**BIOGRAPHICAL SKETCH**

NAME: Adam Frost

eRA COMMONS USER NAME (credential, e.g., agency login): FROSTAD

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Brigham Young University, Provo UT | BS | 04/00 | Biochemistry |
| Yale University, New Haven CT | PhD | 05/08 | Cell & Structural Biology |
| Yale University, New Haven CT | MD | 05/09 | General Medical Studies |
| University of California San Francisco, SF CA | Postdoc | 06/11 | Genetics & Cell Biology |

**A. Personal Statement**

When I matriculated into Yale's MD/PhD program my goals were unclear beyond knowing that I was interested in both science and medicine. Eight years later my enthusiasm for basic science trumped and I decided to focus on fundamental discovery over clinical practice. During my PhD training in structural biology (with Vinzenz Unger) and cell biology (with Pietro De Camilli), I also witnessed amazing accomplishments in DNA sequencing, genetic engineering, and fluorescence microscopy. I was motivated by the idea that we are moving toward a time when structural and functional knowledge of multi-component complexes will be rate-limiting challenges in our efforts to understand biology and pathology. For my post-doctoral work (with Jonathan Weissman), I undertook a genome-scale, unbiased strategy for finding and functionally annotating multi-component complexes. By assembling genetic interaction maps comparing pathways in two model organisms, *S. pombe* and *S. cerevisiae*, I discovered a dozen conserved protein complexes that function in a diversity of processes from cell cycle regulation to co-translation protein quality control. During this same period of time, technology developments in my first area of expertise—electron cryo-microscopy or cryo-EM—were making it possible to see higher-order complexes in molecular and even near-atomic detail. Now as an independent investigator I have assembled a laboratory that is uniquely capable of integrating these disparate tools and levels of analysis. My lab uses structure determination in concert with biochemistry and genetics to advance our understanding of how cellular machines function normally, how they are corrupted by disease, and how they are hijacked by infectious pathogens.

## B. Positions and Honors

2014-present Assistant Professor, Department of Biochemistry and Biophysics
University of California, San Francisco, San Francisco, CA
2014-present Adjust Assistant Professor, Department of Biochemistry and Huntsman Cancer Institute,
University of Utah School of Medicine, Salt Lake City, UT
2011-2014 Assistant Professor, Department of Biochemistry and Huntsman Cancer Institute,
University of Utah School of Medicine, Salt Lake City, UT
2009-2011 Post-Doctoral Scholar, University of California, San Francisco, CA
Mentor: Jonathan Weissman, PhD
2000-2009 MSTP MD/PhD Program, Yale University School of Medicine, CT
Mentor: Vinzenz Unger, PhD. Co-mentor: Pietro De Camilli, MD

- Herbert Boyer Junior Faculty Endowed Chair (2015)
- NIH Director's New Innovator Award (2013)
- Searle Scholar (2013)
- Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation (2009)
- Yale University School of Medicine Dissertation Award and Farr Scholarship Lecture (2009)
- Epilepsy Foundation Pre-Doctoral Research Training Fellowship (2006)
- The Milton C. Winternitz Prize in Pathology, Yale School of Medicine (2004)
- NIH NIGMS, Medical Scientist Training Program Grant GM-07205 (2000)
- *Cum laude* in Honors Chemistry and Biochemistry, Brigham Young University (2000)
- Barry M. Goldwater Scholar, National Scholarship for Math, Science and Engineering (1999)
- Most Outstanding Undergraduate Inorganic Chemistry Student Award (1995)
- Mangum-Lewis Undergraduate Full Support Scholarship (1994)

## C. Contributions to Science

### C1. Protein-mediated membrane remodeling

Eukaryotic cells have evolved the ability to mold their membranes into spheres and tubules in order to make connections between organelles or exchange material with the outside world. Starting with my PhD and continuing into my independent career, I have published 7 papers and reviews in this field that used genetics, biochemistry and structural approaches to resolve how membrane-remodeling proteins bind lipids, oligomerize into scaffolding complexes, and ultimately shape organelles and cells. My graduate work concerned the mechanisms of action of the BAR domain superfamily of proteins, while work in my independent laboratory has shifted focus to the ESCRT-III family of proteins.

1. **Frost, A.,** Perera, R., Roux, A., Spasov, K., Egelman, E., De Camilli, P., and Unger, V. M. (2008) Structural Basis of Membrane Invagination by F-BAR Domains. ***Cell*** 132, 807-817. PMID: 18329367. PMCID: PMC2384079
2. **Frost, A.,** Unger, V.M., and De Camilli, P. (2009) The BAR Domain Superfamily: Membrane-Molding Macromolecules. ***Cell*** 137, 191-196. PMID: 197379681.
3. Guerrier, S., Coutinho-Budd, J., Sassa, T., Chen, K., Wei-Lin, J., **Frost, A**., and Polleux, P. (2009) The F-BAR domain of srGAP2 induces membrane protrusions required for neuronal migration and morphogenesis. ***Cell*** 138, 990-1004. PMID: 19737524. PMCID: PMC2797480.
4. McCullough J., Clippinger, A.K., Talledge, N. Skowyra, M.L., Saunders, M.G., Naismith, T.V., Colf, L.A., Afonine, P.A., Arthur, C., Sundquist, W.I.*****, Hanson, P.I.*****, **Frost A.*** (2015). Structure and Membrane Remodeling Activity of ESCRT-III Helical Polymers. **Science** *In press* ***Co-corresponding authors** PMID: 26634441. PMCID: in process

**C2. Membrane-associated biochemical machines**

In addition to shaping membrane-trafficking activities described in the work cited above, cells have evolved multi-component complexes to pair donor and target membranes and chemical-energy burning machines to catalyze topological changes in these membranes through fusion and fission reactions. I began studying the mechanisms of Dynamin-superfamily GTPases as a graduate student and now in my independent laboratory I have resumed working with this family of proteins specifically in the context of mitochondrial fission and fusion. We have also recently begun studying the structural mechanisms governing the major determinant of secretory vesicle exocytosis, the Exocyst complex.

1. Roux, A., Uyhazi, K., **Frost, A.**, and De Camilli, P. (2006) GTP-Dependent Twisting of Dynamin Implicates Constriction and Tension in Membrane Fission. ***Nature*** 441, 528-531. PMID: 16648839
2. Koirala, S., Guo, Q., Kalia, R., Bui, H.T., Eckert, D.M., **Frost, A.***, Shaw, J.M.* (2013) Interchangeable Adaptors Regulate Mitochondrial Dynamin Assembly for Membrane Scission. ***PNAS*** Mar 25; 110(15):E13442-E1351 ***Co-corresponding authors** PMID: 23530241; PMCID: PMC3625255
3. Kalia, R., Talledge, N.T., and **Frost, A.** (2015) Structural and Functional Studies of Membrane Remodeling Machines. **Methods in Cell Biology** Volume 128, ISSN 0091-679X. http://dx.doi.org/10.1016/bs.mcb.2015.02.007
4. Heider, M.R., Gu, M. Duffy, C.M., Mirza, A.M., Marcotte, L.L., Walls, A.C., Farrall, N., Hakhverdyan, Z., Field, M.C., Rout, M.P., **Frost, A.**, Munson, M. (2015) Subunit Connectivity, Assembly Determinants, and Architecture of the Yeast Exocyst Complex. **Nature Structure and Molecular Biology** *In press* PMID: 26656853; PMCID: TBD

**C3. *De novo* discovery and functional annotation of multi-component complexes**

For my post-doctoral work and beyond, I was motivated by the idea that we are moving toward a time when structural and functional knowledge of multi-component complexes will be rate-determining challenges in our effort to understand biology and pathology. I undertook a genome-scale, unbiased strategy for finding and functionally annotating new complexes. By assembling genetic interaction maps comparing pathways in two model organisms, *S. pombe* and *S. cerevisiae*, I helped discover a dozen conserved multi-component complexes that function in processes ranging from cell cycle regulation to protein quality control. This work also provided novel insights into how—and how often—conserved genes acquire new functions across evolutionary time.

1. **Frost A.**, Elgort M.G., Brandman O., Ives C., Collins S.R., Miller-Vedam L., Weibezahn J., Hein M.Y., Poser I., Mann M., Hyman A.A., Weissman J.S.. Functional repurposing revealed by comparing *S. pombe* and *S. cerevisiae* genetic interactions. ***Cell*** (2012) Jun 8;149(6):1339-52. PMID: 22682253. PMC3613983
2. Brandman, O., Stewart-Ornstein, J., Wong, D., Larson, A., Williams, C.C., Li, G.W., Zhou, S., King, D., Shen, P.S., Weibezahn, J., Dunn, J.G., Rouskin, S., Inada, T., **Frost, A.***, Weissman, J.S.**** A Ribosome-Bound Quality Control Complex Triggers Degradation of Nascent Peptides and Signals Translation Stress. ***Cell*** (2012) Nov 21; 11(5):1042–1054 ***Co-corresponding authors** PMID: 23178123; PMCID: PMC3534965

**C4. Discovery of CAT tails and their role in protein quality control**

Following up on one of the most tantalizing multi-component complexes we discovered from comparative genetic interaction maps, my collaborators and I uncovered a novel mechanism of protein quality control that malfunctions in certain cases of neurodegenerative disease. We discovered that

failed translation products are elongated before being released from the stalled ribosome with a unique tag that we named the Carboxy-terminal Alanine and Threonine tail or "CAT tail." CAT tails are synthesized by the large subunit of the ribosome and a protein we discovered and named Ribosome Quality Control 2 or RQC2. Through a mechanism that was not predicted by the central dogma of biology, CAT tails are not encoded by mRNA. Rather, all of the information necessary for CAT tail synthesis—for marking failed translation products as potentially toxic species and for activating a cellular stress response—is encoded within the structure of the ancient and deeply conserved protein RQC2. Further characterization of RQC2 and the roles(s) of CAT tails across evolution and in disease is one of the major foci of my independent laboratory.


1. Brandman, O., Stewart-Ornstein, J., Wong, D., Larson, A., Williams, C.C., Li, G.W., Zhou, S., King, D., Shen, P.S., Weibezahn, J., Dunn, J.G., Rouskin, S., Inada, T., **Frost, A.***, Weissman, J.S.***** A Ribosome-Bound Quality Control Complex Triggers Degradation of Nascent Peptides and Signals Translation Stress. ***Cell*** (2012) Nov 21; 11(5):1042–1054 ***Co-corresponding authors** PMID: 23178123; PMCID: PMC3534965
2. Shen, S.S., Park, P., Qin, Y., Li, X., Parsawar, P., Larson, M.H., Cox, J., Cheng, Y. Lambowitz, A.L., Weissman, J.S.*, Brandman, J.*, **Frost, A.*** (2015) Rqc2p and 60S ribosomal subunits mediate mRNA-independent elongation of nascent chains. **Science** 347(6217), 75-78 PMID: 25554787 PMCID: PMC4451101 ***Co-corresponding authors**


**Complete List of Published Work in MyBibliography:**
http://www.ncbi.nlm.nih.gov/sites/myncbi/adam.frost.1/bibliography/48465466/public

**D. Research Support**
**Ongoing Research Support**

13SSP218, Searle Scholars Program 07/01/13 – 06/30/16
Structural and Functional Characterization of the Ribosome Quality Control Complex
Major Goal: To determine mechanisms of co-translational protein quality control by determine pseudo-atomic structures of the 60S ribosome bound by components of the Ribosome Quality Control complex.
Role: PI

DP2GM110772 (Frost, PI) 10/01/13 - 06/30/18
Toward Atomic Resolution of Membranes and Membrane-Associated Machines
Major Goals: To develop biochemical sample preparation and imaging and image analysis techniques that will enable near-atomic resolution structure determination of membrane-associated assemblies by cryo-electron microscopy.

BSF2013310, Israel Binational Science Foundation 07/01/14 – 06/30/17
Structural and Functional Characterization of the srGAP Family of Proteins
Major Goal: To determine mechanisms of membrane remodeling by inverse F-BAR proteins, IF-BAR proteins, of the srGAP family and their roles in the development of the nervous system.
Role: PI

2 R01 GM068803-10 (Munson, PI) 09/01/14 - 06/30/18
Structure and Function of the Exocyst Complex
Major Goals: To determine atomic resolution structures of the Exocyst complex
Role: Co-Investigator

New Frontiers Research, Sander Family Foundation and UCSF 07/01/2015 – 06/30/2016

New Concepts for Understanding and Treating Neurodegenerative Disease
Major Goal: To develop mammalian cell and mouse embryonic stem cell reagents in order to characterize the Ribosome Quality control Complex (RQC) in mammalian cells.
Role: PI

**Completed Research Support**

2P50GM082545-06 (Sundquist, PI) 02/01/13-06/30/14
NIH/ NIGMS
P50 Center for the Structural Biology of Cellular Host Elements in Egress, Trafficking, and Assembly of HIV (CHEETAH, Sundquist, PI)
Major Goal: My role in of this mini-grant Collaborator Development Award was to solve a subnanometer resolution structure of the hetero-complex formed by IST1 and CHMP1B by cryoEM.
Role: Co-Investigator