BIOGRAPHICAL SKETCH

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NAME: Adam Frost

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

POSITION TITLE: Associate 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	General 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 leaps forward in genomics, genetic engineering, and fluorescence microscopy. These developments suggested to me that we were approaching a time when *a mechanistic understanding of how macromolecar machines work* would be rate-determining challenges in our quest to understand biology and pathology. Inspired by this notion, I developed genome-scale, unbiased strategies for finding and functionally annotating multi-component complexes as a postdoctoral fellow (with Jonathan Weissman). By assembling genetic interaction maps comparing pathways in two fungi, fission versus budding yeasts, we discovered and characterized conserved protein complexes that function in processes ranging from cell cycle control to protein quality control. During this same period, the development of direct electron detectors 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 atomistic detail. Now, with a team of ardent graduate students and postdoctoral scholars, our laboratory integrates cryo-EM structure determination with biochemistry, genetics, and live-cell imaging to advance our understanding of how cellular machines function, how disease corrupts them, and how pathogens hijack their activities during infection.

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 Postdoctoral 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 with tenure, 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
2015-present Scientific Advisory Board for the Center for Cell Science, University of Utah
2019-present Board of Reviewing Editors, eLIFE

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* graduate 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
2015 Herbert Boyer Junior Faculty Endowed Chair, UCSF
2016 American Asthma Foundation Scholar
2016 Howard Hughes Medical Institute Faculty Scholar
2017 Chan Zuckerberg Biohub Investigator
2018 Faculty of 1000, Cell Signaling & Trafficking Structures
2018 Deleage Prize (with Natalia Jura) from the UCSF Program for Breakthrough Biomedical Research

C. Contributions to Science

1. BAR domain proteins and membrane remodeling: Eukaryotic cells have evolved the ability to shape their membranes into spheres, tubules and other shapes to make connections between organelles and exchange material with their environments. Starting with my work as a graduate student and continuing into my independent career, we have determined how BAR-domain 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 membrane remodeling: In addition to BAR proteins, cells also utilize fuel-driven machines to catalyze membrane remodeling—especially membrane fusion and fission reactions. Our lab has focused on the allosteric and regulatory mechanisms that govern the Dynamin family of large GTPases, which play widely conserved roles in organelle fusion and fission. Our recent work has defined how GTP-dependent conformational changes perform mechanical work upon target membranes through allosteric relays. We have also determined how receptors and other organelle-specific partners bind and regulate Dynamin-family activities during endocytosis and 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: PMC6120343

3. ESCRT proteins and membrane remodeling: The Endosomal Sorting Complexes Required for Transport (ESCRT) are among the most ancient and ubiquitous membrane remodeling proteins. Our lab determined the first atomic-resolution structures of fully assembled, membrane-bound ESCRT-III complexes, answering long-standing questions about the diversity of membrane-binding surfaces and the properties of hetero-oligomeric ESCRT-III polymers. These studies revealed how some ESCRT-III proteins activate by “opening” and co-oligomerize to shape membrane surfaces. We also discovered an evolutionarily ancient mechanism by which specific ESCRTs and their conserved adaptors maintain nuclear envelope integrity.

    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*** Mar 14;114(11): E2166-E2175. PMID: 28242692 PMCID: PMC5358359. *Co-corresponding authors
    c. Nguyen, H.C., Talledge, N., McCullough, J., Sharma, A., Moss, F.R. 3rd, Iwasa, J.H., Vershinin, M.D., Sundquist, W.I., **Frost, A.** (**2020**) Membrane constriction and thinning by sequential ESCRT-III polymerization. ***Nat Struct Mol Biol***. Apr;27(4):392-399. PMID: 32251413. PMCID: in progress
    d. Von Appen, A.[#], LaJoie, D.[#], Johnson, I.E.[#], Trnka, M., Pick, S.M., Burlingame, A.L., Ullman, K.S.* and **Frost, A.*** (**2020**) LEM2 phase separation promotes ESCRT-mediated nuclear envelope reformation. ***Nature*** Jun;582(7810):115-118. PMID: 32494070 PMCID: in progress
    [#]Co-first authors *Co-corresponding authors

4. Discovery of CAT tails in Ribosome-associated Quality Control (RQC): Our collaborative team discovered how “failed” ribosomes are recognized by a multi-component complex named 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 elongates failed nascent chains with a unique modification: Carboxy-terminal Alanine and Threonine tails or "CAT tails." CAT tails are synthesized by the large subunit of the ribosome and a protein we named Ribosome Quality Control 2 (RQC2). CAT tails are not encoded by mRNA; rather, all the information necessary for CAT tail synthesis—for marking failed translation products as potentially toxic and activating a stress response—is encoded within the structure of the ancient RQC2 protein. Our most recent work on CAT tail synthesis revealed an inter-dependence between CAT tail elongation, ubiquitination of failed nascent polypeptides, and proteasomal degradation. We have most recently co-discovered an ancient and conserved release factor for the RQC/CAT tail pathway—a mitochondria-targeting protein known as Vms1—which liberates failed nascent chains from the ribosome following unresolved stalls during translation.

    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 PMID: 29875445; PMCID: PMC5989216 *Co-corresponding authors

5. <u>Discovery of the mechanism of action of ISRIB, a memory-enhancing small molecule:</u> We co-determined the mechanism of action of a potent neuroprotective and cognition-enhancing drug-like molecule known as the Integrated Stress Response Inhibitor or ISRIB. We collaboratively determined the structures of ISRIB's target, the translation initiation factor eIF2B, bound to ISRIB, bound its guanine nucleotide exchange substrate eIF2, and bound to its potent inhibitor, the phosphorylated conformation of eIF2a-P. These structures answered long-standing questions about the rate-determining guanine nucleotide exchange step of translational initiation, the mechanism by which the Integrated Stress Response (ISR) tunes the synthesis of new proteins to restore homeostasis, and pointed the way forward to new therapeutic manipulations of the ISR.

   a. Tsai,J.C.[#], Miller-Vedam,L.E.[#], Anand, A.A.[#], Jaishankar, P., Nguyen, H.C., Renslo,A. **Frost, A.***, Walter, P.* (**2018**) Structure of the nucleotide exchange factor eIF2B reveals mechanism of memory-enhancing molecule*. **Science** 359 (6383) eaaq0939.* PMID:29599213 PMICD: PMC6120582 [#]Co-first authors *Co-corresponding authors

   b. Kenner, L.[#], Anand, A.A.[#], Nguyen, H.C., Myasnikov1, A.G., Klose, C.J., McGeever, L.A., Tsai,J.C., Miller-Vedam, L.E., Walter, P.*, **Frost, A.*** (**2019**) eIF2B-catalyzed GDP exchange and phosphoregulation by the integrated stress response*. **Science*** 3;364(6439):491-495 PMID: 31048491 PMCID: PMC6601628 *Co-corresponding authors

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

D. Research Support

<u>Ongoing Research Support (incomplete list)</u>

1R01 GM127673-01 NIH/NIGMS Frost (PI) 10/01/18 – 09/31/22
Regulated Mitochondrial Morphology
Major Goals: To determine how mitochondria regulate their functional shapes and connectivity in health and disease

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

P50 AI150464-13 NIH/NIAID Sundquist (PI) 08/31/17 - 07/31/22
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 Investigator

Chan Zuckerberg Biohub Investigator Frost (PI) 03/01/2017 – 02/28/2021
Junior Investigator Award
Major Goals: Structural Cell Biology, advance structural cell biology with electron cryo-microscopy (cryo-EM).

University of Massachusetts Munson (PI) 9/21/2018-06/30/2022
NIH/NIGMS R01 GM068803
Structure and Function of the Exocyst Complex
Major Goals: To facilitate, advise, and teach Dr. Munson and her laboratory to use electron microscopy in studies of the exocyst complex.

Relay Therapeutics, Inc Frost (PI) 09/01/2019-08/31/2020
To determine solution-state structures of lipid kinases involved in human cancer

Completed Research Support (incomplete list)

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

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.
Role: PI

American Asthma Foundation Frost (PI) 06/01/16 – 05/31/19
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.
Role: PI

Relay Therapeutics, Inc. Frost (PI) 03/01/2017-02/28/2019
Atomic Structure Determination for Drug Discovery using cryoEM
Major Goals: To utilize cryoEM to understand protein motion and facilitate drug discovery.
Role: PI