BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Mark Donowitz	LeBoff Professor of Medicine
eRA COMMONS USER NAME Donowitz	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Brandeis University, Waltham MA	B.A	1964	Chemistry
Johns Hopkins University School of Medicine	M.D.	1968	Medicine

A. Personal Statement

I am a scientist involved in studies of regulation of intestinal Na absorption which emphasize how the brush border Na/H exchanger NHE3, which we initially cloned and characterized, is regulated normally as part of digestion and abnormally in diarrhea. We are examining the role of the NHE3 C-terminus which acts as a scaffold to form signaling complexes and to attach NHE3 to the cytoskeleton. To carry out these studies and to improve the environment for GI research at Hopkins I have developed the Hopkins Center for Epithelial Disorders, obtained funding for an NIH GI P30 Core Center (offering proteomics, advanced imaging and mouse physiology resources) and an NIH PO1 on trafficking of epithelial transporters. These have provided the equipment/environment to allow the proposed studies to be accomplished. Major goals of my laboratory include to increase understanding of diarrheal diseases as being related to inhibition of Na absorption and to develop anti-diarrheal medications based on the understanding of regulation of intestinal Na absorption in cell models and in intact intestine including in models of diarrhea. We hope to be able to use human intestinal organoids, to increase understanding of intestinal Na absorption at a cellular and molecular level with application to understanding of in vivo human intestinal function.

B. Positions

Special Fellow in Gastroenterology NIAMD, Yale Univ. School of Medicine, 1972-74; Instructor in Medicine, Yale University School of Medicine, 1973-74 ; Investigator, Walter Reed Army Institute of Research, 1974-77; Assistant Professor of Medicine, Tufts University School of Medicine, 1977-79; Associate Professor of Medicine, Tufts University School of Medicine, 1979-84; Assistant Professor of Physiology, Tufts University School of Medicine, 1980-82; Associate Professor of Physiology, Tufts University School of Medicine, 1983-88; Professor of Medicine, Tufts University School of Medicine, 1984-88; Professor of Medicine, The Johns Hopkins University School of Medicine, 1988-present; Paulson Professor of Gastroenterology 1992-1999; Chief, Gastroenterology Division 1988-1996; Director, Meyerhoff Digestive Diseases Center 1988-2000; Director, Hopkins Center for Epithelial Disorders 1996-present; LeBoff Professor for Digestive Diseases Research1999-present; Director, Hopkins Digestive Diseases Basic Research Development Core Center (R24) 2003-present (ending 5/31/11); Director, Conte Center Hopkins GI Basic and Translational Research Center (P30), 6/1/2011-present; Director of Basic Research, GI Division, Johns Hopkins University School of Medicine, 2011-

Honors

Phi Beta Kappa; NIH Research Career Development Award K04-00588, 1979-84; Fellowship, The Medical Foundation, Boston, MA 1977-78; M.I. Grossman AGA Sabbatical Prize, 1983 (Professor Carafoli, Zurich, Switzerland); Am. Soc. of Clin. Invest. 1983; Organizer Kroc Symposium on Intestinal Transport, 1984; Director, NIH GI Core Center P30 AM34928, Center for Gastroenterology Research on Absorptive and Secretary Processes (GRASP),1984-88. Executive Committee, Hopkins Cystic Fibrosis Center, 1989- ; Association of American Physicians, 1991; President, Gastrointestinal Research Group/AGA, 1991-1993; Interurban Clinical Club, President 1996-1997; AGA Research Council Section Intestinal Disorders Head, 1991-1993; Organizer, FASEB - GI Tract VI, 1995; Chairman, AGA Industry Award Committee 1992-96; Chairman, AGA Public Policy Committee, Research - 1997- 2000 and Chairman, 2000-2003; American Physiology Society, Distinguished Achievement Award, 1997; American Physiological Society, GI Steering Committee, 1997-2000; Boursier Rothschild – Mayent Sabbatical Fellowship 1999 (Professor Louvard, Paris, France); Adjunct Professor, Department of Life Sciences, Pohang University, Pohang, Korea, 1999-2004; AGA

Governing Board, 2000-2003; Fellow, American Association for Advancement of Science, 2003; Vice President, American Gastroenterological Association, 2004-2005; President-Elect 2005-2006; President 2006-2007. Chair, American Gastroenterological Association, 2007-2008. Horace Davenport Career Achievement Award, GI Section, American Physiological Society, 2007. Scientific Advisory Board, Institute for One World Health (Gates Foundation), 2007-, Faculty of 1000, Physiology, GI Section, founding member. Faculty of 1000, Section Co-Chair, GI Pharmacology, 2008-present; Co-organizer NIH Single Topic Conference, "Translational Approaches for Pharmacotherapy Development for Acute Diarrhea," September 25-27, 2011.

C. Selected peer-reviewed publications (in chronological order):
Publications (from a total of 247):

1. Mahon, M., Donowitz, M., and G. Segre. Na^+/H^+ Exchanger Regulatory Factor 2 directs parathyroid hormone 1 receptor signaling. Nature, 417:458-461, 2002. PMID: 12075354
2. Donowitz, M. and X. Li. Regulatory binding partners and complexes of NHE3. Physiol. Rev. 87:825-872, 2007. PMID: 17615390
3. Li, X., Donowitz, M. Fractionation of subcellular membrane vesicles of epithelial and nonepithelial cells by OptiPrep density gradient ultracentrifugation. Methods in Molecular Biology, Vol 440, Exocytosis and Endocytosis, pp. 97-110, 2008.
4. Cha, B. and M. Donowitz. The epithelial BB Na/H exchanger NHE3 associates with the actin cytoskeleton by binding to ezrin directly and via PDZ domain containing NHERF proteins. Clin. Exp. Pharmacol. Physiol, 35: 863-871, 2008. PMID: 18430067
5. Maluykova I., Gutsal, O., Laiko, M., Kane, A., Donowitz, M., and O. Kovbasnjuk. Latrunculin B facilitates Shiga toxin I transcellular transcytosis across T84 intestinal epithelial cells. Biochim.Biophys. Acta 1782: 370-377, 2008. PMCID: PMC2509583
6. Sarker, R., Gronborg, M., Cha, B., Mohan, S., Chen, Y., Pandey, A., Litchfield, D., Donowitz, M., and X. Li CK2 binds to the C-terminus of NHE3 and stimulates NHE3 basal activity by phosphorylating a separate site in NHE3. Mol. Biol. Cell. 19: 3859-3870, 2008. PMCID: PMC2526694
7. Broere, N., Chen, M., Cinar, A., Singh, A.K., Hillesheim, J., Riederer, B., Lunnemann, M., Rottinghaus, I., Krabbenhoft, A., Engelhardt, R., Rausch, B., Weinman, E.J., Donowitz, M., Hubbard, A., Kocher, O., de Jonge, H.R., Hogema, B.M., and U. Seidler. Defective jejunal and colonic salt absorption and altered Na^+/H^+ exchanger 3 (NHE3) activities in NHE regulatory factor 1 (NHERF1) adaptor protein-deficient mice. Pflugers Arch, 487:1079-1091, 2008. PMID: 18758809
8. Sullivan, S., Alex, P., Dassopoulos, T., Zachos, N.C., Lacobuzio-Donahue, C., Donowitz, M., Brant, S.R., Cuffari, C., Harris, M.L., Datta, L.W., Conklin, L., Chen, Y., and X. Li. Downregulation of sodium transporters and NHERF proteins in IBD patients and mouse colitis models: Potential contributors to IBD-associated diarrhea. Inflamm. Bowel Dis., 15:261-274, 2008. PMCID: PMC2627787
9. Malyukova, I., Murray, K.F., Zhu, C., Boedeker, E., Kane, A., Patterson, K., Peterson, J.R., Donowitz, M., and O. Kovbasnjuk. Macropinocytosis in Shiga toxin 1 uptake by human intestinal epithelial cells and transcellular transcytosis. Am. J. Physiol. Gastrointest Liver Physiol. 296:G78-G92, 2009. PMCID: PMC2636932
10. Zachos, N.C., Hodson, C., Kovbasnjuk, O., Li, X., Thelin, W.R., Cha, B., Milgram, S., and M. Donowitz. Elevated intracellular calcium stimulates NHE3 activity by an IKEPP (NHERF4) dependent mechanism. Cell Physiol. Biochem. 22:693-704, 2008. PMID: 19088451
11. Zachos, N.C., Li, X., Kovbasnjuk, O., Hogema, B., Sarker, R., Li, M., de Jonge, H., and M. Donowitz. NHERF3 (PDZK1) contributes to basal and calcium inhibition of NHE3 activity in Caco-2BBe cells J. Biol. Chem., 284: 3708-18, 2009. PMCID PMC2749145
12. Zachos, N.C., van Rossum, D.B., Li, X., Caraveo, G., Sarker, R., Cha, B., Mohan, S., Desiderio, S., Patterson, R.L., and M. Donowitz. Phospholipase c-γ binds directly to the Na^+/H^+ exchanger 3 and is required for calcium regulation of exchange activity. J. Biol. Chem., 284:19437-19444, 2009. PMCID PMC2740569
13. Zachos, N.C., Kovbasnjuk, O., and M. Donowitz. Regulation of intestinal electroneutral sodium absorption and the brush border Na^+/H^+ exchanger (NHE3) by intracellular calcium. Annals of the New York Academy of Sciences. 1165: 240-248, 2009. PMCID: PMID 19538312
14. Donowitz, M., Mohan, S., Zhu, C., Chen, T-E., Lin, R., Cha, B., Zachos, N.C., Murtazina, R., Sarker, R., and X. Li. NHE3 regulatory complexes. J. Exp. Biol. 212: 540-550, 2009. PMCID PMC2683010

15. Singh, A.K., Riederer, B., Kraabbenhoft, A., Rausch, B., Bonhagen, J., Leehmann, U., deJonge, H.R., Donowitz, M., Yun, C., Weinman, E.J.,, Kocher, O., Hogema, B.M., Seidler, U. Differential roles of NHERF1, NHERF2, and PDZK1 in regulating CFTR-mediates intestinal anion secretion in mice. J. Clin. Invest. 119: 540-550, 2009. PMCID: PMC2648694.
16. Weinman EJ, Steplock D, Cha B, Kovbasnjuk O, Frost NA, Cunningham R, Shenolikar S, Blanpied TA, Donowitz, M, Blanpied, TA. PTH transiently increases the percent mobile fraction of Npt2a in OK cells as determined by FRAP. Am J Physiol Renal Physiol. 297:F1560-F1565, 2009. PMCID: PMC2801338.
17. Lin S, Yeruva S, He P, Singh AK, Zhang H, Chen M, Lamprecht G, De Jonge HR, Tse M, Donowitz M, Hogema BM, Chun J, Seidler U, Yun CC. Lysophosphatidic acid stimulates the intestinal brush border Na/H exchanger 3 and fluid absorption via LPA (5) and NHERF2. Gastroenterology. 138:649-658, 2010. PMCID: PMC2976485.
18. Laiko, M., Murtazina, R., Malyukova, I., Zhu, C., Boedeker, E.C., Gutsal, O., O'Malley, R., Cole, R.N., Tarr, P.I., Murray, K.F., Kane, A., Donowitz, M. and O. Kovbasnjuk. Shiga Toxin 1 interaction with enterocytes causes apical protein mistargeting through the depletion of intracellular galectin-3. Exp. Cell Res, 316:652666, 2010. PMCID: PMC2815162
19. Hartley, J.L., Zachos, N.C., Dawood, B., Donowitz, M., Forman, J., Pollitt, R.J., Morgan, N.V., Tee, L., Gissen, P., Kahr, W.H., Knisely, A.S., Watson, S., Chitayat, D., Booth, I.W., Protheroe, S., Murphy, S., de Vries, E., Kelly, D.A., Maher, E.R., Mutations in TTC37 cause trichohepatoenteric syndrome (phenotypic diarrhea of infancy). Gastroenterology, 138:2388-2398, 2010. PMID: 20176027
20. Cha, B., Zhu, X.C., Chen, W., Jones, M., Ryoo, S., Zachos, N.C., Chen, T.E., Lin, R., Sarker, R., Kenworthy, A.K., Tse, M., Kovbasnjuk, O., Donowitz, M. NHE3 mobility in brush borders increases upon NHERF2-dependent stimulation by lyophosphatidic acid. J Cell Sci, 123:2434-2443, 2010. PMCID: PMC2936692
21. Donowitz, M. Singh, S. Singh, P., Salahuddin, F.F., Chen, Y., Chakraborty, M., Murtazina R., Gucek M., Cole, R.N. Zachos, N.C., Kovbasnjuk, O., Broere, N., Smalley-Freed, W.G., Reynolds, A.B., Hubbard, A.L., Seidler, U.E., Weinman, E.J. de Jonge, H.R., Hogema, B.M., Li, X, Alterations in the Proteome of NHERF1 Knockout Mouse jejunal Brush Border Membrane Vesicles. Physiol Genomics, 42:200-210, 2010. PMID: 20736413; PMCID: PMC3008364
22. Mohan, S., Tse, C.M., Gabelli, S.B., Sarker, R., Cha, B., Fahie, K., Nadella, M., Zachos, N.C., Tu-Sekine, B., Raben, D., Amzel, L.M., Donowitz, M., NHE3 activity is dependent on direct phosphoinositide binding at the N-terminus of its intracellular cytosolic region. J Biol Chem, 285:34566-34578, 2010. PMC2966072
23. Chen M, Sultan A, Cinar A, Yeruva S, Riederer B, Singh AK, Li J, Bonhagen J, Chen G, Yun C, Donowitz M, Hogema B, de Jonge H, Seidler U. Loss of PDZ-adaptor protein NHERF2 affects membrane localization and cGMP- and [Ca2+]- but not cAMP-dependent regulation of Na+/H+ exchanger 2 in murine intestine, J Physiol. 588:5049-5063, 2010. PMID: 20962002; PMCID: PMC3036796
24. Lin, R., Murtazina, R., Cha, B., Chakraborty, M., Sarker, R., Chen, T.E., Lin, Z., Hogema, B., de Jonge, H.R., Seidler, U., Turner, J., Li, X., Kovbasnjuk, Donowitz, M., D-Glucose/SGLT1 activates a NHERF2 dependent process that stimulates NHE3 activity in mouse jejunum and enhances ORS efficacy. Gastroenterology, 140:560-571, 2011. PMID: 20977906; PMC3031713
25. Sarker R, Valkhoff VE, Zachos NC, Lin R, Cha B, Chen TE, Guggino S, Zizak M, de Jonge H, Hogema B, Donowitz M. NHERF1 and NHERF2 are necessary for multiple but usually separate aspects of basal and acute regulation of NHE3 activity. Am J Physiol Cell Physiol, 300:C771-C782, 2010. PMID: 21191106
26. Lee, LJ, Zachos NC, Donowitz M, NHE3, UCSD-Nature Signaling Page, A001593, 2011.
27. Grillon E, Farion R, Fablet K, De Waard M, Tse CE, Donowitz M, Remy C, Coles, J. The spatial organization of proton and lactate transport in a rate brain tumor. PLoS One 6:e17416, 2011. PMID: 21390324
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29. Donowitz M, Singh S, Singh P, Chakraborty M, Chen Y, Murtazina R, Gucek M, Cole RN, Zachos NC, Salahuddin FF, Kovbnasnjuk O, Broere N, Smalley-Freed WG, Reynolds AB, Hubbard AL, Seidler UE, Weinman EJ, de Jonge HR, Hogema BM, Li X. Alterations in the proteome of the NHERF2 knockout

mouse jejunal brush border membrane vesicles. Physiol Genomics, 43:674-684, 2011. PMID: 21427361.
30. Murtazina R, Kovbasnjuk O, Chen TE, Zachos NC, Chen Y, Kocinsky H, Hogema BM, Seidler UE, de Jonge HR, Donowitz M. NHERF2 is necessary for mouse distal ileal basal, second messenger inhibition, and LPA stimulation of NHE3 activity. Am J Physiol Cell Physiol, 301:C126-C136, 2011. PMID: 21430287.
31. Lin Z, Jin S, Duan X, Wang T, Martini S, Hulamm P, Cha B, Hubbard A, Donowitz M, Guggino SE. Chloride channel (CLC)-5 is necessary for exocytic trafficking of NHE3. J Biol Chem, 286:22833-22845, 2011. PMID: 21561868.
32. Zhu X, Cha B, Zachos NC, Sarker R, Chakraborty M, Chen TE, Kovbasnjuk O, Donowitz M. Elevated calcium acutely regulates dynamic interactions of NHERF2 and NHE3 in OK cell microvilli. J Biol Chem. 286:34486-34496, 2011. PMID: 21799002; PMCID: 3186394.
33. Donowitz M, Alpers DH, Binder HJ, Brewer T, Carrington J, Grey MJ. Translational approaches for pharmacotherapy development for acute diarrhea. Gastroenterology.142: e 1-9, 2012. PMID: 22266149.
34. Donowitz M, Tse CM, Fuster D. SLC9 or NHE gene family, a plasma membrane and organellar family of Na/H antiporters. Journal Mol Aspects Med. In press, 2012.
35. Zizak M, Bartonicek D, Sarker R, Chen T, Zachos N, Cha B, Kovbasnjuk O, Korac J, Mohan S, Cole R, Chen Y, Tse CM, Donowitz M. Calmodulin kinase II constitutively binds, phophorylates, and inhibits the brush border Na+/H+ exchanger NHE3. J Biol Chem. 287: 13442-13456, 2012. PMID: 22371496

Other Support

RO1 DK026523-31 (Donowitz PI) **04/01/08-03/31/12**
NIH/NIDDK
Diarrheal Disease: A Physiologic Approach to Treatment
This proposal will advance understanding of mechanisms of stimulation of the intestinal Na absorptive cell brush border (BB) Na^+/H^+ exchanger, NHE3, which is part of the intestinal neutral NaCl absorptive process.

RO1 DK061765-08 (Donowitz and Tse Co-PI) **04/01/09-03/31/14**
NIH/NIDDK
PDZ Domain Proteins and NHE3 Regulation
This proposal examines how acute stimulation of NHE3 occurs via a single α-helix to engage ezrin and PI 3-kinase signaling.

P30 DK089502-01 (Donowitz PI) **06/01/11-05/31/16**
NIH/NIDDK
Hopkins Digestive Diseases Basic and Translational Research Core Center
Cores are (1) Administrative Core; (2) Proteomics Core; (3) Imaging Core; (4) Mouse Physiology Core; and (5) Translational Research Enhancement Core.

PO1 DK072084-05 (Donowitz PI) **09/15/06 – 08/31/14**
NIH/NIDDK
Transporters and Trafficking in Polarized Epithelial Cells
Project 1 (Donowitz PI) **Title:** Knockout Models of PDZ Proteins and NHE3 Regulation
Role of NHERF Family of PDZ domain proteins in regulation of NHE3 studied by mouse knock out models of NHERF1, NHERF2 and NHERF3/1PDZK1.

Project 2 (Li PI, Donowitz Co-investigator) **Title**: ClC-5 and NHE3 Trafficking
Role of ClC-5 in NHE3 exocytosis and identification of endosomal compartment involved.

T32 DK07632-23 (Donowitz PI) **07/01/09 – 06/30/14**
NIH/NIDDK
Basic Science Research in Digestive Diseases
Research training for GI fellows.

Concluded: none