ELIZABETH H. KELLOGG

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My dual training in computational methods development and high-resolution cryo-EM poise my lab to make large strides in in pursuit of characterizing highly dynamic protein complexes using cryo-EM. During my PhD, I focused on developing computational methods to study the intrinsic links between protein sequence, structure, and dynamics. I first developed a method to formalize the relationship between protein structure and thermodynamics. The method, which estimates the free-energy change of folding upon mutation ($\Delta\Delta G$), is widely used by experimentalist and theorists alike. Cited ~300 times (Kellogg EH. et al., Prot. Sci. 2011), this work remains one of my most highly cited publications and is a testament to its generality and accuracy. I then focused on developing a method to fully characterize protein dynamics using molecular dynamics (MD) simulations (Kellogg EH et al. J. Phys. Chem. 2012). The outcome of this work was to provide a fully automated method to characterize protein folding pathways (by generating a free-energy landscape) as well as identify transiently stable intermediates along the folding pathway.

I complemented this training during my postdoc by doing experimental structural biology in the lab of Eva Nogales, a leader in the field of cryo-EM. Stemming from my interest in dynamic structures, I first characterized the structural dynamics of Taxol-stabilized microtubules (MTs). A long-standing mystery in the field of microtubule structure began with the observation that, while the anti-cancer drug Taxol stabilized microtubules, it clearly also induced structural heterogeneity which precluded high-resolution structural analysis (Alushin et al. Cell 2014). Using 3D image-sorting techniques, I discovered that the source of structural heterogeneity arose from flexibility within the microtubule walls (Kellogg EH. JMB 2015); we went on to show that this flexibility could be induced by any small molecule which targeted the Taxol-binding pocket.

I next became fascinated by the intrinsically disordered protein (IDP) tau, which lacks stable secondary and tertiary structure and had, until now, been refractory to structural characterization. Within the cell, tau can form phase-separated droplets (a frequently observed property of IDPs) that can subsequently nucleate microtubule growth. By using a combination of computational modeling (with Rosetta) and cryo-EM, I was able to determine the structure of tubulin-bound tau (Kellogg EH Science 2018), which has since been supported by a number of studies, including Fluorescence Correlative Spectroscopy (Fung et al. BioRxiv doi:10.1101/647016 2019) and by subsequent cryo-EM structures (Shigematsu H et al. JCB 2018). We discovered that a single ordered stretch of tau, corresponding to a highly conserved sequence motif, bound to the interface between tubulin-dimers along the microtubule protofilament. By serving as a link between tubulin dimers, this explained tau's ability to nucleate microtubule growth. The synergistic combination of computational modeling and cryo-EM has allowed me to approach questions that have long been considered inaccessible by other techniques. In my lab, I plan to expand on this hybrid approach to become a general framework for understanding dynamic protein complexes.

Positions

2019 – present	Cornell University, Ithaca, NY Molecular Biology and Genetics Assistant Professor
2013-2018	University of California, Berkeley Molecular Biophysics and Integrated Bio-imaging Advisor: Dr. Eva Nogales

Education

2012	University of Washington Ph.D. Biochemistry Thesis Title: "Assessing and Improving Computational Models of Protein Thermodynamics and Kinetics using Rosetta" Advisor: Dr. David Baker
2006	University of California, Berkeley B.S., *summa cum laude* Bioengineering

Funding

01/2019	R00 Pathway to Independence Award
10/2017	K99 Pathway to Independence Award
06/2016-12/2017	Burroughs Wellcome Fund Collaborative Research Travel Grant

Selected Awards and Honors

2020	Biophysical Society Cryo-EM subgroup Program Co-Chair
2019	Sumner Lecture Organizing Committee
2014	Session Chair "Rosetta and Structural Biology", Rosetta-Conference
2006	UC Berkeley Bioengineering Department Award Winner **Significance:** Top honor bestowed on one Bioengineering graduate per year

Publications

Citations (since 2014): 1431

1. Ghanim G.*, **Kellogg EH.*#,** Nogales E., and Rio DC.# "Cryo-EM structure of the P element transposase strand transfer complex" *Accepted, Nature Structural Molecular Biology*

   * equal contribution

   # co-corresponding authors
   ***Significance*:** Cryo-EM structure of the historically important P element transposase reveals the structural basis underlying its unique transposition mechanism.

2. **Kellogg EH.*,** Hejab N*, Poepsel S., Downing KH, Dimaio F., and Nogales E. "Near-atomic cryo-EM reconstruction of microtubule-tau interactions" *Science* 360(6394):1242-46, June 2018

   ***Significance*:** First high-resolution (3.5 Å) cryo-EM structure of tau reveals details of MT-tau interactions and explains discrepancies in biochemical data as well as reveals structural mechanism of tau-mediated tubulin stabilization.

3. Nogales E., and **Kellogg EH.** “Challenges and opportunities in the high-resolution cryo-EM visualization of microtubules and their binding partners” *Curr. Op. Struct. Biol.* 46:65-70, October 2017

4. Howes SC., Geyer E., LaFrance BJ., Zhang R., **Kellogg EH**., Westermann S., Rice L., and Nogales E., “Structural and functional differences between yeast and mammalian microtubules revealed by cryo-EM” *Journal of Cell Biology* DOI: 10.1083/jcb.201612195, June 2017

5. **Kellogg EH.**, Hejab N., Howes S., Northcote P., Miller JH., Diaz FJ., Downing KH. and Nogales E. “Insights into the distinct mechanisms of action of taxane and non-taxane microtubule stabilizers from cryo-EM structures” *Journal of Molecular Biology* 429 (5):633-646, March 2017

   Significance: Multiple stabilizing chemotherapeutic drugs are studied in the context of the microtubule lattice and are found to have distinct structural effects, therefore, distinct mechanisms of action.

6. **Kellogg EH***, Howes S.*, Ti SH., Kapoor T., Chacon P., and Nogales E. “Near-atomic cryo-EM structure of PRC1 bound to the microtubule” *PNAS* 113(34):9430-9, August 2016

7. Alushin GM.*, Lander GC.*, **Kellogg EH***, Zhang R., Baker D., Nogales E. “High-resolution microtubule structures reveal the structural transitions in αβ-tubulin upon GTP hydrolysis” *Cell* 157(5):1117-29, May 2014

   ***Significance*:** The first high-resolution cryo-EM reconstruction of microtubules in different nucleotide states enable atomic flexible-fitting of tubulin to describe, at a detailed level, how nucleotide-hydrolysis induces strain in the microtubule lattice and how chemotherapy drug Taxol relieves this strain.

8. Leaver-Fay A., O’Meara M., Tyka M., Jacak R., Song Y., **Kellogg EH**, Thompson J., Davis I., Pache R., Kortemme T., Lyskov S., Gray J., Snoeyink J., Baker D., Kuhlman B. “Scientific Benchmarks for Updating the Rosetta Energy Function” *Methods Enzymol*. 523:109-43, July 2013

9. **Kellogg EH**, Lange OF., Baker D., “Evaluation and optimization of discrete state models of protein folding” *Journal of Physical Chemistry B*. 116(37):11405-13, September 2012

10. Liu Y., **Kellogg EH**, Liang H. “Canonical and Micro-canonical Analysis of Folding of Trpzip2: An All-atom Replica Exchange Monte-carlo Simulation Study” *Journal of Chemical Physics.* 137(4):045103, July 2012

11. **Kellogg EH**, Leaver-Fay A., Baker D., “Role of conformational sampling in computing mutation-induced changes in protein structure and stability” *Proteins: Structure, Function, Bioinformatics.* 29(3):830-8, March 2011

    ***Significance*:** The first computational method in Rosetta to incorporate backbone refinement in order to improve thermodynamic predictions of protein stability with respect to sequence changes.

12. Fowler DM., Araya CL., Fleishman SJ., **Kellogg EH.**, Stephany JJ., Baker D., Fields S. “High-Resolution Mapping of Protein Sequence-Function Relationships” *Nature Methods.* 7(9):741-6, September 2010

13. Jung HS, Okegawa Y., Shih PM., **Kellogg EH**, Abdel-Ghany SE., Pilon M., Sjolander D., Shikanai T., Niyogi K., "Aradopsis Thaliana PGR7 Encodes a Conserved Chloroplast Protein that is Necessary for Efficient Photosynthetic Electron Transport" *PloS One* 5(7):e11688, July 2010

14. Leung CC., **Kellogg EH**., Kuhnert A., Hanel D., Baker D., Glover JN., "Insights from the Crystal Structure of the Sixth BRCT Domain of Topoisomerase IIBeta Binding Protein 1" *Proteins: Structure, Function, Bioinformatics.* 19(1):162-7, Jan 2010

15. Raman S., Vernon R., Thompson J., Tyka M., Sadreyev R., Pei J., Kim D., **Kellogg EH**., DiMaio F., Lange O., Kinch L., Sheffler W., Kim B, Das R., Grishin N., Baker D. "Structure Prediction for CASP8 with All-Atom Refinement using Rosetta" *Proteins: Structure, Function, Bioinformatics.* 77(S9):89-99, Jul 2009

* indicates co-first author

Talks, Workshops, and Conferences

2019 Attendee NYC Computational Cryo-EM Summer Workshop, Flatiron Institute, New York NY, August 8-9

Invited Speaker "Cryo-EM structure of the P-element transposase strand transfer complex" Microscopy and Microanalysis, Portland OR, August 4-8

Invited Speaker "Cryo-EM structure of the P-element transposase strand transfer complex" 3DEM GRC, Hong Kong, June 9-14

Invited Speaker "When life gives you lemons: Cryo-EM of difficult and heterogeneous samples" Cornell University, April 11th

Invited Speaker "When life gives you lemons: Cryo-EM of difficult and heterogeneous samples" Columbia University, April 10th

Invited Speaker "Cryo-EM structure of the P-element transposase strand transfer complex" ASBMB, Orlando FL, April 7-10

2018 Invited speaker "Near-atomic model of microtubule-tau interactions" ASCB, San Diego,CA, December 8-12

Poster Presenter "Cryo-EM structure of the P element transposase" CSHL Meeting on Transposable Elements, November 1-4

Poster Presenter "Near-atomic model of microtubule-tau interactions" 3DEM GRC, Newport RI, June 3-8

Invited speaker "Towards a high-resolution structure of the P element transposase" Keystone Symposia on Mobile Genetic Elements and Genome Plasticity, Santa Fe, NM February 11-15

2017 Poster Presenter "Cryo-EM Structure of Microtubule-bound Tau", Understanding Biology Through Structure Symposium, Santa Fe, NM May 13-17

2016 Poster Presenter “Near-atomic cryo-EM structural studies of microtubules, microtubule-stabilizers, and microtubule-associated proteins” ASCB, San Francisco CA, December 2-6

2015 Invited Speaker “Near-atomic cryo-EM structural studies of microtubule stabilizers and microtubule-associated proteins” Bay area cryo-EM meeting, UC Berkeley, December 4

Poster Presenter “Microtubule-associated proteins and Microtubule-stabilizing drugs: how they recognize and affect microtubule structure” HHMI conference, Bethesda Maryland, November 1-3

Invited Speaker “Insights into the stabilizing mechanism of microtubule-targeting agents at near-atomic resolution using cryo-EM” Gordon Research Conference 3D EM, New London NH, June 21-26

Student invited Speaker “High-resolution cryo-EM studies of microtubule-stabilizing agents”, Louisiana state university, Baton Rouge LA, May 13

2014 Invited Speaker, “Combining High-Resolution Cryo-EM Rosetta to Study the Effect of Taxol on the Microtubule Lattice”, Rosetta Conference, Leavenworth Washington, August 1

Invited Speaker “Studying the Structural Origins of Microtubule Dynamic Instability through Combining Computational Modeling and CryoEM” MCB retreat, Asilomar CA, Jan 12-14

2013 Invited Speaker, “Studying the Structural Origins of Microtubule Dynamic Instability through Combining Computational Modeling and CryoEM”, Theoretical and Computational Biophysics Group, University of Illinois, Urbana-Champaign Illinois, August 22

Poster Presenter “Studying the structural origins of microtubule dynamic instability through computational modeling and cryoEM”, GRC 3D EM, New London NH, June 23-28

2012 Poster Presenter “Evaluation and optimization of discrete state models of protein folding” Protein Society Meeting, San Diego CA, August 5 – 8

2009 Invited Speaker, “Predicting $\Delta\Delta$Gs”, Rosetta Conference, Leavenworth WA, August 1

Teaching and Other Activities

2019, Spring	Cryo-EM image processing workshop, Chemistry and Chemical Biology, Cornell University
2013-current	Biophysical Society, member
2016-2017	American Society of Cell Biology, member