

APPLICANT BIOGRAPHICAL SKETCH

NAME: Eshun-Wilson, Lisa

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POSITION TITLE: Postdoctoral Fellow

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		Integrative Computational and Structural Biology

A. Personal Statement

For my doctoral thesis, I chose to tackle a long-standing controversy: whether the relationship between the chemical modification α K40 acetylation and MT stability was causative or correlative. Interestingly, α K40 acetylation is the only post-translational modification (PTM) to occur on the inside of MTs and mark long-lived, stable MT populations, including those that compose the cytoskeleton of a cancerous cell. Moreover, the misregulation of α K40 acetylation is linked to axonal transport defects associated with Huntington's disease, Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis, Parkinson's disease, and the growth of "microtentacles" that promote metastatic breast cancer. To elucidate the potential causative effects of this modification, I applied a reductionist approach to tease out the direct effects of this modification on MT structure by using cryo-electron microscopy (cryo-EM). By visualizing purely acetylated and deacetylated MTs, I showed that acetylation changes the conformational ensemble of the α K40 loop in α -tubulin, or in other words it changes the rhythm of the modification site of this PTM and may serve as an evolutionarily conserved 'electrostatic switch' to regulate MT stability. This work was launched in close collaboration with Drs. James Fraser at UCSF and Max Bonomi at the University of Cambridge.

Similar to PTMs, therapeutic agents can affect MT structure and stability as well. Taxol, a major breast cancer chemotherapy agent, can block the cell cycle in its G1 or M phases by stabilizing MTs and limiting MT critical dynamics. Surprisingly, lankacidins (LCs) were shown to have both in vivo antitumor activity in multiple cancer cell lines and antimicrobial activity against Gram-positive pathogens. We observed that the effects of LCs were minimal and focused on uncovering the structural basis of their antimicrobial activity and resistance. I resolved a 2.8 Å structure of the LC-ribosome complex. I discovered that LC forms an elaborate hydrophobic network within the peptidyl transferase center (PTC) of the exit (E) site of the ribosome which is essential for its inhibitory effect on translation and common for this class of macrolides, consistent with previous research. Moreover, we show that the ring closure is important for the inhibitory effect of LC on harmful bacteria. Previous evidence supports that when the macrocyclic ring is hydrogenated its ring conformation changes and its inhibitory effects are reduced. Thus, bacteria may resist LC over time by manipulating the identity of the nucleotides that compose the hydrophobic network, so as not to lethally affect ribosome function, but weaken LC binding to the PTC site. This work was done in collaboration with Drs. James Fraser and Ian Sieple at UCSF.

Now, as a postdoctoral fellow in the lab of Dr. Gabriel Lander, in close collaboration with Dr. Luke Wiseman, at the Scripps Research Institute, I am thrilled to study the swiss-army knife of mitochondrial quality-control machines YME1L. Located in the inner membrane of the mitochondria, YME1L is an ATP-dependent protease that can cleave, disentangle, and recycle multiple substrates, but how it distinguishes these different targets and adapts its machinery to uniquely process each one remains a completely open question. I will use cryo-electron tomography and in vivo microscopy studies to visualize YME1L with a range of substrates and unlock the

mechanism behind its impressive decision-making skills, and fundamentally, decipher the “proteolytic code” necessary to maintain mitochondrial proteostasis.

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.

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-Present Postdoctoral Fellow, Department of Integrative Computational and Structural Biology, Scripps Research Institute, La Jolla, CA

Other Experience and Professional Memberships

- 2020-Present Member, Biophysical Society
- 2015-Present National Society for Leadership and Success
- 2014-Present Member, American Society of Cell Biology
- 2014-Present Member, American Society of Biochemistry and Molecular Biology

Honors

- 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 publications 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. UCB, Berkeley, CA. *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. UCSF, San Francisco, CA. *Manuscript in preparation*.