A. *Structural and functional insight into regulation of kinesin-1 by microtubule-associated protein MAP7*. **Science** (2022) 375(6578):326–331.
3. **Eshun-Wilson L**[#], Torrents de la Peña A[#], Sliepen K[#], Newby ML, Allen JD, Zon I, Koekkoek S, Chumbe A, Crispin M, Schinkel J, Lander GC, Sanders RW, Ward AB. *Structure of the hepatitis C virus E1E2 glycoprotein complex.* **Science** (2022) 378(6617):263–269.

B. Positions and Honors

Positions and Employment

2014–2015 Intramural Research Training Award Postbaccalaureate Fellow, Membrane Biology Section, National Heart, Lung and Blood Institute, Bethesda, MD

2020–2024 Postdoctoral Fellow, Department of Integrative Computational and Structural Biology, Scripps Research Institute, La Jolla, CA

2024–2025 Scientist II, Profluent Bio, Inc., Berkeley, CA

2025–Present Principal Investigator, Genoma, Berkeley, CA

Other Experience and Professional Memberships

2020–Present Member, Biophysical Society

2014–Present Member, American Society of Cell Biology

2014–Present Member, American Society of Biochemistry and Molecular Biology

Honors

2020 Cris Alvaro PhD Commencement Prize

2019 Carl Storm Underrepresented Minority Fellowship (CSURM), Gordon Research Conference

2019 Summer Conference Travel Grant, UC Berkeley Graduate Division

2019 Chancellor's Award for Public Service Nominee

2019 Dean of Students Outstanding Leadership Award Nominee

2019 RISE Award Winner, Gender Resource Center

2018 MCB Equity & Inclusion Award

2016 National Science Foundation Graduate Fellowship

2016 Ford Foundation Predoctoral Fellowship, National Academy of Sciences

2014 Travel Award, King Abdullah University of Science and Technology

2014 John. Y. Young Service Memorial Scholarship

2014 Grinnell Ladies Education Society Scholarship

2013 Howard Hughes Medical Institute Summer Fellowship, CalTech

2013 POSSE Foundation Summer Leadership Award

2012 Amgen Scholars Summer Fellowship, UCSF

2010 Fulfillment Fund Higher Education Scholarship

2010 POSSE Foundation Undergraduate Full Scholarship, Grinnell College

C. Contribution to Science

1. My first publication focused on the role post-translational modifications, enzymes, and therapeutic agents have on microtubule structure, dynamics and regulations, due the important role of these cytoskeletal polymers in cancer, neurogenerative disease and aneuploidy. I was interested in how unique modulators could alter the conformation and plasticity of the microtubule lattice. For instance, the structure and mechanics of microtubules are not only dependent on the modification state of each tubulin, but also on tubulin isotypes, interacting drugs, or MT-binding partners, all of which can cause changes in tubulin structure and subunit packing within the MT and affect local mechanical strain and other physical properties of the lattice. I started to appreciate the MT as an allosteric macromolecular machine that interprets multifaceted inputs and reacts by transforming its rigidity and mechanical resistance. This appreciation launched an exploratory project into the complex world of chemical modifications, specifically on acetylation, the main post-translational modification to occur on the inside of the microtubule, and lankacidins, a unique class of antibiotics. I served as the lead author in all of these studies.

a. 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.

b. Eshun-Wilson L., Pellegrino, J. Ward, F., Toso, D., Brilot, A., Nogales, E., Seiple, I., Fraser, J. *CryoEM and synthetic studies reveal that ring closure of lankacidin, and related metabolites mediates antibiotic activity.* Manuscript in preparation.