BIOGRAPHICAL SKETCH

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NAME: Barlowe, Charles

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POSITION TITLE: Professor and Chair of Biochemistry & Cell 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
College of William & Mary, Williamsburg, VA	B.S.	1979-1983	Chemistry
University of Texas, Austin, TX	Ph.D	1985-1990	Biochemistry
University of California, Berkeley, CA	Postdoctoral	1990-1994	Cell Biology

A. Personal Statement

My research program is focused on defining the mechanisms that catalyze protein transport through the early secretory pathway. We use biochemistry, cell biology, microscopy, molecular genetics and in vitro assays primarily in the model organism *S. cerevisiae* to investigate underlying mechanisms. My goals have been to generate fundamental new knowledge that can be applied to the treatment and prevention of human diseases in addition to training student scientists in the methods of experimental research. I have directed a research program for over 20 years with significant impact on areas of protein trafficking and have trained 16 PhD students and 4 postdoctoral fellows. I have also worked collaboratively across departments, centers and schools at Dartmouth as director of the multi-disciplinary Molecular and Cellular Biology Graduate Program, as dean of Graduate Studies at Dartmouth College and as chair of the Medical School's Biochemistry department.

B. Positions and Honors

Positions and Employment

1990-1994	Postdoctoral Fellow, Department of Molecular and Cell Biology, University of California
1994-1999	Assistant Professor of Biochemistry, Dartmouth Medical School
1999-2004	Associate Professor of Biochemistry, Dartmouth Medical School
2004-present	Professor of Biochemistry & Cell Biology, Geisel School of Medicine at Dartmouth
2002-2004	Director, Molecular and Cellular Biology Graduate Program at Dartmouth
2004-2008	Dean of Graduate Studies, Dartmouth Arts and Sciences Graduate Programs
2008-present	Chair, Department of Biochemistry & Cell Biology, Geisel School of Medicine at Dartmouth
2017	James C. Chilcott Professorship, Geisel School of Medicine at Dartmouth

Other Experience and Professional Memberships

1995-	Member, American Society for Cell Biology
1995	American Cancer Society Scientific Review Committee
1998-2002	Ad hoc reviewer, National Science Foundation, Cell Biology Program
1999-2010	Ad hoc reviewer CDF2, CDF4, CSF and MBPP Study Sections, NIH CSR
2000	Co-Chair, Symposium on Vesicle Docking and Fusion, ASCB National Meeting
2001-2017	Member of the Faculty of 1000
2009	Vice-Chair, Molecular Membrane Biology Gordon Conference
2011	Chair, Molecular Membrane Biology Gordon Conference
2011-2015	Membrane Biology and Protein Processing Study Section, NIH CSR
2016-2017	Reviewer, NIH Director's Pioneer Award Program, NIH

Honors and Awards

1989	University of Texas Continuing Fellowship
1990	Eakin Biochemistry Award, University of Texas
1990-1993	Damon Runyon-Walter Winchell Cancer Fund Fellow
1995	Hitchcock Foundation Research Award, Dartmouth Medical School
1996-2000	Pew Scholars Program in the Biomedical Sciences
2007	NIH MERIT Award (R37 GM52549 yr 12-22)
2011	Fellow, American Association for the Advancement of Science
2012	Fellow, American Academy of Microbiology

C. Contribution to Science

1. Regulated formation of the COPII coat

As a postdoctoral fellow with Randy Schekman, I made several contributions to the membrane trafficking field. I identified and characterized the first guanine nucleotide exchange factor (GEF) that acts on a secretory pathway GTPase. This work revealed that Sec12, an ER-localized transmembrane protein, catalyzes nucleotide exchange on Sar1, to initiate transport vesicle formation from the ER. In collaboration with Tohru Yoshihisa, we were able to demonstrate that Sec23 acts as a GTPase activating protein (GAP) for Sar1, linking the Sar1 GTPase cycle to coated vesicle formation at the ER. Finally, I discovered the coat protein complex II (COPII), which consists of the proteins Sar1, Sec23-Sec24 and Sec13-Sec31. COPII assembles on ER membranes to produce transport intermediates and incorporates secretory cargo into these coated vesicles. Here I lead the effort to purify COPII coated vesicle to document protein composition and structural morphology by thin section electron microscopy. This work was mentioned briefly in Schekman's Nobel Lecture in December 2013.

a. Barlowe, C., d'Enfert, C. and Schekman, R. (1993) Purification and characterization of Sar1p, a small GTP-binding protein required for transport vesicle formation from the endoplasmic reticulum. J. Biol. Chem. 268, 873-879.

b. Yoshihisa, T., Barlowe, C. and Schekman, R. (1993) Requirement for a GTPase-activating protein in transport vesicle budding from the endoplasmic reticulum. Science 259, 1466-1468.

c. Barlowe, C., and Schekman, R. (1993) Sec12p encodes a guanine nucleotide exchange factor essential for transport vesicle formation from the ER. *Nature* 365, 347-349.

d. Barlowe, C., Orci, L., Yeung, T., Hosobuchi, D., Hamamoto, S., Salama, N., Rexach, M., Ravazzola, M., Amherdt, M., and Schekman, R. (1994) COPII: A membrane coat formed by Sec proteins that drive vesicle budding from the ER. *Cell* 77, 895-907.

2. Reconstitution of ER-Golgi transport to define Uso1-dependent vesicle tethering

With purified COPII vesicles in hand, I directed a research effort in my new lab to purify the soluble factors needed to reconstitute targeting and fusion of vesicles with Golgi membranes. We found that the extended coiled-coil domain protein Uso1 in addition to Sec18/NSF and LMA1 supported fusion of vesicles with washed Golgi membranes. Moreover, we could drive overall ER-Golgi transport with washed semi-intact cell membranes and 6 purified proteins (Sar1, Sec23-Sec24, Sec13-Sec31, Uso1, Sec18 and LMA1). This allowed for a full dissection of transport stages. Uso1 and the membrane bound Rab GTPase Ypt1 produced a dilution resistant tethered vesicle intermediate. The SNARE proteins (Sed5, Bos1, Bet1 and Sec22) in addition to Sly1 catalyzed fusion of tethered vesicles. These results fit well with genetic analysis of the fusion stage.

a. Barlowe, C. (1997) Coupled ER to Golgi transport reconstituted with purified cytosolic proteins. *J. Cell Biol.* 139, 1097-1108.

b. Cao, X., Ballew, N., and Barlowe, C. (1998) Initial docking of ER-derived vesicles requires Uso1p and Ypt1p but is independent of SNARE proteins. *EMBO J.* 17, 2156-2165.

c. Cao, X., and Barlowe, C. (2000) Asymmetric requirements for a Rab GTPase and SNARE proteins in fusion of COPII vesicles with acceptor membranes. *J. Cell Biol.* 149, 55-65.

d. Liu, Y., and Barlowe, C. (2002) Analysis of Sec22p in Endoplasmic Reticulum/Golgi Transport reveals cellular redundancy in SNARE protein function. *Mol. Biol. Cell* 13, 3314-3324.

3. Molecular definition of anterograde cargo receptors in the early secretory pathway
For efficient export of soluble secretory proteins in COPII vesicles, we hypothesized that transmembrane receptors would bind to the soluble cargo for linkage to COPII coat subunits. Until discovery of COPII, a non-specific "bulk-flow" model had been the prevailing explanation for ER export of soluble cargo. To test our receptor-dependent export model, we have undertaken comprehensive proteomic analyses of purified COPII vesicles. We reasoned that the purified vesicles should contain transmembrane cargo receptors in addition to proteins required for vesicle formation and vesicle targeting/fusion. Our proteomic analysis led to the discovery of several conserved transmembrane cargo receptors (Erv14, Erv25, Erv26 and Erv29) that are required for efficient ER export of soluble cargo as well as certain integral membrane secretory cargo that have type II topology or have lengthy transmembrane domains. These findings have provided significant new mechanistic insights on the biogenesis of secretory proteins. Moreover, the binding and release of secretory cargo by these receptors is likely a site for cellular regulation and may provide opportunities for therapeutic intervention.

a. Belden, W. J., and Barlowe, C. (1996) Erv25p, a component of COPII-coated vesicles, forms a complex with Emp24p that is required for efficient ER to Golgi transport. *J. Biol. Chem.* 271, 26939-26946.
b. Powers, J., and Barlowe, C. (1998) Transport of Axl2p depends on Erv14p, an ER-vesicle protein related to the Drosophila cornichon gene product. *J. Cell Biol.* 142, 1209-1222.
c. Belden, W.J., and Barlowe, C. (2001) Role of Erv29p in collecting soluble secretory proteins into ER-derived transport vesicles. *Science* 294, 1528-1531.
d. Bue, C.A., Bentivoglio, C.M., and Barlowe, C. (2006) Erv26p directs pro-alkaline phosphatase into ER-derived COPII transport vesicles. *Mol. Biol. Cell* 17, 4780-4789.

4. Molecular definition of retrograde cargo receptors in the early secretory pathway
While purified COPII vesicles were expected to contain anterograde cargo receptors required for efficient ER export, we had not anticipated that retrograde receptors would also be enriched in these intermediates. Forward transport from the ER to the Golgi complex is balanced by a retrograde pathway that is carried out by COPI coated vesicles. Therefore, most constituents of COPI vesicles are also present in COPII vesicles as these proteins cycle dynamically between the ER and Golgi compartments. In our characterization of the Erv41 and Erv46 vesicle proteins, we determined that this complex functions as a retrograde receptor to retrieve specific ER resident proteins that have escaped to Golgi compartments. The KDEL-receptor had been previously characterized as an important retrograde cargo receptor, we propose that the Erv41-Erv46 complex plays a key role as a retrograde receptor for non-KDEL bearing ER resident proteins. This story is currently evolving as the mechanism by which Erv41-Erv46 binds and releases cargo appears to be quite novel.

a. Otte, S., Belden, W., Heidtman, M., Liu, J., Jensen, O. and Barlowe, C. (2001) Erv41p and Erv46p: New components of COPII vesicles involved in transport between the ER-Golgi complex. *J. Cell Biol.* 152, 503-517.
b. Otte, S. and Barlowe, C. (2002) The Erv41p-Erv46p complex: Multiple export signals are required in trans for COPII-dependent transport from the ER. *EMBO J.* 21, 6095-6104.
c. Shibuya A, Margulis N, Christiano R, Walther TC, and Barlowe C. (2015) The Erv41-Erv46 complex serves as a retrograde receptor to retrieve escaped ER proteins. *J Cell Biol.* 208, 197-209.

Complete List of Published Work in PubMed:
https://www.ncbi.nlm.nih.gov/pubmed/?term=Barlowe+C

D. Research Support

Project Number: R01 GM52549-23 05/01/2017-04/30/2021
Principal Investigator: Charles Barlowe
Source: NIGMS
Title of Project: Mechanisms of COPII-dependent Transport

The focus of this research program is to elucidate mechanisms that catalyze protein sorting and transport through the early secretory pathway. Defects in biogenesis and sorting of secretory proteins have wide-ranging effects on human health and disease including atherosclerosis, blood clotting disorders and cystic fibrosis.