BIOGRAPHICAL SKETCH

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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	04/2000	Biochemistry
Yale University, New Haven, CT	PhD	05/2008	Structural Biology
Yale University, New Haven, CT	MD	05/2009	Medicine
University of California San Francisco, SF, CA	Postdoc	06/2011	Systematic Genetics

A. Personal Statement

When I matriculated as an MD/PhD student, my goals were unclear beyond knowing that I was interested in both science and medicine. Eight years later my enthusiasm for basic science eclipsed my other interests, 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 witnessed amazing accomplishments in genomics, genetic engineering, and fluorescence microscopy. These developments suggested that we were approaching the time when structural and functional knowledge of *multi-component machines* would be rate-determining challenges in our quest to understand biology and pathology. So for my post-doctoral work, I developed genome-scale, unbiased strategies for finding and functionally annotating multi-component complexes (with Jonathan Weissman). By assembling genetic interaction maps comparing pathways in two fungal model organisms, *S. pombe* and *S. cerevisiae*, we helped discover a dozen conserved protein complexes that function in processes ranging from cell cycle regulation to protein quality control. During this same period, technology developments in my first area of expertise—electron cryo-microscopy or cryo-EM—were making it possible to resolve the structures of even the most intricate machines in atomic-resolution detail. Now, as an independent investigator, I have assembled a laboratory that is uniquely capable of integrating cryo-EM structure determination with biochemistry, genetics and live cell imaging to advance our understanding of how cellular machines usually function, how disease corrupts them, and how pathogens hijack them. With a network of outstanding collaborators, major projects in our lab now include investigating: 1) Nascent protein quality control by the Ribosome-associated Quality control Complex or RQC; 2) Membrane remodeling activities that govern endocytosis and mitochondrial fission, with a focus on Dynamin-family GTPases and their partners; and 3) Membrane remodeling activities that govern the cell cycle, with a focus on the ESCRT pathway.

B. Positions and Honors

Positions and Employment

2000-2009 MSTP MD/PhD Program, Yale University School of Medicine, CT
Mentor: Vinzenz M. Unger, PhD. Co-mentor: Pietro De Camilli, MD

2009-2011 Post-Doctoral Scholar, University of California, San Francisco, CA
Mentor: Jonathan S. Weissman, PhD

2011-2014 Assistant Professor, Department of Biochemistry and Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT

2014-present Adjunct Assistant Professor, Department of Biochemistry and Huntsman Cancer Institute,

University of Utah School of Medicine, Salt Lake City, UT Professor,
2014-2018 Assistant Professor, Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA
2018-present Associate Professor, Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA

Other Experience and Professional Memberships

2014-present American Society for Cell Biology, American Society for Biochemistry and Molecular Biology, Biophysical Society
2105-present Scientific Advisory Board for the Center for Cell Science, University of Utah

Honors

1994 Mangum-Lewis Undergraduate Full Support Scholarship
1995 Most Outstanding Undergraduate Inorganic Chemistry Student Award
1999 Barry M. Goldwater Scholar, National Scholarship for Math, Science and Engineering
2000 *Cum laude* in Honors Chemistry and Biochemistry
2000 NIH NIGMS, Medical Scientist Training Program Grant GM-07205
2004 The Milton C. Winternitz Prize in Pathology, Yale School of Medicine
2006 Epilepsy Foundation Pre-Doctoral Research Training Fellowship
2009 Yale University School of Medicine Dissertation Award and Farr Scholarship Lecture
2009 Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation
2013 Searle Scholar
2013 NIH Director's New Innovator Award
2015 Herbert Boyer Junior Faculty Endowed Chair
2016 American Asthma Foundation Scholar Award
2016 Howard Hughes Medical Institute Faculty Scholar
2017 Chan Zuckerberg Biohub Investigator

C. Contributions to Science

1. BAR domain proteins and membrane remodeling: Eukaryotic cells have evolved the ability to shape their membranes into spheres and tubules to make connections between organelles or exchange material with the outside world. Starting with my work as a graduate student and continuing into my independent career, I have used genetics, biochemistry, and structural biology to define how the BAR-domain superfamily of proteins bind their target membranes and oligomerize into scaffolds that shape organelles and membrane trafficking intermediates.

   a) Frost, A., Perera, R., Roux, A., Spasov, K., Egelman, E., De Camilli, P., Unger, V. M. (**2008**) Structural basis of membrane invagination by F-BAR domains. ***Cell*** 132, 807-817. PMID: 18329367. PMCID: PMC2384079
   b) Frost, A., Unger, V.M., De Camilli, P. (**2009**) The BAR domain superfamily: membrane-molding macromolecules. ***Cell*** 137, 191-196. PMID: 197379681. PMCID: PMC4832598
   c) Guerrier, S., Coutinho-Budd, J., Sassa, T., Chen, K., Wei-Lin, J., Frost, A., 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.
   d) Hohendahl, A., Talledge, N. Galli, V. Shen, P.S., Humbert, F., De Camilli, P., Frost, A.*, Roux, A. * (**2017**). Structural inhibition of dynamin-mediated membrane fission by endophilin. ***eLIFE***, Sep 21;6. pii: e26856. PMID: 28933693. PMCID: PMC5663480 *Co-corresponding authors

2. Dynamin-family GTPases and organelle fission: In addition to shaping membrane-trafficking intermediates as described above, cells also utilize chemical fuel-driven machines of the Dynamin-family of GTPases to catalyze membrane fusion and fission reactions. Our focus has been on the allosteric and regulatory mechanisms governing these large GTPases, especially those employed by their binding partners. Our recent work has defined how GTP-dependent conformational changes perform mechanical work upon target membranes through long-range allostery. We have also determined how receptors and other organelle-specific binding partners bind and regulate Dynamin-family activities during endocytosis versus mitochondrial fission.

a) Roux, A., Uyhazi, K., Frost, A., De Camilli P. (**2006**). GTP-dependent twisting of dynamin implicates constriction and tension in membrane fission. ***Nature***, 441(7092), 528-531. PMID: 16648839
b) 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. PMID: 23530241; PMCID: PMC3625255 *Co-corresponding authors
c) Antonny, B., Burd, C., De Camilli, P., Chen, E., Daumke, O., Faelber, K., Ford, M., Frolov, V.A., Frost, A., Hinshaw, J.E., Kirchhausen, T., Kozlov, M.M., Lenz, M., Low, H.H., McMahon, H., Merrifield, C., Pollard, T.D., Robinson, P.J., Roux, A., Schmid, S. (**2016**) Membrane fission by dynamin: what we know and what we need to know. ***EMBO J***., Sep 26. PMCID: PMC5090216
d) Kalia, R., Wang, R.Y., Yusuf, A., Thomas, P.V., Agard, D.A., Shaw, J.M., and Frost, A. (**2018**) Structural basis of mitochondrial receptor binding and constriction by DRP1. ***Nature*** 558, 401–405. PMID: 29899447; PMCID: in process

3. <u>ESCRT proteins and membrane remodeling:</u> In addition to BAR domain-containing proteins and Dynamin-family GTPases, the Endosomal Sorting Complexes Required for Transport or ESCRT proteins are among the most ancient and ubiquitous membrane remodeling activities. We co-discovered a role for specific ESCRTs in maintaining nuclear envelope integrity in yeast and human cells. We also co-discovered how certain ESCRTs participate in an unexpected endosome recycling pathway for certain transmembrane receptors. Finally, our lab determined the first near atomic-resolution structure of fully assembled, multi-component membrane-shaping ESCRT-III complex. Our studies revealed the mechanism of ESCRT-III activation, “opening” and co-oligomerization and have opened new investigations in our lab into ESCRT receptors and functions at the reforming nuclear envelope in human cells, their role(s) in micronuclei formation, and finally in protecting cells from DNA damage.

a) 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*** 350, 1548–51. PMCID: PMC4684769. *Co-corresponding authors
b) Gu, M., LaJoie, D., Chen, O.S., Von Appen, A. Ladinsky, M.S., Redd, M.J., Nikolova, L. Bjorkman, P.J., Sundquist, W.I.*, Ullman, K.S.*, and Frost, A.* (**2017**) LEM2 recruits CHMP7 for ESCRT-mediated nuclear envelope closure in fission yeast and human cells. ***PNAS***, 2017 Mar 14;114(11): E2166-E2175. PMID: 28242692 PMCID: PMC5358359. *Co-corresponding authors

4. <u>Discovery and Functional Annotation of Multi-Component Complexes:</u> My lab remains motivated to discover and characterize the structures and functions of multi-component complexes and believe this effort remains a rate-determining challenge for biomedical science. Using both classical and high-throughput genetics and by comparing pathways in two model organisms, *S. pombe* and *S. cerevisiae*, we continue to search for conserved and fundamentally important complexes for eukaryotic cells. This work has also provided novel insights into how—and how often—genes acquire new functions across evolutionary time by acquiring new motifs and domains.

a) 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. (**2012**) Functional repurposing revealed by comparing *S. pombe* and *S. cerevisiae* genetic interactions. ***Cell*** Jun 8;149(6):1339-52. PMID: 22682253; PMC3613983. *Corresponding author
b) 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.***** (**2012**) A ribosome-bound quality control complex triggers degradation of nascent peptides and signals translation stress. ***Cell*** Nov 21; 11(5):1042–1054. PMID: 23178123; PMCID: PMC3534965. *Co-corresponding authors
c) Hwang, J., Ribbens, D., Raychaudhuri, S., Cairns, L., Gu, H., Frost, A., Urban, S., Espenshade.P.J. (**2016**) A Golgi rhomboid protease Rbd2 recruits Cdc48 to cleave yeast SREBP. ***EMBO J***. 2016 Nov 2;35(21):2332-2349. PMCID: PMC5090219
d) Gu, M., LaJoie, D., Chen, O.S., Von Appen, A. Ladinsky, M.S., Redd, M.J., Nikolova, L. Bjorkman, P.J., Sundquist, W.I.*, Ullman, K.S.*, and Frost, A.* (**2017**) LEM2 recruits CHMP7 for ESCRT-

mediated nuclear envelope closure in fission yeast and human cells. ***PNAS*** Mar 14;114(11):E2166-E2175. PMID: 28242692 PMCID: PMC5358359. *Co-corresponding authors

5. Discovery of CAT tails in Protein Quality Control: In our follow-up structural characterization of one of the complexes discovered in the work cited above, we uncovered a novel mechanism of protein quality control that malfunctions in certain neurodegenerative diseases. We discovered that failed translation complexes are recognized by a multi-component complex now known as the Ribosome-associated Quality control Complex or RQC. In addition to detecting failed ribosomes and marking their incomplete translation products with poly-ubiquitin, we discovered that the RQC also elongates failed nascent chains with a unique modification 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 named Ribosome Quality Control 2 or RQC2. Using a mechanism that was not predicted by the central dogma of biology, CAT tails are not encoded by mRNA. Rather, all 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 conserved protein we named RQC2. Our most recent work on CAT tail synthesis has revealed an intimate interplay between CAT tail elongation and ubiquitination of failed nascent polypeptides. We have most recently co-discovered an ancient and conserved release factor for the RQC/CAT tail pathway, a cryptic tRNA hydrolase that liberates failed nascent chains from the large subunit of the ribosome after an unresolved stall.

   a) 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.* (**2012**) A ribosome-bound quality control complex triggers degradation of nascent peptides and signals translation stress. **Cell** Nov 21; 11(5):1042–1054. PMID: 23178123; PMCID: PMC3534965. *Co-corresponding authors
   b) 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
   c) Osuna, B.A., Howard, C.J., Kc, S., Frost, A.*, Weinberg, D.E.* (**2017**) In vitro analysis of RQC activities provides insights into the mechanism and function of CAT tailing. ***eLIFE*** Jul 18;6 pii: e27949. PMID: 28718767 PMCID: PMC5562442. *Co-corresponding authors
   d) Rendón, O.R.[#], Fredrickson, E.K. [#], Howard, C.J. [#], Van Vranken, J., Fogarty, S., Tolley, N.D., Osuna, B.A., Shen, P.S., Hill, C.P., Frost, A.*, Rutter, J.* (**2018**) Vms1p is a release factor for the Ribosome-associated Quality control Complex. ***Nature Communications*** Jun 6;9(1):2197 *Co-corresponding authors

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

D. Research Support
Ongoing Research Support

American Asthma Foundation Frost (PI) Frost (PI) 06/01/16 – 05/31/18
The Structural Basis of Heritable Human Asthma and Related Disorders of Sphingolipid Synthesis
Major Goal: To determine the structure of the human SPOTS complex in a lipid bilayer to understand sphingolipid homeostatic mechanisms and the mechanisms of deregulated lipid pathology. This grant is now in now in no-cost extension and pending a renewal decision.
Role: PI

Howard Hughes Medical Institute Faculty Scholar Program Frost (PI) 11/01/16 – 10/31/21
Function Follows Form: Investigating the Structural Basis of Cell Biology
Major Goal: Structural cell biology
Role: PI

Chan Zuckerberg Biohub Investigator Program Frost (PI) 03/15/17 – 03/14/22

The Cell Atlas and the Infectious Disease Initiatives
Major Goal: Structural cell biology
Role: PI

P50 GM082545-06 Sundquist (PI) 08/31/17-07/31/22
NIH/ NIGMS
Center for the Structural Biology of Cellular Host Elements in Egress, Trafficking, and Assembly of HIV (CHEETAH Center Grant)
Major Goal: To determine the structural basis of ESCRT-III mediated HIV egress.
Role: Project 1 Lead Investigator

1 R01 GM127673-01 (GRANT12415861) Frost (PI) 07/01/18 - 06/30/22
Regulated Mitochondrial Morphology
Major Goals: To determine how mitochondria change shape and connectivity in health and disease (notice of award pending).
Role: PI

Completed Research Support

13SSP218, Searle Scholars Program Frost (PI) 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

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 for 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

New Frontiers Research, Sander Family Foundation and UCSF Frost (PI) 07/01/15 – 12/31/16
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

NIH New Innovator 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. This grant is coming to an end, but the major projects are now funded through new NIH- and other sources of support.
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. We are awaiting a funding decision for the next renewal.
Role: Co-Investigator