BIOGRAPHICAL SKETCH

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NAME: Hughson, Frederick M.

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POSITION TITLE: Professor of Molecular Biology

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
Yale University	B.S.	05/1984	Molecular Biophysics & Biochemistry
Stanford University School of Medicine	Ph.D.	08/1990	Biochemistry
Harvard University	Postdoctoral	10/1994	Biochemistry

A. Personal Statement

My group uses diverse methods, and especially x-ray crystallography, to study fundamental problems in cell biology. We have been focusing our attention in two different areas, intracellular trafficking in eukaryotes and cell-cell communication ("quorum sensing") in bacteria. Several of our current projects involve structural and mechanistic studies of large multi-subunit protein complexes that orchestrate the docking and fusion of transport vesicles. These complexes guide cargo-laden vesicles to their destinations and coordinate the activities of other components of the trafficking machinery, including the SNARE proteins that catalyze membrane fusion itself. A second major focus within our group is bacteria, and the remarkable finding that these single-celled organisms communicate with one another by emitting and receiving small-molecule signals. We are interested in cataloging the signal molecules and in understanding their biosynthesis and detection. Moreover, since bacteria often respond to these signals in undesirable ways – like forming antibiotic-resistant biofilms or mounting an attack on a human host – we are interested in discovering and characterizing molecules that interfere with bacterial communication.

I am well-qualified for these studies based on my graduate work studying protein folding, my postdoctoral work determining the crystal structure of influenza hemagglutinin in its active, low-pH induced conformation, and my 20 years as a structural biologist at Princeton, during which we have determined almost thirty x-ray crystal structures. I have extensive experience administering a productive laboratory as shown by our funding and publication records. I have trained over 25 Ph.D. students and postdoctoral fellows, many of whom have gone on to tenure-track faculty positions (and four of whom are now tenured). I maintain a highly interactive environment where lab members are encouraged to share ideas, expertise, and reagents. Moreover, I continue to perform laboratory research, ensuring that I remain connected and accessible to my trainees.

Publications most relevant to the proposed research:

1. Ren, Y., Yip, C., Tripathi, A., Huie, D., Jeffrey, P.D., Walz, T., and Hughson, F.M. (2009) Structural basis for vesicle tethering by the Dsl1p complex. Cell 139, 1119-1129. PMC2806190
2. Baker, R.W., Jeffrey, P.D., and Hughson, F.M. (2013) Crystal structures of the Sec1/Munc18 (SM) protein Vps33, alone and bound to the homotypic fusion and vacuolar protein sorting (HOPS) subunit Vps16. PLoS One 8, e67409. PMC3693963

3. Ha, J.Y., Pokrovskaya, I.D., Climer, L.K., Shimamura, G.R., Kudlyk, T., Jeffrey, P.D., Lupashin, V.V., and Hughson, F.M. (2014) Cog5-Cog7 crystal structure reveals interactions essential for the function of a multisubunit tethering complex. Proceedings of the National Academy of Sciences USA 111, 15762-15767. PMC4226102
4. Baker, R.W., Jeffrey, P.D., Zick, M., Phillips, B.P., Wickner, W.T., and Hughson, F.M. (2015) A direct role for the Sec1/Munc18-family protein Vps33 as a template for SNARE assembly. Science 349, 1111-1114.

B. Positions and Honors

Positions and Employment

1984-1990	Graduate Fellow, Stanford Department of Biochemistry Robert L. Baldwin, advisor. Research: Protein folding
1990-1994	Postdoctoral Fellow, Harvard Dept. of Biochemistry & Molecular Biology Don C. Wiley, advisor. Research: X-ray crystal structure of low-pH hemagglutinin
1994-2002	Assistant Professor of Molecular Biology, Princeton University
2002-2009	Associate Professor of Molecular Biology, Princeton University
2006-2015	Director, Princeton/HHMI Undergraduate Science Education Program
2009-	Professor of Molecular Biology, Princeton University

Other Experience and Professional Memberships

1999-2012	Member of nine different NIH Special Emphasis Panels
2003-	Editorial Board, PLoS Biology
2003	Ad hoc reviewer, NIH CDF-4 Study Section
2008	Ad hoc reviewer, NIH MSFB Study Section
2010-	Member, AHA Peer Review Committee (PC1: Basic Cell Biology)
2011-	Member, ASBMB Education and Professional Development Committee
2015	Chair, Gordon Research Conference on Molecular Membrane Biology
2015-	Board of Reviewing Editors, Science

Honors

1984-87	NSF Pre-doctoral Fellowship
1990-94	Helen Hay Whitney Postdoctoral Fellowship
1995-98	Searle Scholar
1995-97	Beckman Young Investigator
2015	President's Award for Distinguished Teaching

C. Contribution to Science

1. The mechanisms by which cells distribute materials among intracellular organelles, and execute exo- and endocytosis, are of fundamental importance in cell biology. SNARE proteins, discovered in 1993 by Jim Rothman's group, play central roles in these processes, yet when I started my lab in 1994 little was known about the structures and conformational dynamics of this protein family. Our early work, focused on exocytic SNAREs in yeast and neurons, helped to fill this gap by (1) characterizing the pathway of SNARE assembly in vitro and its relationship to protein folding, (2) showing that SNARE assembly is kinetically controlled by the requirement for a conformational change in a key SNARE protein, (3) investigating this conformational change in energetic and structural terms, and (4) characterizing SNARE assembly in vivo.

    a. Nicholson, K.L., Munson, M., Miller, R.B., Filip, T.J., Fairman, R., and Hughson, F.M. (1998) Regulation of SNARE complex assembly by an N-terminal domain of the t-SNARE Sso1p. Nature Structural Biology 5, 793-802.

b. Lerman, J.C., Robblee, J., Fairman, R., and Hughson, F.M. (2000) Structural analysis of the neuronal SNARE protein syntaxin-1A. Biochemistry 39, 8470-8479.
c. Munson, M., Chen, X., Cocina, A.E., Schultz, S.M., and Hughson, F.M. (2000) Interactions within the yeast t-SNARE Sso1p that control SNARE assembly. Nature Structural Biology 7, 894-902.
d. Munson, M. and Hughson, F.M. (2002) Conformational regulation of SNARE assembly and disassembly in vivo. Journal of Biological Chemistry 277, 9375-9381.

2. In a second phase of our work on the machinery of vesicle trafficking, we turned to the multisubunit 'tethering' complexes (MTCs) that interact with SNAREs to orchestrate vesicle docking and fusion. We have worked on three MTCs, one of which (the Dsl1 complex) is described here and another of which (the COG complex) is described in the next section. By combining single particle EM (carried out in collaboration with Tom Walz at Harvard) and x-ray crystallography, we were able to propose a nearly complete atomic-resolution model for the hetero-trimeric, 260-kDa Dsl1 complex. Our results strongly suggested that even the simplest MTC is capable of orchestrating vesicle capture, uncoating, and fusion.

a. Tripathi, A., Ren, Y., Jeffrey, P.D., Hughson, F.M. (2009) Structural characterization of Tip20p and Dsl1p, subunits of the Dsl1p vesicle tethering complex. Nature Structural and Molecular Biology 16, 114-123. PMC2635920
b. McMahon, C., Studer, S.M., Clendinen, C., Dann, G.P., Jeffrey, P.D., and Hughson, F.M. (2012) The structure of Sec12 implicates potassium ion coordination in Sar1 activation. Journal of Biological Chemistry 287, 42599-43606. PMC3527946
c. Rogers, J.V., McMahon, C., Baryshnikova, A., Hughson, F.M., and Rose, M.D. (2014) ER-associated retrograde SNAREs and the Dsl1 complex mediate an alternative, Sey1p-dependent homotypic ER fusion pathway. Molecular Biology of the Cell 25, 3401-3412. PMC4214786

3. Another and much larger multisubunit tethering complex (MTC), the hetero-octameric COG complex (650 kDa), was initially isolated on the basis of its ability to stimulate an in vitro Golgi transport assay. Subsequent work strongly implied that COG functions to tether vesicles carrying cargo between Golgi cisternae. It therefore plays a key role in maintaining the proper distribution of glycosylation enzymes and other materials within the Golgi. As a consequence, COG defects can lead to fatal glycosylation disorders. To provide a foundation for understanding COG function in mechanistic terms, we have invested a major effort in elucidating its architecture and are working toward determining its high-resolution structure. Specifically, we have (1) determined the subunit architecture of the mammalian COG complex, (2) elucidated the structural basis for human glycosylation disorders caused by mutations in several COG subunits, and (3) used x-ray crystallography and EM to begin dissecting the structural basis for the subunit interactions that hold COG (and other multisubunit tethering complexes) together.

a. Ungar, D., Oka, T., Krieger, M., and Hughson, F.M. (2005) Subunit architecture of the conserved oligomeric Golgi complex. Journal of Biological Chemistry 280, 32729-32735.
b. Cavanaugh, L.F., Chen, X., Richardson, B.C., Ungar, D., Pelczer, I., Rizo, J., and Hughson, F.M. (2007) Structural analysis of conserved oligomeric Golgi complex subunit 2. Journal of Biological Chemistry 282, 23418-23426.
c. Richardson, B.C., Smith, R.D., Ungar, D., Nakamura, A., Jeffrey, P.D., Lupashin, V.V., and Hughson, F.M. (2009) Structural basis for a human glycosylation disorder caused by mutation of the *COG4* gene. Proceedings of the National Academy of Sciences USA 106, 13329-13334. PMC2716380
d. Lees, J.A., Yip, C.K., Walz, T., and Hughson, F.M. (2010) Molecular organization of the COG vesicle tethering complex. Nature Structural and Molecular Biology 17, 1292-1297. PMC3113405

4. In 2002, we initiated a major collaboration with my Princeton colleague Bonnie Bassler to study bacterial cell-cell communication, or quorum sensing. Our work has elucidated (1) the structures of signal molecules used to mediate quorum sensing, (2) structures of the bacterial receptors for these signal molecules, and (3) mechanisms whereby quorum sensing can be modulated by synthetic molecules. The last of these represents a new approach to the discovery and optimization of broad spectrum anti-bacterial compounds.

a. Chen, X., Schauder, S., Potier, N., Van Dorsselaer, A., Pelczer, I., Bassler, B.L., and Hughson, F.M. (2002) Structural identification of a bacterial quorum sensing signal containing boron. Nature 415, 545-549.
b. Neiditch, M.B., Federle, M.J., Pompeani, A.J., Kelly, R.C., Swem, D.L., Jeffrey, P.D., Bassler, B.L., and Hughson, F.M. (2006) Ligand-induced asymmetry in histidine sensor kinase complex regulates quorum sensing. Cell 126, 1095-1108.
c. Kelly, R.C., Higgins, D.A., Pomianek, M.E., Lu, W., Jeffrey, P.D., Rabinowitz, J.D., Semmelhack, M.F., Hughson, F.M., and Bassler, B.L. (2009) The *Vibrio cholerae* quorum-sensing autoinducer CAI-1: Structural and mechanistic analysis of the biosynthetic enzyme CqsA. Nature Chemical Biology 5, 891-895. PMC2847429
d. Chen, G., Swem, L.R., Swem, D.L., Stauff, D.L., O'Loughlin, C.T., Jeffrey, P.D., Bassler, B.L., and Hughson, F.M. (2011). A strategy for antagonizing quorum sensing. Molecular Cell 42, 199-209. PMC3982643

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1ZWDwyXl9p/bibliography/40445178/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01 GM071574 Hughson (PI) 3/1/2005 – 2/28/2017
NIH - NIGMS
Structural Analysis of Golgi Trafficking Proteins
The goal of this study is structure-function analysis of three multisubunit tethering complexes (MTCs) – Dsl1, COG, and HOPS – and their interactions with other trafficking proteins.

Completed Research Support

R01 AI054442 Hughson (PI) 3/1/2003 - 2/28/2013
NIH - NIAID
Structure-Function Analysis of AI-2 Quorum Sensing
This project was focused on studies of bacterial signaling via AI-2 and CAI-1. Co-investigators were Bonnie Bassler and Martin Semmelhack, both at Princeton University.

1R56 AI091681 Hughson (PI) 4/1/2012 - 3/31/2013
NIH - NIAID
Manipulating Quorum Sensing to Control Bacterial Pathogenicity
The goal of this one-year, non-renewable grant was a cross-disciplinary investigation of LuxR-type quorum-sensing receptors from two human pathogens, *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Co-investigators were Bonnie Bassler and Martin Semmelhack, both at Princeton University.