

**University of California, San Francisco**  
**CURRICULUM VITAE**

**Name:** Adam S Frost, MD/PhD

**Position:** Associate Professor, Step 1  
Biochemistry & Biophysics  
School of Medicine

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**EDUCATION**

-	Degree	Institution (Area of Study)
2009 - 2011	Postdoctoral Fellow	University of California, San Francisco (Cellular and Molecular Pharmacology) San Francisco, CA
2000 - 2009	M.D.	Yale University School of Medicine (Medical Scientist Training Program) New Haven, CT
2000 - 2009	Ph.D.	Yale University (Interdepartmental Neuroscience Program), New Haven, CT
1996 - 2000	B.S.	Brigham Young University (Honors Biochemistry) Provo, UT

**LICENSES, CERTIFICATION**

NA

**PRINCIPAL POSITIONS HELD**

2018 - present	University of California, San Francisco, San Francisco, CA	Associate Professor	Biochemistry and Biophysics
2014 - 2018	University of California, San Francisco, San Francisco, CA	Assistant Professor	Biochemistry and Biophysics
2011 - 2014	University of Utah and Huntsman Cancer Center, Salt Lake City, UT	Assistant Professor	Biochemistry

**HONORS AND AWARDS**

2018	Deleage Prize (with Natalia Jura)	UCSF Program for Breakthrough Biomedical Research
2018	Faculty of 1000, Cell Signaling & Trafficking Structures	Faculty of 1000
2017	Chan Zuckerberg Biohub Investigator	Chan Zuckerberg Initiative
2016	HHMI Faculty Scholar	Howard Hughes Medical Institute
2016	American Asthma Foundation Scholar	American Asthma Foundation
2015	Herbert Boyer Junior Faculty Endowed Chair	Department of Biochemistry and Biophysics, UCSF
2013	NIH Director's New Innovator Award	Office of the NIH Director, New Innovator DP2 program
2013	Searle Scholars Award	The Chicago Community Trust and the Kinship Foundation
2009	Life Sciences Research Foundation Post-Doctoral Scholar	Howard Hughes Medical Institute
2009	Dissertation Award and Farr Scholarship Lecture	Yale University School of Medicine
2008	Sara and Frank McKnight Fellowship (Declined)	UT Southwestern Medical Center
2006	Pre-Doctoral Research Training Fellowship	Epilepsy Foundation
2006	Invited Student Delegate to the 45th Annual International	The Academy of Achievement
2004	Milton C. Winternitz Prize in Pathology	Yale School of Medicine
2000	Medical Scientist Training Program Grant GM-07205	NIH / NIGMS
2000	Cum laude in Honors Biochemistry	Brigham Young University
1999	Finalist	Harry S. Truman Scholarship
1999	Scholarship for Math, Science and Engineering	Barry M. Goldwater Foundation
1995	Most Outstanding Inorganic Chemistry Undergraduate Student Award	Brigham Young University
1994	Mangum-Lewis Undergraduate Scholarship (full support)	Magnum-Lewis Family Foundation

## **KEYWORDS/AREAS OF INTEREST**

Structural biology, electron microscopy, image analysis, membrane biology, lipid synthesis, protein synthesis, protein quality control, neurodegeneration, ribosome, translation, membrane curvature, cell cycle, nuclear envelope, mitochondria

## **CLINICAL ACTIVITIES**

### **CLINICAL ACTIVITIES SUMMARY**

NA

## **PROFESSIONAL ACTIVITIES**

### **MEMBERSHIPS**

2016 - present American Society for Biochemistry and Molecular Biology

2014 - present American Society for Cell Biology

### **SERVICE TO PROFESSIONAL ORGANIZATIONS**

2017 - 2018	American Society of Cell Biology Program Committee	2018 ASCB   EMBO Program Committee Subcommittee 3
2015 - present	The Center for Cell and Genome Science, University of Utah	Scientific Advisory Board

### **SERVICE TO PROFESSIONAL PUBLICATIONS**

2019 - present Board of Reviewing Editors, eLIFE

2018 - present Guest Editor, PLOS

2017 - present Reviewer for Molecular Biology of Cell

2013 - present Reviewer for Biochemistry, ACS

2012 - present Reviewer for eLIFE

2012 - present Reviewer for Current Opinion in Structural Biology

2011 - present Reviewer for Journal of Cell Biology

2011 - present Reviewer for Journal of Molecular Biology

2011 - present Reviewer for Current Biology

2010 - present Reviewer for European Molecular Biology Organization (EMBO) and EMBO reports

2010 - present Reviewer for Proceedings of the National Academy of Sciences (PNAS)

2010 - present Reviewer for Science

2010 - present Reviewer for Nature Publishing: Nature, Nature Structural and Molecular Biology, Nature Communications, Nature Cell Biology, Scientific Reports

2009 - present Reviewer for Cell Press: Cell, Developmental Cell, Molecular Cell, Cell Reports, Structure

### INVITED PRESENTATIONS - INTERNATIONAL

2019	University of Geneva, Life Sciences Seminar Symposium, Geneva, Switzerland	Invited Speaker
2019	University of Oslo, Oslo, Norway	Invited Speaker
2019	University of Helsinki, Helsinki, Finland	Invited Speaker
2018	International Symposium: Proteins from the Cradle to the Grave, Kyoto, Japan	Invited Speaker
2018	Gordon Research Conference, Three Dimensional Electron Microscopy (3DEM), RI USA	Invited Speaker
2018	Cold Spring Harbor Laboratory Meeting on Proteostasis, New York, NY USA	Speaker
2018	Biochemistry Society, New Horizons in ESCRT Biology, Royal Holloway College, University of London College, UK	Invited Speaker
2018	Keystone Symposium: Three Dimensional Cryo-EM: from Molecules to Cells. Granlibakken, CA USA	Invited Speaker, Session Chair
2017	American Society for Biochemistry and Molecular Biology, COMBIO, Adelaide, Australia	Plenary Lecture
2017	EMBO Endocytosis Conference, Warsaw, Poland	Invited Speaker
2017	Max-Delbrück Center for Molecular Medicine, Berlin, Germany	Invited Speaker
2017	Structural Biology Related to HIV/AIDS, NIH/NIGMS, Bethesda, MD, USA	Invited Speaker
2017	American Society for Biochemistry and Molecular Biology, Chicago, IL, USA	Invited Speaker
2016	American Society of Cell Biology, San Francisco, CA USA	Symposium co-chair and speaker
2016	3rdth Annual BioMembranes Symposium, Max Planck Society in Berlin-Dahlem, Berlin, Germany	Invited Speaker
2016	Hey What is the Big Idea? Symposium for the Center for Cell and Genome Science, Salt Lake City, UT USA	Keynote
2016	Keystone Symposium: Mitochondrial Dynamics	Invited Speaker
2015	Horizons in Molecular Biology, Max Planck Institute of Biophysical Chemistry, Goettingen, Germany	Invited Speaker
2015	How Do Large GTPases of the Dynamin Family Fission Membranes?, Les Treilles, France	Invited Speaker

2015	Gordon Research Conference, Molecular Membrane Biology, NH USA	Invited Speaker
2015	Membrane Protein Structures Meeting (MPS 2015), Argonne National Lab, Chicago USA	Invited Speaker
2014	Molecular Basis for Membrane Remodeling and Organization, Roscoff of Brittany, France	Invited speaker
2014	Microscopy of Infectious Disease Agent Symposia (MIDAS), NIH Hamilton MT, USA	Invited Speaker
2014	Structural Biology Related to HIV/AIDS, NIH, Bethesda, MD USA	Invited Speaker
2014	Gordon Research Conference, Lysosomes and Endocytosis, NH USA	Invited Speaker
2014	Bioimaging at the Nanoscale. Oregon Health Science and the FEI Living Labs 1st Annual Workshop and Conference. Portland, OR USA	Invited Speaker
2014	American Society for Biochemistry and Molecular Biology, San Diego, CA USA	Invited Speaker
2014	Keystone Symposium, Aging: Pushing the Limits of Cellular Quality Control, Steamboat Springs, CO USA	Invited Speaker
2013	Synaptic Vesicle Biogenesis, Janelia Farm Research Campus, Virginia USA	Invited Speaker
2013	Structural Biology Related to HIV/AIDS, NIH, Bethesda, MD	Invited Speaker
2013	Department of Biochemistry Seminar Series, University of Geneva, Geneva, Switzerland	Invited Speaker
2013	1st Annual Workshop on Cryo-Techniques for Electron Microscopy. Department of Nanochemistry, Istituto Italiano Di Tecnologia, Genova, Italy	Invited Speaker
2012	3rd Annual Delaware Membrane Protein Symposium, Newark, DE	Invited Speaker
2011	Sixth International Fission Yeast Meeting. Harvard University, Boston, MA USA	Invited Speaker
2008	4th International Conference on Structural Analysis of Supramolecular Assemblies by Hybrid Methods. Lake Tahoe, CA, USA	Invited Speaker
2007	1st International Conference on PCH/F-BAR Proteins: Adaptor Proteins for Macromolecular Complexes. Schloß Waldthausen, Mainz, Germany	Invited Speaker

2007	61st Annual Meeting of the Symposium of the Society of General Physiologists. Membrane Biophysics of Fusion, Fission, and Rafts in Health and Disease. Marine Biological Laboratory. Woods Hole, MA, USA	Invited Speaker
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### INVITED PRESENTATIONS - NATIONAL

2019	Department of Chemistry and Biochemistry, University of California, San Diego, San Diego CA USA	Seminar Speaker
2018	Life Science Graduate Research Symposium, Cornell University, Ithaca, NY	Invited Speaker
2017	Annual Signaling and Cellular Regulation (SCR) Symposium, University of Colorado, Boulder CO USA	Keynote Speaker
2017	Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, USA	Seminar Speaker
2017	Department of Cell Biology, Johns Hopkins School of Medicine, Baltimore, USA	Seminar Speaker
2017	Division of Physical Biosciences, Lawrence Berkeley National Laboratory, Berkeley, USA	Seminar Speaker
2016	Membrane Traffic Symposium, University of California, Berkeley, Berkeley, CA USA	Keynote speaker
2016	Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, USA	Seminar Speaker
2016	Department of Molecular Biology, Princeton University, Princeton NJ USA	Seminar Speaker
2016	Department of Cell Biology, University of Texas Southwestern Medical Center	Seminar Speaker
2015	Department of Biochemistry, University of Washington, School of Medicine, Seattle, WA USA	Seminar Speaker
2015	Department of Molecular Biology, Brigham Young University, Provo, UT USA	Seminar Speaker
2015	Department of Cell Biology, Symposium to Honor James Jamieson, Yale University School of Medicine, New Haven, CT USA	Plenary Speaker
2015	Department of Genetics, Cell & Developmental Biology, and Institute for Regenerative Medicine Seminar Series at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA USA	Seminar Speaker
2015	Department of Biochemistry, Weill Medical College of Cornell University, NYC, NY USA	Seminar Speaker

2014	Department of Biochemistry & Molecular Pharmacology, University of Massachusetts, Worcester, MA USA	Seminar Speaker
2014	Department of Biomolecular Chemistry, University of Wisconsin-Madison, Madison, WI USA	Seminar Speaker
2014	Department of Molecular Biosciences, Northwestern University, Evanston, IL USA	Seminar Speaker
2013	Weill Institute for Cell and Molecular Biology, Cornell University, Ithaca, NY	Seminar Speaker
2012	Department of Cell Biology & Molecular Biology Seminar Series, University of Maryland, College Park, MD	Seminar Speaker
2011	Department of Cell Biology Informal Seminar, Yale University, New Haven, CT	Seminar Speaker

### **GOVERNMENT AND OTHER PROFESSIONAL SERVICE**

2019 - present	eLIFE	Board of Reviewing Editors
2019 - present	National Center for CryoEM Access and Training (NCCAT) of the New York Structural Biology Center	User Review Committee
2019 - present	NIH / NIGMS	Ad hoc reviewer for Biochemistry and Biophysics of Membranes (BBM) study section
2018 - present	NIH / NIGMS	Ad hoc reviewer for ESI R35/MIRA study section
2014 - present	NIH / NIGMS	Ad hoc reviewer for Membrane Biology and Protein Processing (MBPP) study section

### **UNIVERSITY AND PUBLIC SERVICE**

#### **SERVICE ACTIVITIES SUMMARY**

In 2014-16 I served on the Biochemistry Faculty Search Committee and on the Faculty Search Committee for the Institute of Neurodegenerative Disease (IND).

I have served four concurrent terms on the selection and placement committee for the summer research training program, chaired by Carol Gross (SRTP).

I currently serve on the Committee for Research Technology, chaired by Charles McCullough (CRT).

In addition, I have contributed to five collaborative NIH proposals, four of which have been funded. I was the principal investigator most recently of a successful NIH major instrumentation S10 grant to expand access to electron cryo-microscopy UCSF.

### **UCSF CAMPUSWIDE**

2018 - present Committee on Research Technology member

### **SCHOOL OF MEDICINE**

2015 - present Faculty Member, Summer Research Training Program (SRTP) Selection and Placement Committee, chaired by Carol Gross. Admission committee member

2012 - 2014 Faculty Member, University of Utah Research Microscopy Facility, Center for Advanced Microscopy, Oversight Committee (University of Utah) chair

2012 - 2014 Faculty Member, University of Utah Core Research Facilities, Cell Imaging/Fluorescence Microscopy Facility, Oversight Committee (University of Utah) member

2011 - 2013 Member and Chair, University of Utah Biological Chemistry Graduate Program, Admissions committee member

### **DEPARTMENTAL SERVICE**

2018 - present Departmental Diversity Committee member

2014 - 2015 Faculty Search Committee member

2014 - present Biochemistry Seminar Series Selection Committee Co-chair, now member

### **CONTRIBUTIONS TO DIVERSITY**

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##### Summer Research and Training Program, Selection and Placement Committee:

Under the leadership of Dr. Carol Gross, I have served four terms as a research mentor and member of the selection and placement committee for UCSF's Summer Research Training Program (SRTP). This program recruits students broadly from all of California and beyond, with a special emphasis on finding applicants from disadvantaged backgrounds.

### **TEACHING AND MENTORING**

#### **TEACHING SUMMARY**

During my three years as an Assistant Professor at the University of Utah I taught a graduate seminar in Genetic Engineering, an upper-division course in Cell Biology for graduate, medical, pharmacy, and senior undergraduate students, and small-group problem solving workshops for medical students.



During my first five years at UCSF I have been a regular lecturer and small group leader for the Tetrad program's cell biology course, which I began co-directing in 2016. In 2018, I started a structural biology mini-course that is available to all graduate students interested in electron microscopy. Finally, I lead small group discussion and problem solving sessions for first year medical students focused on cancer biology and endocrinology.

In each of these forums, I focus on the logic of problem solving and data interpretation--in the context of the unique needs of students in these different environments. I typically assign readings to be completed prior to the lecture and use class time to work through problems and discuss student questions interactively. Typically, I call on students from the audience to answer questions, or to come to the board with me to explain data, make a diagnosis, or propose an experimental of a test. My examinations center on evaluating data and require the students to defend their interpretations, diagnoses or proposed experimental tests.

### FORMAL TEACHING

Not UCSF	Academic Yr	Course No. & Title	Teaching Contribution	School	Class Size
	2018 - present	CryoEM mini-course	Course Director	Grad	12
	2017 - present	IDS121C (REGulationN)	Small group	Medicine	12
	2016 - present	Cell Biology 245	Course Director	Grad	30
	2015 - 2017	Macromolecular Interactions	Course Faculty	Grad	20
	2015 - 2016	Mechanisms, Methods, and Malignancies (M3)	Small group	Medicine	12
	2014 - 2016	Cell Biology 245	Lecturer	Grad	30
X	2012 - 2014	Instructor, BLCHM C 6400: Genetic Engineering, University of Utah, 2 credit hours, 12 lecture hours, 20 students, Team taught with Dana Carroll			
X	2012 - 2014	Lecturer, M BIOL 6480: Cell Biology I, 1.5 credit hours, 37 students, University of Utah. 5 lectures			

Not UCSF	Academic Yr	Course No. & Title	Teaching Contribution	School	Class Size
X	2011 - 2014	Instructor, BIO C 7020: Biochem Research in Progress, University of Utah, Biochemistry			
X	2011 - 2014	Instructor, MBIOL 6100: Seminar Journal Club, University of Utah			
X	2011 - 2014	University of Utah School of Medicine, Third Year Internal Medicine Clerkship Facilitator and Lecturer			

### INFORMAL TEACHING

2014 - present Journal club discussion leader for Tetrad (Cell Biology) and iPQB first year students

### MENTORING SUMMARY

Mentoring young scientists remains the most meaningful and enduring aspect of our work. We have had the privilege of mentoring thirteen postdoctoral scholars and nine graduate students so far. The first six postdoctoral fellows to pass through the lab are now alumni and have positions in academic research or in the private sector. Three of them, Dr. Peter Shen, Dr. Kimberly Dickson, and Dr. Michał Gabruk, are tenure-track professors. Four others are employed by hospitals, biotechnology, or pharmaceutical companies. Our first four PhD-level graduate students have also completed their doctorates and are now engaged in post-doctoral training.

Our lab has hosted four high school students, ten undergraduate volunteers, and employed two technicians. All of whom have gone on to college as chemistry or biology majors, have been accepted to medical school, or in the case of the two technicians who worked in the lab, have been accepted to outstanding PhD programs (Stanford genetics and UCSF iPQB). Please see <http://frostlab.org/members/> for contact information and a lab census with alumni.

### PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Program or School	Mentor Type	Role	Current Position
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Dates	Name	Program or School	Mentor Type	Role	Current Position
2018 - present	Lakshmi Miller-Vedam	iPQB - Biophysics	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Co-supervisor	still in training
2016 - present	Paul Thomas	iPQB - Biophysics	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	still in training
2016 - present	Conor Howard	Tetrad	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	still in training
2016 - 2020	Isabel Johnson	Tetrad	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	Interim post-doctoral scholar (Frost lab)
2015 - 2019	Lillian Kenner	iPQB - Biophysics	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	Post-doctoral scholar (Genentech)
2014 - 2018	Valentin Romanov	Univeristy of Utah, Mechanical Engineering	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	Co-supervisor	Post-doctoral scholar (University of Sydney)
2013 - 2018	Nathaniel Talledge	University of Utah Biological Chemistry	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	Post-doctoral scholar (University of Minnesota)
2011 - 2018	Raghav Kalia	University of Utah Biological Chemistry	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	Post-doctoral scholar (UCSF)
2011 - 2012	Seth Lilavivat	University of Utah Biological Chemisry	Research/Scholarly Mentor, Project Mentor, Career Mentor	Supervisor	R&D scientist, Illumina, San Diego CA

**POSTDOCTORAL FELLOWS AND RESIDENTS MENTORED**

Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
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Dates	Name	Fellow	Mentor Role	Faculty Role	Current Position
2018 - 2020	Michał Gabruk, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	Assistant Professor, Jagiellonian University, Poland
2018 - present	Arthur Melo, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training
2018 - present	Frank Moss, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training
2017 - 2018	Rachael Di Santo	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor, Co-Mentor/Clinical Mentor	co-supervisor	Scientist, Synpromics, Edinburgh, Scotland
2017 - present	Ming Sun, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training
2016 - present	Halil Aydin, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training
2016 - present	Alexander Von Appen, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training
2016 - present	Henry Nguyen, Ph.D.	post-doctoral	Research/Scholarly Mentor, Project Mentor, Career Mentor	supervisor	still in training



Threonine tails, and our discovery raised new questions about both the basic biology of protein synthesis and its malfunction in disease. The RQC as a whole, and Rqc2 in particular, have subsequently been linked to neurodegeneration in mammals. Understanding 1) how CAT tails are synthesized and released from the ribosome; and 2) the functional impact of CAT tails within organelles versus the cytoplasm are current projects in our lab. We recently demonstrated that a key function of CAT tail synthesis is to enhance the efficiency of nascent chain ubiquitination by mobilizing and "delivering" chemically accessible lysine residues to the active site of an E3 ubiquitin ligase named Ltn1/LISTERIN (Osuna et al. *eLife*, 2017, also Kostova et al. *Science*, 2017). Finally, we co-discovered a unique release factor for CAT tail-modified nascent chains, a protein named Vms1. We showed how Vms1 protects cells and organelles from accumulating aggregation-prone, CAT tail-modified proteins through a unique ribosome release mechanism (Zurita, et al. *Nature Communications*, 2018).

In the second field, we collaborated with Peter Walter's lab to determine the mechanism of action of a potent neuroprotective and cognition-enhancing molecule known as the Integrated Stress Response Inhibitor, or ISRIB. We 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 step of translation initiation, the mechanism by which the Integrated Stress Response (ISR) tunes new protein synthesis to restore homeostasis, and pointed the way forward to new therapeutic manipulations of the ISR (Tsai et al. *Science* 2018, and Kenner et al. *Science* 2019). Understanding how synaptic activity is communicated to eIF2 and eIF2B, and how ISRIB-like molecules modulate synaptic protein synthesis, are new, forward-looking foci for our lab.

In the third field, we continued our longest-term exploration of how cells shape their membranes into spheres, tubes, and other striking shapes to exchange goods and services between organelles or with the outside world. Although we are approaching the fortieth anniversary of the 'fluid mosaic' model of cell membranes, basic questions about membrane structure and dynamics remain unanswered. We know that cells have evolved mechanisms to sense, shape, and remodel their membranous compartments—but because biological membranes are fluid sheets only ~4 nanometers thick, few experimental approaches can probe their structure or dynamics. We have determined cryoEM structures of membrane-bound and membrane-embedded machines involved in i) organelle division and inheritance, ii) exocytosis, iii) endocytosis, iv) endosome recycling, and v) reformation of the nuclear envelope. Using these structures as hypothesis generators, we have also have used genetics, biochemistry, and live cell imaging to probe the mechanisms through which both soluble and transmembrane proteins (re)shape organelles or generate membrane trafficking intermediates. Most recently, we have collaborated with outstanding labs (Brennwald, Hill, Jura, Munson, Roux, Rutter, Shaw, Sundquist, Ullman, and Weissman) to determine new structures and functions for: 1) the ESCRT pathway during the cell cycle, with a particular focus on nuclear envelope reformation; 2) Dynamin family proteins bound to regulatory partners involved in organelle homeostasis and endocytosis; 3) the exocyst complex and its regulatory GTPases; and 4) a new project aimed at understanding the structural basis of transmembrane protein folding and complex assembly by the conserved ER Membrane Protein Complex or EMC.

Our lab is grateful for support from an NIH/NIGMS R01, a Faculty Scholar Grant from the Howard Hughes Medical Institute, an Investigator grant from the Chan Zuckerberg Biohub, the Sandler Foundation Program for Breakthrough Biomedical Research (PBBR), an S10 major instrumentation grant, and a P50 Center grant from NIH/NIAID. In the past we have been supported by an NIH Director's New Innovator Award, a Scholar Award from the American Asthma Foundation, a co-PI R01 from NIH/NIGMS, a Searle Scholars Award, and the Bi-National Israeli-US Science Foundation (BSF).

**RESEARCH AWARDS - CURRENT**

1. HHMI Grant #55108523	PI	2.0 CM % effort	Frost (PI)
Howard Hughes Medical Institute		11/01/2016	10/31/2021
Structural Cell Biology		\$ 100,000	\$ 500,000 total
		direct/yr 1	
To advance cryoEM for the study of structural cell biology.			
Principal Investigator			
2. NA	PI	2.0 CM % effort	Frost (PI)
Chan Zuckerberg Biohub		04/01/2017	03/31/2022
Structural Cell Biology		\$ 150,000	\$ 750,000 total
		direct/yr 1	
To advance cryoEM for the study of structural cell biology.			
Principal Investigator.			
3. P0522785	PI	1.0.CM % effort	Frost (PI)
Relay Therapeutics LLC		04/17/2017	08/31/2021
Near atomic reconstruction structure determination of PI3K using cryoEM		\$ 320,000	\$ 750,000 total
		direct/yr 1	
To determine the atomic resolution structure of PI3K in solution, bound to different inhibitors, and bound to a phospholipid membrane.			
The conception of the project, design of the experimental strategy, evaluation of the results, writing the manuscript(s)			
4. P50 AI150464-13	Project 1 PI	2.0CM % effort	Sundquist (PI)
NIH / NIAID		08/31/2017	07/31/2022
Center for the Structural Biology of Cellular Host Elements in Egress, Trafficking, and Assembly of HIV		\$ 150,000	\$ 750,000 total
		direct/yr 1	
To determine the structural basis of the HIV lifecycle, with a particular focus on the role of the ESCRT-III machinery.			
The conception of the project, design of the experimental strategy, evaluation of the results, writing the manuscript(s)			
5. 1 R01 GM127673-01	PI	3.0 CM % effort	Frost (PI)
NIH / NIGMS		10/01/2018	09/30/2022
Regulated Mitochondrial Morphology		\$ 200,000	\$ 800,000 total
		direct/yr 1	
To determine how mitochondria change their shape and connectivity in health and disease.			
The conception of the project, design of the experimental strategy, evaluation of the results, writing the manuscript(s)			
6. 1S10OD026881-01	PI	1.0 % effort	Frost (PI)
NIH / NIGMS		09/01/2019	08/31/2020
Acquisition of a Glacio Cryo Transmission Electron Microscope with 200 kV XFEG optics		\$ 1,845,637	\$ 1,845,637 total
		direct/yr 1	

To expand UCSF's electron cryo-microscopy resources by acquiring a new, state-of-the-art instrument for the UCSF Center for Advanced CryoEM.

Identifying the opportunity, building a consensus to apply, coordination and overall project management

### RESEARCH AWARDS - SUBMITTED

1. P0538884	PI	2.0 CM % effort	Frost (PI)
NIH / NIGMS		07/01/2020	06/30/2025
ESCRT Structures and Emerging Functions		\$ 250,000 direct/yr 1	\$ 1,250,000 total

To determine the structural basis of multi-vesicular endosome formation, nuclear envelope resealing, and regulated gene expression by the ESCRT pathway.

### RESEARCH AWARDS - PAST

1. 2P50GM082545-06	Principal Investigator		Frost (PI)
NIH Institute of General Medical Science. Structural Biology Center for HIV/Host Interactions in Trafficking and Assembly. P50 Principal Investigator: Wesley I. Sundquist		01/01/2012	06/30/2014
The Molecular Mechanisms of Membrane Remodeling by the ESCRT Pathway		\$ 81,000 direct/yr 1	\$ 162,000 total

My role in this collaborative development award through the P50-funded CHEETAH center was to determine the high resolution structure of an ESCRT-III polymer

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2. 13SSP218	Principal Investigator		Frost (PI)
Searle Scholars Program		07/01/2013	06/30/2016
Structural and Functional Characterization of the Ribosome Quality Control Complex		\$ 100,000 direct/yr 1	\$ 300,000 total

We discovered and characterized the Ribosome Quality Control Complex or RQC complex. In this project we will determine high resolution structures of the RQC in its ribosome-bound state and determine its mechanism(s) of action.

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3. BSF2013310	Principal Investigator		Frost (PI)
Binational United States – Israel Science Foundation		09/01/2014	08/31/2016
Structure of srGAP Proteins		\$ 60,000 direct/yr 1	\$ 120,000 total

Major Goal: to reconstitute membrane remodeling of Inverse-BAR and Inverse-F-BAR domain proteins of the srGAP family for structural and functional studies.

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4. NA	Principal Investigator		Frost (PI)
Sandler Foundation and UCSF Program for Breakthrough Biomedical Research		07/01/2015	06/30/2016



New Concepts for Understanding and Treated Neurodegenerative Disease	\$ 150,000 direct/yr 1	\$ 150,000 total
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Major Goals: to determine whether CAT tailing is conserved in mammalian cells and to determine how CAT tails impact proteostasis and neurodegenerative disease.

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5. 1DP2GM110772-01	Principal Investigator	Frost (PI)
NIH/NIGMS New Innovators High Risk High Reward Director' s Program	09/30/2013	06/30/2018
Toward Atomic Resolution of Membranes and Membrane-Associated Machines	\$ 300,000 direct/yr 1	\$ 2,345,000 total

Biochemical reconstitution of membrane remodeling machinery and their reactions for atomic-resolution structure determination by electron cryomicroscopy.

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6. R01GM06880309	Subcontractor	Munson (PI)
NIH NIGMS	07/01/2014	06/30/2018
Structure and Function of the Exocyst Complex	\$ 98,000 direct/yr 1	\$ 294,000 total

My role as a Co-PI/subcontractor on this award is to determine high resolution structures of the intact Exocyst complex by electron cryomicroscopy.

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7. 16-0052	PI	
American Asthma Foundation Research Program	06/01/2016	06/30/2019
The structural basis of heritable human asthma and related disorders of sphingolipid synthesis	\$ 150,000 direct/yr 1	\$ 450,000 total

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8. NA	PI	0.6 CM % effort	Frost (PI)
Relay Therapeutics, Inc		03/01/2017	02/28/2018
Near atomic reconstruction structure determination of PI3K using cryoEM	\$ 172,068 direct/yr 1	\$ 172,068 total	

To advise Relay scientist on assembling a membrane mimetic for P13K; collect TEM negative stain images, screen for freezing conditions, collect data and evaluate the future utility of structural studies.

Principal Investigator

## PEER REVIEWED PUBLICATIONS

1. Jackson ME, Frost AS, Moghaddam B. Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J Neurochem. 2001 Aug; 78(4):920-3. PMID: 11520912

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42. Von Appen, A.#, LaJoie, D. #, Johnson, I.E. #, Trnka, M., Pick, S.M., Burlingame, A.L., Ullman, K.S.\* and Frost, A.\* LEM2 phase separation governs ESCRT-mediated nuclear envelope reformation. *Nature* 2020 In press bioRxiv 577460 #Co-first authors \*Co-corresponding authors

## REVIEW ARTICLES

1. Kalia, R., and Frost, A. (2019) Open and Cut: Allosteric Motion and Membrane Fission by Dynamin Superfamily Proteins. *Molecular Biology of the Cell* In press
2. McCullough, M., Frost, A., Sundquist, W.I. (2018) Structures, Functions, and Dynamics of ESCRT-III/Vps4 Membrane Remodeling and Fission Complexes. *Ann Rev Cell Dev Biol*. 2018 Oct 6;34:85-109
3. McBride, H., & Frost, A., (2016) Double agents for mitochondrial division. *Nature*, Dec 1;540(7631):43-44
4. Frost, A. (2011). Membrane trafficking: decoding vesicle identity with contrasting chemistries. *Curr Biol*, 21(19), R811-3.
5. Frost, A, De Camilli, P., Unger, V.M. (2007). F-BAR proteins join the BAR family fold. *Structure*, 15(7), 751-3.

## BOOKS AND CHAPTERS

1. **Frost A**, Unger VM, De Camilli P. (2009). Boomerangs, Bananas and Blimps: Structure and Function of F-BAR Domains in the Context of the BAR Domain Superfamily. <http://www.landesbioscience.com/curie/chapter/3985/http://www.ncbi.nlm.nih.gov/books/elf/br.fcgi?book=eurekah&ch=3985>. In *The Pombe Cdc15 Homology Proteins* (Pontus Aspenström). Landes Biosciences.

## SIGNIFICANT PUBLICATIONS

1. 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. \*Co-corresponding authors. PMID: 26634441. PMCID: PMC4684769

In collaboration with the laboratories of Wes Sundquist and Phyllis Handon, this was the second paper in our long-term effort to understand the structures and functions of ESCRT-mediated membrane remodeling. This paper revealed a new class of membrane remodeling activities and revealed the "open" and assembled state of ESCRT-III proteins for the first time. The mechanistic principles of polymerization and membrane remodeling we demonstrated have implications for membrane remodeling activities at diverse organelles and their usurpation by enveloped viruses. This paper was foundational to our subsequent papers and grants related to the structure/function of ESCRT pathway proteins. As a co-corresponding author, I set the research direction and led the biochemical reconstitutions, structure determination and validation, and membrane remodeling activity assays.

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 \*Co-corresponding authors. PMCID: PMC4451101

In collaboration with UCSF's Jonathan Weissman and Stanford's Onn Brandman, this paper established a new concept in protein quality control and untemplated peptide synthesis. The study of CAT tails quickly became a fast-moving new field of inquiry in both unicellular organisms and human cells, including human disease states. This foundational paper led to one of our first grants and three new studies from our group and our set of outstanding collaborators in this field (Kostova et al. *Science*; 2017 and Osuna et al. *eLIFE*, 2017; Zurita et al. *Nature communications*, 2018). As a co-corresponding author, I set the research direction and led the biochemical purifications, structure determination and validation, and analysis of the tRNA sequencing data.

3. 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

This paper represents the first milestone in our long-term effort to determine how mitochondria change shape and connectivity to adapt to fluctuating cellular environments. We determined how a receptor protein anchored in the outer mitochondrial membrane, MID49, recruits periodic arrays of the large GTPase, DRP1, to mitochondria through a phospho-regulated coassembly mechanism. We further showed how GTP hydrolysis catalyzes long range allosteric motions that drive low-curvature DRP1 polymers to curl up into high-curvature and closed rings. We postulated that these closed rings correspond with the "core" of the in vivo organelle fission machine and discussed how our model explains a set of human genetic disease associations. I set the research direction, led the biochemical reconstitutions, structure determination, modeling and validation assays as the corresponding author.

4. Kenner, L.R., Anand, A.A., Nguyen, H.R., Myasnikov, A.G., Klose, C.J., McGeever, L.A., Tsai, J.C., Miller-Vedam, L.E., Watler, P.\*, and **Frost, A.\*** (2019) Structural basis of eIF2B-catalyzed GDP exchange and phosphoregulation by the integrated stress response. **Science** 05 03; 364(6439):491-495. #Co-first authors \*Co-corresponding authors

In collaboration with UCSF's Peter Walter, we used cryoEM structure determination to decipher the mechanism of action of a neuro-protective and cognition-enhancing drug known as the Integrated Stress Response Inhibitor or ISRIB. We collaboratively determined atomic resolution structures of ISRIB's target, the translation initiation factor eIF2B, eIF2b bound to ISRIB, bound its guanine nucleotide exchange substrate eIF2, and bound to its potent inhibitor and the transducer of cellular stress, the phosphorylated conformation of eIF2a-P. These structures answered long-standing questions about the rate-determining step of translational initiation, the mechanism by which the Integrated Stress Response (ISR) tunes protein synthesis to restore homeostasis, and pointed the way forward to new therapeutic manipulations of the ISR (see also Tsai, J.C.\*, et al. *Science* 2018 359 (6383); PMID:29599213). As a co-corresponding author, I set the research direction and led the biochemical reconstitutions, structure determination and validation efforts.

5. 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 governs ESCRT-mediated nuclear envelope reformation. **Nature** In press bioRxiv 577460 #Co-first authors \*Co-corresponding authors

This is the third paper in our long-term effort to understand the structures and emerging functions of the ESCRT pathway. As a co-corresponding author with Katharine Ullman, we validated our prior genetic identification of the nuclear ESCRT receptor, the inner nuclear envelope protein named LEM2 (Gu et al. *PNAS* 2017). We further showed how LEM2 targets ER membranes to the surface of chromatin disks in late anaphase where LEM2 condenses into a proteinaceous liquid droplet around the microtubule spindle. This phase transition enables LEM2 to concentrate and self-assemble with the ESCRTII/III hybrid protein, CHMP7. Together LEM2 and CHMP7 copolymerize into a molecular ring to initiate compartmentalization of the nascent nucleus--initiating nuclear transport and disassembly of the spindle to seal the remaining gaps in the nuclear envelope. As a co-corresponding author, I set the research direction and led the biochemical reconstitutions, in vivo STORM imaging, EM structure determination, crosslinking mass spectrometry, and membrane remodeling activity assays.