BIOGRAPHICAL SKETCH

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NAME: Scott D. Emr

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

POSITION TITLE: Professor of Molecular Biol. and Genetics; Director, Weill Institute for Cell and Mol. Biol.

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
University of Rhode Island, Kingston	B.S.	06/76	Biology
Harvard University, Cambridge, MA (& Harvard Med)	Ph.D.	5/81	Molecular Genetics
University of California, Berkeley	Postdoc	1981-83	Biochemistry/Cell Biology

A. Personal Statement

My lab has devoted its efforts over the past 35 years to developing yeast as a genetic and biochemical model system to study numerous problems in protein trafficking and phosphoinositide (PIP) lipid signaling. The goal of our research efforts has been to define the complex regulatory processes that ensure the temporal and spatial specificity of the vesicular transport pathways that convey cargo in and out of cells via the endocytic and secretory pathways. A large collection of novel genetic approaches, strains, and biochemical techniques (plus state-of-the-art equipment) are now available in the lab to address these problems. We are in a unique position to answer numerous questions related to organelle assembly and the regulation of protein and membrane trafficking pathways. I have the knowledge, leadership and mentoring skills to motivate and challenge the students and postdocs who are carrying out these projects. Indeed, the students and postdocs who I have been fortunate to train are my greatest legacy to science. During my career as a Professor at Caltech, UCSD School of Medicine and now at Cornell, I have trained over 30 graduate students and more than 50 postdocs. These previous students and postdocs have gone on to excellent academic appointments (U Penn, UC Berkeley, Johns Hopkins, UCLA, Yale, U of Michigan, Vanderbilt, U of Utah, U of Texas Southwestern Medical Center, U of Colorado, Boulder, U of Wisconsin, and faculty positions in Germany, UK, Austria, Switzerland, China, Japan, S Korea, etc.) as well as research scientist positions at private biotech and large pharmaceutical companies

Our research focuses on three topics: (1) the genetics of endocytic trafficking and receptor down-regulation (mediated by the ART and ESCRT proteins); (2) genetic and biochemical analysis of phosphoinositide lipid- and ubiquitin-dependent membrane sorting and signaling pathways and (3) defining the pathways for maintaining the composition and quality of membrane proteins both at the plasma membrane and the lysosomal membrane (nutrient transporters, channels, receptors, etc.).

To better understand membrane protein down-regulation and quality control, we are interested in deciphering how the ubiquitin conjugation machinery is targeted to specific proteins at the PM and the lysosomal membrane. Previously, we identified and characterized a family of *a*rrestin-*r*elated *t*rafficking adaptors, or ARTs, which recruit the Rsp5 ubiquitin ligase to specific targets at the PM and we also identified the ESCRT (Endosomal Sorting Complexes Required for Transport) complexes as essential components of the MVB (multi-vesicular body) sorting pathway. ESCRT proteins play critical roles in MVB formation as well as the budding of many retroviruses including HIV and the abscission event during cytokinesis. The formation of MVBs is a key step in the delivery of cargo destined for degradation in the vacuole or lysosome. Failure to attenuate plasma membrane (PM) signaling processes, by endocytic and MVB down-regulation of growth factor receptors, can lead to hyper-proliferation and cancer.

B. Positions and Honors

Research and Professional Experience

1976-1981	Graduate Student & Teaching Fellow, Department of Microbiology & Molecular Genetics, Harvard Medical School, Boston, MA, with Dr. Thomas Silhavy & Dr. Jonathon Beckwith
1978	Visiting Scholar, Pasteur Institute, Paris, France, with Drs. M. Hofnung and Maxime Schwartz
1981-1983	Miller Institute Fellow, Biochemistry Department, UC Berkeley, with Dr. Randy Schekman
1983-1991	Assistant/Associate Professor w/tenure, Division of Biology, California Institute of Technology, Pasadena, CA
1991-2007	Distinguished Professor, Dept. of Cellular & Molecular Med., UC San School of Medicine, La Jolla, CA
1991-2007	Howard Hughes Medical Institute Investigator, UCSD School of Medicine, La Jolla, CA
2007-present	Founding Director, Weill Institute for Cell and Molecular Biology, Cornell University, Ithaca, NY
2007-present	Frank H.T. Rhodes Professor, Dept. of Molecular Biology & Genetics, Cornell Univ., Ithaca, NY
2007-present	Adjunct Professor, Department of Molecular Medicine, College of Veterinary Medicine, Cornell Univ., Ithaca, NY
2008-present	Professor, Dept. of Biochemistry, Weill Cornell Medical College, Cornell Univ., NY, NY

Honors

1981-1983	**Miller Fellow**, Awarded by Miller Inst. for Basic Research in Science, UC Berkeley
1984-1987	**Searle Research Scholar**
1985-1990	**NSF Presidential Young Investigator**
1991-2007	Investigator, **Howard Hughes Medical Institute**
1998	Elected Member, **American Academy of Microbiology**
2000	Elected Fellow, **American Association for the Advancement of Science**
2003	Awarded the **Gold Medal Prize** by the Hansen Foundation for “central role in elucidating the intracellular sorting and transport of proteins”, Copenhagen, Denmark
2004	Elected Member, **American Academy of Arts and Sciences**
2007	Elected Member, **National Academy of Sciences**
2008	Elected Associate (Foreign) Member, **European Molecular Biology Organization**
2014	Awarded the **van Deenan Medal** “in recognition of his outstanding career in biomembrane research that includes discoveries of the role for polyphosphoinositol lipids (PIPs) in membrane trafficking, the role for the ESCRT machinery in receptor down-regulation, and for his identification of protein complexes (e.g., Retromer, HOPS, ART’s) that direct protein trafficking to the lysosome”; University of Utrecht, The Netherlands

Scientific & Academic Advisory Committees

1986	Special Reviewer, NIH Microbial Physiology and Genetics Study Section
1990	Ad hoc reviewer, NIH Microbial Physiology and Genetics Study Section
1990-1993	Member, NIH Biological Sciences Study Section
1994-1996	Member, FASEB Research Conferences Advisory Committee
2001-2002	Member, Searle Scholars Program Scientific Advisory Board and Review Panel
2003-2010	Member, Pew Scholars in Biomedical Sciences Advisory Board and Review Panel
2012-present	Elected member (4-yr term) of the Section on Medical Sciences, American Association for the Advancement of Science
2012-2013	Member, Richard Lounsbery Award Selection Committee, National Academy of Sciences
2012-2014	ASBMB Awards Nominating Committee
2014-2015	Director of Graduate Studies(DGS), Field of Biochemistry, Molecular and Cellular Biology (BMCB Field – 120 graduate students), Cornell University
2014-present	Elected to the Board of Trustees (6-yr term), Gordon Research Conferences
2016-pesent	Postdoc careers advisor - coordinate postdoc seminars series and career workshops, Cornell

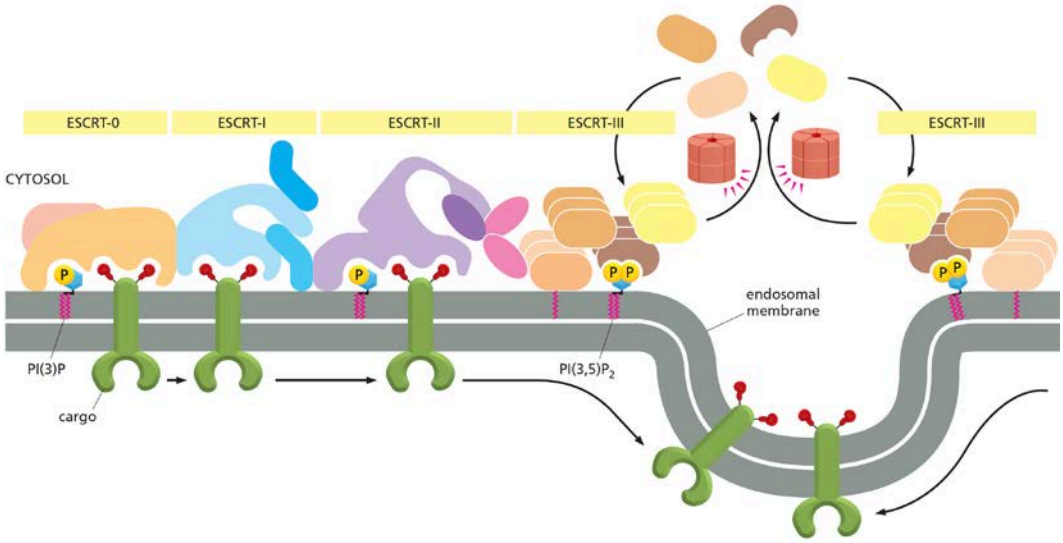
C. Contribution to Science

1. The ESCRT machinery and receptor down-regulation:

Intracellular membrane trafficking fundamentally involves vesicles that bud from various membranes to be transported elsewhere within the endomembrane system of the eukaryotic cell. An important step for the delivery of membrane proteins to the lumen of the lysosome for degradation is the formation of multivesicular bodies (MVBs). MVBs form from late endosomes when cargo is sorted and the limiting membrane invaginates and buds into the lumen of endosome. The MVB then fuses with the lysosomal membrane, delivering cargo to the lysosomal lumen for degradation.

Our lab characterized the machinery required for MVB formation: the endosomal sorting complexes required for transport (ESCRTs). The ESCRTs comprise five distinct complexes – ESCRTs-0, -I, -II, -III, and Vps4, which we have shown assemble sequentially to bind ubiquitinated cargo, cluster and sequester cargo, and remodel the membrane.

ESCRT-mediated membrane remodeling is topologically opposite to the formation of clathrin-coated endocytic vesicles, or COP-I and COP-II coated vesicles between the endoplasmic reticulum and the Golgi complex. Therefore, several seemingly unrelated biological processes require the ESCRT machinery and its unique membrane remodeling function, including: the formation of intralumenal vesicles, enveloped virus budding at the plasma membrane (including HIV), and abscission during cytokinesis, plasma membrane repair, and nuclear envelope reformation after mitosis.



1. Tang, S., W.M. Henne, P.P. Borbat, N.J. Buchkovich, J.H. Freed, Y. Mao, J.C. Fromme, **S.D. Emr**. 2015. Structural Basis for Activation, Assembly and Membrane Binding of ESCRT-III Snf7 Filaments. **eLife.** 10: 1-22.

2. Buchkovich, N.J.. W.M. Henne, S. Tang, **S.D. Emr**. 2013. Essential N-Terminal Insertion Motif Anchors the ESCRT-III Filament during MVB Vesicle Formation. **Dev. Cell**, 27(2):201-14.

3. Henne WM, Buchkovich NJ, Zhao Y, **S.D. Emr**. 2012.The Endosomal sorting complex ESCRT-II mediates the assembly and architecture of ESCRT-III helices. **Cell** 151(2):356-371.

4. Saksena S, Wahlman J, Teis D, Johnson AE, **S.D. Emr**. 2009. Functional reconstitution of ESCRT-III assembly and disassembly. **Cell.** 136: 97-109.

5. Katzmann, D.J., M. Bast and **S.D. Emr**. 2001. Ubiquitin-dependent sorting into the multivesicular body pathway requires the function of a conserved endosomal protein sorting complex, ESCRT-I. **Cell,** 106: 145-155.

2. Arrestin-Related Trafficking adaptors (ARTs) regulate endocytosis:

The plasma membrane contains numerous receptors and permeases which respond to external stimuli to regulate cellular processes such as nutrient uptake, cellular growth, and differentiation. These proteins can be down-regulated through ubiquitin-mediated endocytosis and delivery to the lysosome for degradation. Proper regulation of plasma membrane proteins is vital for cell homeostasis, as defects in endocytic down-regulation can lead to hyperproliferation and cancer. Despite the diversity of plasma membrane proteins, many are ubiquitinated by the same E3 ligase: Rsp5. Therefore, we were interested in deciphering how specific regulation of individual plasma membrane proteins is achieved.

We identified and characterized a family of arrestin-related trafficking adaptors (ARTs), which recruit Rsp5 to specific plasma membrane proteins, and have been shown by us and by others that the ARTs are key determinants of target selection for ubiquitin-mediated endocytosis. We have found that Art1 is regulated by phosphorylation mediated by a TORC1-Npr1 kinase signaling cascade, and is additionally regulated by ubiquitination.

1. *251. Guiney, E., T. Klecker, **S.D. Emr**. 2016. Identification of the endocytic sorting signal recognized by the Art1-Rsp5 ubiquitin ligase complex. Mol. Biol. Cell, 27(25):4043-54.

2. Zhao Y, Macgurn JA, Liu M, **S.D. Emr**. 2013. The ART-Rsp5 ubiquitin ligase network comprises a plasma membrane quality control system that protects yeast cells from proteotoxic stress. **eLife**2:e00459.

3. MacGurn JA, Hsu PC, Smolka MB, **S.D. Emr**. 2011. TORC1 Regulates Endocytosis via Npr1-Mediated Phosphoinhibition of a Ubiquitin Ligase Adaptor. **Cell** 147(5): 1104-17.

4. Lin CH, MacGurn JA, Chu T, Stefan CJ, **S.D. Emr**. 2008. Arrestin-related ubiquitin-ligase adaptors regulate endocytosis and protein turnover at the cell surface. **Cell**. 135: 714-725.

3. Phosphoinositide lipid signaling (Vps34 PI 3-kinase):

Phosphatidylinositol phosphates (PIPs) are low-abundance lipids that are essential in the regulation of diverse cellular processes which include cell growth, survival, differentiation, cytoskeletal organization, and membrane trafficking. Specific PIPs are enriched in specific subcellular compartments, and provide a binding platform to recruit and activate downstream effector proteins. PIPs are regulated by lipid kinases and phosphatases, and misregulation of PIPs is associated with human pathologies including cancer and various neurodegenerative diseases.

Our genetic dissection of the vacuolar protein sorting (VPS) pathway in yeast and the discovery of the Vps34 type III PI 3-kinase as an essential enzyme in vacuolar/lysosomal protein traffic provided the first direct evidence for the role PIPs/PI3P in membrane trafficking. We have also defined the composition of the PI 4-kinase, PI4P 5-kinase and PI3P 5-kinase complexes, and we have uncovered key regulatory pathways for each of these lipid kinases.

Our work has has led to the identification of numerous effector proteins which bind to PIPs. These include transcription factors involved in metabolic reprogramming from glycolysis to gluconeogenesis which are regulated by $PI(3,5)P_2$; and the $PI(4,5)P_2$ binding proteins Slm1 and Slm2 which regulate sphingolipid metabolism and actin organization as well as the FYVE domain containing proteins that bind PI(3)P and regulation membrane traffic in the endosome-lysosome pathways.

1. Han BK, **S.D. Emr**. 2011. Phosphoinositide [PI(3,5)P2] lipid-dependent regulation of the general transcriptional regulator Tup1. **Genes Dev.** 25(9): 984-95.

2. Stefan CJ, Manford AG, Baird D, Yamada-Hanff J, Mao Y, **S.D. Emr**. 2011. Osh proteins regulate phosphoinositide metabolism at ER-plasma membrane contact sites. **Cell.** 144(3): 389-401.

3. Audhya, A. and **S.D. Emr**. 2002. Stt4 PtdIns 4-kinase localizes to the plasma membrane and functions in the Pkc1-mediated MAP kinase cascade. **Dev. Cell,** : 2: 593-605.

4. Burd, C.G. and **S.D. Emr.** 1998. Phosphatidylinositol(3)-phosphate signaling mediated by specific binding to RING FYVE domains. **Molecular Cell.** 2(1):157-62.

5. Schu, P. V., K. Takegawa, M. J. Fry, J. H. Stack, M. D**.** Waterfield and **S.D. Emr**. 1993. Phosphatidylinositol 3-kinase encoded by yeast *VPS*34 gene essential for protein sorting. **Science**, 260: 88-91.

4. <u>Vacuolar protein sorting and homeostasis (Retromer, Class C Vps complex, MCS tethers, etc.):</u>

The transport of soluble (luminal) vacuolar/lysosomal proteins is an active process that requires specific sorting receptors. After translation, proteins with a vacuolar targeting signal are sorted through the secretory pathway to endosomes, and then they are delivered to the vacuole. Through a genetic screen, using the enzyme invertase as a reporter with the vacuolar targeting sequence of carboxypeptidase Y fused to it amino terminus, we identified the molecular machinery involved in this pathway. This genetic selection approach identified over 35 vacuolar protein sorting defective (*vps*) mutants. Through analysis of the *VPS* proteins, we characterized multiple steps in intracellular membrane traffic, identifying the components of their complexes (e.g., the Retromer complex, the Class C core complex in HOPS, the ESCRT complexes, membrane tethering complexes, as well as the PIP kinase and phosphatase complexes) and elucidating aspects of their regulation. Recently, we devised a new approach to study a recycling and degradation pathway for vacuolar/lysosomal membrane proteins. This approach has uncovered two new ubiquitin ligase complexes that modify a subset of vacuolar membrane proteins and target them for sorting and degradation in the vacuole lumen.

1. Li, M., Koshi, T., **S.D. Emr**. 2015. Membrane-anchored ubiquitin ligase complex is required for the turnover of lysosomal membrane proteins. **J Cell Biol.**, 211(3):639-52.

2. Li, M., Y. Rong, Y. Chuang, D. Peng, **S.D. Emr.** 2015. Ubiquitin-dependent lysosomal membrane protein sorting and degradation. **Mol. Cell**, 57: 467-478.

3. Manford AG, Stefan CJ, Yuan HL, Macgurn JA, **S.D. Emr**. 2012. ER-to-plasma membrane tethering proteins regulate cell signaling and ER morphology. Dev. Cell. 23(6):1129-40.

4. Seaman, M. N. J., J. M. McCaffery and **S.D. Emr**. 1998. A membrane coat complex essential for endosome to Golgi retrograde transport in yeast. **J. Cell Biol**. 142(3):665-81.

5. Herman PK, Stack JH, DeModena JA, **S.D. Emr**. 1991. A novel protein kinase homolog essential for protein sorting to the yeast lysosome-like vacuole. **Cell**. 64(2):425-437.

Complete List of Published Work in MyBibliography:

(Total publications = 252 with a Google Scholar h-index = 121)

http://www.ncbi.nlm.nih.gov/sites/myncbi/1b7ZvCTQnsyk7/bibliography/44302723/public/?sort=date&direction=ascending