BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
T. Kendall Harden	Kenan Professor
eRA COMMONS USER NAME (credential, e.g., agency login) KENDALL HARDEN	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Delta State University, Cleveland, MS	B.S.	05/70	Chemistry
University of Mississippi School of Medicine	Ph.D.	06/74	Pharmacology
University of Colorado School of Medicine	Post-doc	07/77	Pharmacology

A. Personal Statement

A long-term goal of our research is to delineate the molecular mechanisms of receptor-regulated inositol lipid signaling. Our laboratory has studied phosphoinositide-mediated signaling for approximately twenty-five years and has strengths in application of biochemical and biophysical analyses to the study of purified G protein-coupled receptors, heterotrimeric and Ras superfamily G proteins, and phospholipase C (PLC) isozymes. Our early work provided some of the key data implicating a G protein in hormonal regulation of PLC, and concurrent with several other labs, we discovered that Gαq directly activates PLC-β and that certain PLC-β isozymes also are directly activated by G$\beta\gamma$ subunits. More recent studies delineated the regulation of PLC isozymes by Ras superfamily GTPases. Our research is increasingly driven by high resolution crystal structures of PLC isozymes alone and in complexes with their activating G proteins. We have defined the mechanism whereby G proteins activate PLC, and we recently discovered the mechanism whereby PLC-β isozymes promote GTP hydrolysis to terminate their activation by GTP-bound Gαq. Our mechanistic studies also underpin new research directions using high throughput screens to identify selective small molecule inhibitors of PLC and of Gαq.
A second area of research focuses on the family of eight G protein-coupled P2Y receptors that recognize extracellular nucleotides as their cognate agonists. These studies currently focus on development of selective high affinity drugs for these receptors and on delineation of the potential role(s) of the $P2Y_{14}$ receptor in immune/inflammatory responses.

B. Positions and Honors

Positions and Employment

1977 - 1982 Assistant Professor, Dept. of Pharmacology, University of North Carolina School of Medicine
1982 - 1986 Associate Professor, Dept. of Pharmacology, University of North Carolina School of Medicine
1986 - Professor, Dept of Pharmacology, University of North Carolina School of Medicine
1/85 - 8/86 Acting Chairman, Dept of Pharmacology, University of North Carolina School of Medicine
2003 - Kenan Distinguished Professor, University of North Carolina

Experience and Professional Memberships

1981 - Editorial Boards: J. Biol. Chem., Nature Signaling Gateway, Mol. Pharmacol., JPET
1986 - 1987 Visiting Scientist, with P. Downes and T. Rink, Smith Kline French, Ltd., Welwyn, England
1988 - 1991 Member, Pharmacology Study Section, NIH
1990 - 1994 Editor, Molecular Pharmacology
1993 - 1996 Member, Established Investigator Review Panel, American Heart Association

1994 - 1999 IUPHAR Committee on Receptor Nomenclature; Chair IUPHAR Committee on P2Y receptors
1996 - 2001 Chair, Board of Publications Trustees, ASPET
1996 - 2000 Member, Biomedical Research and Research Training Review Subcommittee, NIH, NIGMS
1997 - 2006 Burroughs Wellcome Fund, Basic Pharmacological Sciences Award Advisory Committee
1999 Visiting Professor, with Dr. A. G. Gilman, Univ. of Texas Southwestern Medical School
2009 Chair, Gordon Research Conference on Phosphorylation and G protein signaling networks

Honors

1975 - 1977 USPHS Postdoctoral Fellowship, University of Colorado
1981 - 1986 Established Investigator, American Heart Association
1993 - 2003 Merit Award, NIGMS
2002 Most Highly Cited (top 50 Scientists) in Pharmacology, 1981 to 1999 (ISI)
2003 Most-cited Scientist (top 10) in Pharmacology and Toxicology, (1993-2003)

C. Selected Publications (of ~270 total)

Hicks SN, Jezyk M, Seifert JP, Harden TK, and Sondek J. General and versatile autoinhibition of phospholipase C isozymes. Mol. Cell 31:383-394, 2008.

Seifert JP, Zhou Y, Hicks SN, Sondek J, and Harden TK. Dual regulation of phospholipase C-ε by Rho and Ras GTPases. J. Biol. Chem., 283:29690-29698, 2008.

Zhou Y, Sondek J, and Harden TK. Activation of human phospholipase C-η2 by Gβγ. Biochemistry 47:4410-4417, 2008

Elliot MR, Chekeni FB, Lazarowski ER, Harden TK, Leitinger N, and Ravichandran KS. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature, 461:282-286, 2009.

Carter RL, Fricks IP, Barrett MO, Burianek LB, Zhou Y, Jacobson KA, Lazarowski,ER, and Harden TK. Quantification of Gi-mediated inhibition of adenylyl cyclase activity reveals that UDP is a potent agonist of the human $P2Y_{14}$ receptor. Mol Pharmacol, 76:1341-1348, 2009.

Gresset A, Hicks SN, Harden TK, and Sondek J. Mechanism of phosphorylation-induced activation of phospholipase C-γ isozymes. J. Biol. Chem. 285:35836-35847, 2010.

Waldo GL, Ricks TK, Hicks SN, Cheever ML, Kawano T, Tsuboi K, Wang X, Montell C, Kozasa T, Sondek J, and Harden TK. Kinetic scaffolding mediated by a phospholipase C-β and Gq signaling complex. Science 330:974-980, 2010.

Tang W, Zhang Y, Xu W, Harden TK, Sondek J, Sun L, Li L, and Wu D. A PLC-β/PI3Kγ-GSK3 signaling pathway regulates cofilin phosphatase slingshot2 and neurtrophil polarization and chemotaxis. Dev. Cell 21:1038-1050, 2011.

Wang X, Barrett M, Sondek H, Harden TK, and Zhang Q. Fluorescent phosphatidylinositol 4,5-bisphosphate derivatives with modified 6-hydroxy group as novel substrates for phospholipase C. Biochemistry 51:5300-5306, 2012.

Sesma JI, Kreda SM, Steinckwich-Besancon N, Dang H, Garcia-Mata R, Harden TK, and Lazarowski ER. The UDP-sugar-sensing $P2Y_{14}$ receptor promotes Rho-mediated signaling and chemotaxis in human neutrophils. A. J. Physiol. Cell Physiol. 303:C490-498, 2012.

Dbouk HA, Vadas O, Shymanets A, Burke JE, Barrett MO, Waldo GL, Harden TK, Smrcka AV, Taussig R, Bresnick AR, Nurnberg B, Williams RL and Backer JM. G protein-coupled receptor-mediated activation of p110β by Gβγ is required for cellular transformation and invasiveness. Science Signaling 5(253):ra89, 2012.

Huang W, Barrett MO, Hajicek N, Hicks S, Harden TK, Sondek J, and Zhang Q. Small molecule inhibitors of phospholipase C from a novel high-throughput screen. J. Biol. Chem. 288:5840-5848, 2013.

Barrett MO, Sesma JI, Ball CB, Jayasekara PS, Jacobson KA, Lazarowski ER, and Harden TK. A selective high affinity antagonist of the $P2Y_{14}$ receptor inhibits UDP-glucose-stimulated chemotaxis of human neutrophils. Mol. Pharmacol. 84:41-49, 2013.

D. Research Support

Ongoing

R01 GM038213-23 (Harden) 01/01/2009 – 12/31/2013 3.60 calendar
P2Y - Purinergic Receptors
The major goals of this research are to define in molecular terms the structural/functional properties of P2Y receptors and to develop receptor-selective agonists and antagonists for the P2Y receptors.
Role: PI

R01GM057391-12 (Harden/Sondek MPI) 04/01/2012-03/31/2016 3.60 calendar
Regulation of Phospholipase C
This research is designed to understand the molecular mechanism(s) of regulation of phospholipase C isozymes by heterotrimeric G proteins and Rho-family GTPases.
Role: MPI

P01 HL034322-25 (Boucher/Harden Co-Investigator Core A) 04/01/2012 – 01/31/2017 0.60 calendar
Pulmonary Epithelial in Health and Disease
The long-range goal of this program project is to provide an integrated, quantitative formulation of how ASL volume is controlled in the mammalian lung in health and disease.
Role: Co-investigator