

PROMOTION RECOMMENDATION
THE UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY
COLLEGE OF LITERATURE, SCIENCE, AND THE ARTS
DEPARTMENT OF BIOPHYSICS

Daniel Southworth, Ph.D., assistant professor of biological chemistry, Department of Biological Chemistry, Medical School, and assistant professor of biophysics, Department of Biophysics, College of Literature, Science, and the Arts, is recommended for promotion to associate professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School, and associate professor of biophysics, without tenure, Department of Biophysics, College of Literature, Science, and the Arts [also being promoted to research associate professor, Life Sciences Institute].

Academic Degrees:

Ph.D.	2004	Johns Hopkins School of Medicine
B.S.	1997	University of California, Santa Cruz

Professional Record:

2011-present	Research Assistant Professor, Life Sciences Institute, University of Michigan
2011-present	Assistant Professor of Biological Chemistry, University of Michigan
2011-present	Assistant Professor of Biophysics, University of Michigan

Summary of Evaluation:

Teaching: Dr. Southworth has been a role model in his dedication to teaching. He has given lectures in multiple courses since 2012, including Biol Chem 552 (Biochemistry), Chem 452 (Advanced Biochemistry II: Cellular Processes), Biolchem 597 (Critical Analysis), Biophysics 521 (Biophysical Chemistry II) and Biophysics 520 (Methods of Biophysical Chemistry). His evaluations have all been in the above average range. Dr. Southworth has also trained two post-doctoral fellows, four graduate students, and two undergraduate students, and served as a member on six dissertation committees.

Research: Dr. Southworth's core research focus is on chaperone proteins that maintain protein homeostasis in cells through coordination of protein folding, activation and clearance. He investigates the dynamics of chaperone function and chaperone interaction with client proteins. By using both state-of-the-art cryo-EM and powerful biochemical tools, he has discovered new aspects of chaperone function. His most significant accomplishment to date is the discovery of a mechanism for the Hsp104 disaggregase. Hsp104 and other Hsp100 class AAA+ proteins respond to cellular stress by re-solubilizing toxic or aggregated proteins. The hexameric Hsp104 harnesses ATP hydrolysis in 12 nucleotide-binding domains to translocate client proteins through a central channel. Dr. Southworth discovered that the ATP-bound state of Hsp104 is arranged as a helix with a spiral of substrate-binding loops arranged to "pull" client proteins

through the central channel. This discovery was transformative because for decades it was thought that these highly conserved complexes were arranged as two separate ATPase rings, leaving the substrate-pulling mechanism unexplained. In the spiral structure Dr. Southworth identified, the ATPase domains are staggered down the channel and thus optimally positioned to power processive translocation events during disaggregation. Building on this just-published result, he has already characterized different conformations for other nucleotide states of Hsp104 and for a complex with a client protein. He is thus poised to become the leader in this rather competitive field. Dr. Southworth has several other biomedically significant chaperone projects, including the Hsp70/Hsp90 role in defending against toxic aggregation of Tau, α synuclein, and poly-Gln-containing proteins; the small heat shock protein response to hypoxic or ischemic stress; nitric oxide synthase dynamics and stress-induced clearance by chaperones; and Rvb1/2 AAA+ assembly of several macromolecular complexes. We are confident that Dr. Southworth will be highly successful and that his strong start in building a focused, biomedically relevant research program in the chaperone field will continue to produce spectacular results. Dr. Southworth is well funded with four active R01 grants on which he is the principal investigator or co-investigator. The high level and importance of Dr. Southworth's work is recognized by the abundance of speaking engagements over the past few years, both nationally and internationally. Dr. Southworth is well recognized within the cryo-EM community, but also in the general science community. He has a stellar publication record, with 15 articles printed in high impact journals since joining the University of Michigan.

Recent and Significant Publications:

Yokom AL, Morishima Y, Lau M, Su M, Glukhova A, Osawa Y, Southworth DR: Architecture of the nitric oxide synthase holoenzyme reveals large conformational changes and a calmodulin-driven release of the FMN domain. *Journal of Biological Chemistry* 289:16855-16865, 2014. Paper of the Week/Cover.

Voth W, Schick M, Gates S, Li S, Vilardi F, Gostimskaya I, Southworth DR, Schwappach B, Jakob U: The protein targeting factor GET3 moonlights as ATP independent chaperone under oxidative stress conditions. *Molecular Cell* 56:116-127, 2014.

Rajagopal P, Tse E, Borst AJ, Delbecq SP, Shi L, Dove KK, Baker D, *Southworth DR, *Klevit RE: A conserved histidine modulates HSPB5 structure to trigger chaperone activity in response to stress-related acidosis. *Elife*. 4:1-21, 2015. *Co-corresponding authors.

Ewens CA, Su M, Zhao L, Nano N, Houry WA and Southworth DR: Architecture and nucleotide-dependent conformational changes of the Rvb1-Rvb2 AAA+ complex revealed by cryo- electron microscopy. *Structure* 24:657-666, 2016.

Yokom AL, Gates S, Jackrel ME, Mack KL, Su M, Shorter J, Southworth DR: Spiral architecture of the Hsp104 disaggregase reveals the structural basis for polypeptide translocation. *Nature Structure Molecular Biology* 2016 August 1. (Epub ahead of print)

Service: Dr. Southworth's participation in department administrative activities has been exemplary. He has served on the Departmental Retreat Committee and the Prelim Exam

committee. He is a member of several programs here at the University of Michigan, including the Chemical Biology Training Program, the Pharmacological Sciences Training Program, the Chemical Biology Graduate Admissions Committee, and the Protein Folding Diseases Initiative. Dr. Southworth has served as an ad hoc reviewer for *Molecular Microbiology*, *Structure*, *Proteins and Proteomics*, *Nature Communications*, *Analytical Chemistry*, and the *Journal of Biological Chemistry*. Dr. Southworth has participated in organizing the Life Sciences Institute Annual Symposium in 2016.

External Reviewers:

Reviewer A: “In sum, Dr. Southworth has and will continue to make a significant impact in the research communities through his focus on chaperone structure and function and nitric oxide synthase. Along with other investigators, he is also at the cutting-edge of those scientists who are utilizing methods in single molecule electron microscopy. Thus, his expertise will undoubtedly be sought for many years to come, and on the tail of these collaborations and his own efforts high-profile papers and new funding streams will continue to emerge.”

Reviewer B: “I judge Dr. Southworth to be an excellent scientist who is making exceptional contributions to his scientific community, most especially in the area of understanding the role of chaperones for protein quality control. His publication record is overall excellent and has surged forward over the past few years with 8 important papers published, culminating in a very nice piece of work that appeared in NSMB a few months ago. Dr. Southworth also appears to be exceptionally well funded for these hard times and perhaps this is the most clear indication of the strength of his research program. I have no doubt that he will continue to make further contributions to his community and to science and thus have no hesitation in providing this recommendation in favor of his promotion.”

Reviewer C: “Thus, based on his establishment of a well-funded and productive lab, on the array of research accomplishments that are coming from his independent lab, and on the promise that is offered by a talented investigator with expertise in cryo-EM and research interests broadly directed to chaperones and protein remodeling/quality control, I would give Dan Southworth a very strong positive evaluation.”

Reviewer D: “Southworth has been successful with grant support, both independent and collaborative, and as you know that is no easy task these days. He looks to be an involved and excellent citizen of the university....Awards from the Alzheimer’s Association and AHA are evidence of outside recognition of his contributions and scholarship. His external visibility is good and getting better. He has made substantive contributions to the understanding of chaperone function and I expect more to come with the excellent foundation that has been laid thus far....You are very fortunate to have Southworth as a colleague.”

Reviewer E: “I think that Dan is an excellent electron microscopist and I greatly respect his scholarly and focused approach to science, which has already produced exciting new insights into macromolecular machines involved in protein folding and quality control. I have absolutely no hesitations to strongly support his promotion to Associate Professor with tenure at the University of Michigan at Ann Arbor.”

Summary of Recommendation:

Dr. Southworth has made excellent progress as an independent investigator and is a superb academic citizen. He has performed well in research, teaching, and service. Accordingly, we are pleased to recommend Daniel Southworth, Ph.D. for promotion to associate professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School, and associate professor of biophysics, without tenure, Department of Biophysics, College of Literature, Science, and the Arts.



Marschall Runge, M.D., Ph.D.
Executive Vice President for Medical Affairs
Dean, Medical School



Andrew D. Martin, Dean
Professor of Political Science and Statistics
College of Literature, Science, and the Arts

May 2017