School of Molecular Sciences
Arizona State University

SMS Fall 2021 Seminar Series

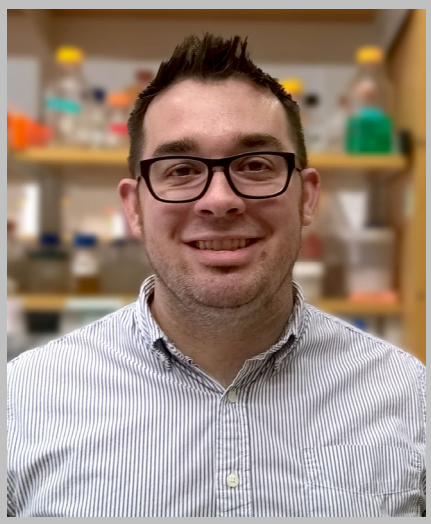
Friday Oct 8 | 2:30pm | Biodesign Auditorium*

Impact of Co- and Post-Translational Folding Constraints on the Mutational Tolerance of Integral Membrane Proteins

Membrane proteins must balance the structural constraints of function against those of biosynthesis and folding. Transmembrane domains (TMDs), for instance, must retain sufficient hydrophobicity to undergo translocon-mediated membrane integration- a prerequisite for folding and expression. To explore how the constraints of hydrophobicity shape mutational tolerance, we have compared the proteostatic effects of mutations within hydrophobic and semi-polar TMDs. In the GPCR rhodopsin, we show that the expression of the mature protein at the plasma membrane is exquisitely sensitive to mutations within TMD7, which contains several functional polar residues. Using deep mutational scanning, we show TMD7 has a lower mutational tolerance relative to a more hydrophobic TMD, and an analysis of the sensitivity of these variants to temperature and to retinal suggest a larger fraction of TMD7 variants appear to be irreversibly misfolded. In the context of the gonadotropin-releasing hormone receptor GPCR, we show that these hydrophobicity constraints appear to have shaped evolutionary pathways. Moreover, in the voltage-gated ion channel KCNQ1 we provide evidence that functional expression levels seem to account for the misfolding caused by the inefficient translocon-mediated membrane integration of the S4 voltage sensor domain. Together, our findings shed light on how the biophysical constraints of folding impact membrane protein evolution and the molecular basis of disease.

Jonathan Schlebach, PhD

Assistant Professor, Indiana University, Bloomington



Jonathan received a BS in Biochemistry from the University of Illinois at Urbana-Champaign in 2007 after which he began his graduate studies at Purdue University in the laboratory of Chiwook Park. In 2012 he received a PhD for his studies on the kinetics and thermodynamics of integral membrane protein folding. Jonathan went on to pursue postdoctoral training in the laboratory of Charles R. Sanders at the Vanderbilt University School of Medicine, where he was awarded a Ruth L. Kirschstein National Research Service Award from the NIH for his studies of integral membrane protein misfolding and disease.

He joined the Department of Chemistry at Indiana University, Bloomington as an assistant professor in 2016. His group currently studies the mechanisms of cellular protein homeostasis, and how this relates to the mechanisms of evolution and disease.

**ZOOM option available: https://asu.zoom.us/j/87081218152*