

BIOGRAPHICAL SKETCH

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NAME Thomas Michel, M.D., Ph. D.	POSITION TITLE Senior Physician, Brigham & Women's Hospital Professor of Medicine, Harvard Medical School		
eRA COMMONS USER NAME			
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
Harvard College, Cambridge, MA	A.B.	1977	Biochemical Sciences
Duke University, Durham, NC	Ph.D.	1983	Biochemistry
Duke University, Durham, NC	M.D.	1984	Medicine

A. Positions and Awards:**Internship and Residency:**

1984-1987 First, Second and Third Year Resident Physician, Research Residency Program, Department of Medicine, Brigham and Women's Hospital (BWH)

Fellowships:

1984-1987 Clinical and Research Fellow in Medicine, Harvard Medical School, Boston, MA
1987-1989 Clinical Fellow in Cardiology, Department of Medicine, BWH
1988-1990 Research Fellow in Genetics, Harvard Medical School

Academic and Clinical Appointments:

1988-1989 Instructor in Medicine, Harvard Medical School
1988-present Associate Physician, Physician (1999-2004), and Senior Physician (2004-present), BWH
1989-1995 Assistant Professor of Medicine, Harvard Medical School
1995-2004 Associate Professor of Medicine, Harvard Medical School
1998-2006 Chief of Cardiology, VA Boston Healthcare System
2004-present Professor of Medicine (Biochemistry), Harvard Medical School
2007-present Director, Harvard Program in Human Biology and Translational Medicine

Awards and Honors: Harvard National Scholarship (1973-1977); Fellowship, Medical Scientist Training Program, Duke University (1977-1984); Clinician-Scientist Award, American Heart Association (1988-1993); Diplomate in Cardiovascular Disease, ABIM (1989); Young Scholars Award, American Society of Hypertension (1991); Henry Christian Award for Excellence in Research, American Federation of Clinical Research (1992 and 1993); Cecilie Greig Visiting Professor, Royal Postgraduate Medical School, London (1993); Established Investigator, American Heart Association (1993-present). Fellow, American College of Cardiology (1994); John J. Abel Award in Pharmacology, American Society for Pharmacology and Experimental Therapeutics (1995); American Society for Clinical Investigation (1996); Burroughs Wellcome Fund Scholar Award in Experimental Therapeutics (1996). Member, Editorial Committee: *Journal of Clinical Investigation* (1996-); Member (1996-2002) and Chair (2000-2) Pharmacology Study Section, National Institutes of Health. Editorial Board, *Journal of Biological Chemistry* (2000-5); Association of University Cardiologists (2002); Association of American Physicians (2003). Eugene Braunwald Award for Excellence in Teaching in Clinical Cardiology (2005).

B. Publications (selected from a total of >120):

Lamas S, Marsden P, Li GK, Tempst P and Michel T. Endothelial nitric oxide synthase: molecular cloning and characterization of a distinct constitutive enzyme isoform. *Proc Natl Acad Sci USA* 1992; 89:6348-6352.
Busconi L and Michel T. Endothelial nitric oxide synthase: N-terminal myristoylation determines subcellular localization. *J Biol Chem* 1993; 268:8410-8413.
Michel T, Li GK and Busconi L. Phosphorylation and intracellular translocation of endothelial nitric oxide synthase. *Proc Natl Acad Sci USA* 1993; 90:6252-6256.
Robinson LJ, Busconi L and Michel T. Agonist-modulated palmitoylation of endothelial nitric oxide synthase. *J Biol Chem* 1995; 270: 995-998.
Robinson LJ and Michel T. Mutagenesis of palmitoylation sites in endothelial nitric oxide synthase identifies a

- novel motif for dual acylation and subcellular targeting. *Proc Natl Acad Sci USA* 1995; 92:11776-11780.
- Shaul P, Smart E, Robinson LJ, Ying Y, Anderson RGW and Michel T. Acylation targets endothelial nitric oxide synthase to plasmalemmal caveolae. *J Biol Chem* 1996 271: 6518-23.
- Feron O, Belhassen, L, Kobzik L, Smith TW, Kelly RA and Michel T. Endothelial nitric oxide synthase targeting to caveolae: specific interactions with caveolin isoforms in cardiac myocytes and endothelial cells. *J Biol Chem* 1996; 271:22810-22814.
- Michel JB, Feron O, Sacks D and Michel T. Reciprocal regulation of endothelial NO synthase by caveolin and Ca^{++} -calmodulin. *J Biol Chem* 1997; 272: 15,583-15,586.
- Michel JB, Feron O, Prabhakar P, Sase K and Michel T. Caveolin versus calmodulin: counterbalancing allosteric regulators of endothelial nitric oxide synthase. *J Biol Chem* 1997, 272: 25,907-12.
- Michel T and Feron F. Nitric oxide synthases: which, where, how and why? *J Clin Invest*; 1997, 100: 2146-52.
- Feron O, Saldana F, Michel JB and Michel T. The endothelial nitric oxide synthase-caveolin regulatory cycle. *J Biol Chem*; 1998: 273: 3125-8.
- Prabhakar P, Thatte H, Goetz R, Cho M, Golan D and Michel T. Receptor-mediated redistribution of endothelial nitric oxide synthase. *J Biol Chem*, 1998; 273:27,389-94.
- Yeh D, Duncan JA, Yamashita S and Michel T. Depalmitoylation of endothelial nitric oxide synthase by acyl-protein thioesterase-1 is potentiated by Ca^{2+} -calmodulin. *J Biol Chem* 1999, 274:33148-54.
- Prabhakar P, Cheng V and Michel T. A chimeric transmembrane domain directs eNOS palmitoylation and targeting to plasmalemmal caveolae. *J Biol Chem* 2000; 275:19416-19421.
- Bernier SG, Haldar S and Michel T. Bradykinin-regulated interactions of the mitogen-activated protein kinase pathway with the endothelial nitric oxide synthase. *J Biol Chem* 2000, 275:30707-30715.
- Igarashi J and Michel T. Agonist-modulated targeting of the EDG-1 receptor to plasmalemmal caveolae: eNOS activation by sphingosine 1-phosphate and the role of caveolin-1 in sphingolipid signal transduction. *J Biol Chem* 2000, 275:32,363-32, 370.
- Igarashi J, Bernier SG and Michel T. Sphingosine 1-phosphate and activation of endothelial nitric oxide synthase. *Journal of Biological Chemistry*, 2001; 276: 12420-12426.
- Igarashi J and Michel T. Sphingosine 1-phosphate modulates isoform-specific activation of phosphoinositide 3-kinase- β in vascular endothelial cells: implications for eNOS regulation by G-protein coupled receptors. *J Biol Chem* 2001; 276:36281-8.
- Trimmer B, Aprille J, Dudzinski D, Lagace C, Lewis S, Michel T and Zayas R. Regulation of firefly flashing by nitric oxide. *Science* 2001; 292:2486-8.
- Gonzalez E, Kou R, Lin AJ, Golan DE, and Michel T. Subcellular targeting and agonist-induced site-specific phosphorylation of eNOS. *Journal of Biological Chemistry* 2002, 277:39554-60.
- Kou R, Greif D, and Michel T. Dephosphorylation of endothelial nitric oxide synthase by vascular endothelial growth factor: implications for the vascular responses to cyclosporin A. *J Biol Chem* 2002; 277:29669-73.
- Dantas AP, Igarashi J and Michel T. Sphingosine 1-phosphate and control of vascular tone. *Am J Physiol*. 2003, 274:H2045-2052
- Igarashi J, Erwin P, Dantas AP, Chen, H and Michel T. VEGF induces S1P1 receptor expression in endothelial cells: implications for crosstalk between sphingolipid and growth factor receptors in eNOS regulation. *Proc Natl Acad Sci USA* 2003; 100:10664-9.
- Greif DE, Sacks DB and Michel T. Calmodulin phosphorylation and modulation of endothelial nitric oxide synthase catalysis. *Proc Natl Acad Sci USA* 2004 10:1165-1170.
- Gonzalez E, Nagiel A, Lin A, Golan DE and Michel T. siRNA-mediated downregulation of caveolin-1 differentially modulates signaling pathways in endothelial cells. *J Biol Chem* 2004, 279: 20659-20669.
- Mitchell DA, Erwin PA, Michel T, and Marletta MA. S-Nitrosation and regulation of inducible nitric oxide synthase. *Biochemistry* 2005; 44: 4636-4647.
- Erwin PA, Lin A, Golan DE and Michel T. Receptor-regulated dynamic S-nitrosylation of endothelial nitric oxide synthase in vascular endothelial cells. *J Biol Chem* 2005, 280: 19888-19894.
- Kou R, SenBannerjee S, Jain M and Michel T. Differential regulation of vascular endothelial growth factor receptors revealed by RNA interference: interactions of VEGFR-1 and VEGFR-2 in endothelial cell signaling. *Biochemistry* 2005, 44:15064-15073.
- Erwin PA, Mitchell D, Sartoretto J, Marletta M and Michel T. Subcellular targeting and S-nitrosylation of endothelial nitric oxide synthase. *J Biol Chem* 2006, 281: 151-157.

- Gonzalez E, Kou R and Michel T. Rac1 modulates sphingosine 1-phosphate-mediated activation of PI3-kinase/Akt pathways in vascular endothelial cells. *J Biol Chem* 2006, 281:3210-3216.
- Dudzinski D, Igarashi J, Greif D and Michel T. Pharmacology and molecular regulation of nitric oxide synthases. *Annu Rev Pharmacol Toxicol*, 2006, 46:235-276.
- Levine Y, Li GK and Michel T. Agonist-modulated regulation of AMPK-activated protein kinase in endothelial cells: Evidence for an AMPK-Rac1-Akt-eNOS pathway. *J Biol Chem* 2007, 282:20351-2036
- Kou R and Michel T. Epinephrine regulation of eNOS: roles of Rac1 and β 3-adrenergic receptors in endothelial NO signaling. *J Biol Chem* 2007 <http://www.jbc.org/cgi/doi/10.1074/jbc.M706815200>

C. Research Support:

ACTIVE:

NIH RO-1 GM36259

7/1/85-7/31/10

"Protein interactions in cardiovascular signaling"

Principal Investigator Thomas Michel

Specific Aims: 1) Explore the role of caveolin in the regulation of phosphoinositide targeting to caveolae and in the regulation of interactions between lipid rafts, MARCKS and PIP-2; 2) Identify signaling pathways that regulate interactions between caveolin, calmodulin and MARCKS leading to alterations in eNOS activation and Ca^{2+} mobilization; 3) Explore the effects of calmodulin phosphorylation on its association with MARCKS and eNOS; 4) Determine the effects of caveolin-1 on S1P₁ receptor targeting and turnover in endothelial cells; 5) Apply siRNA methodologies to identify mechanisms whereby selected caveolin-modulated proteins affect endothelial cell migration, angiogenesis, secretion, and permeability.

NIH RO-1 HL46457

4/1/92-1/31/12

"Endothelial nitric oxide synthase"

Principal Investigator Thomas Michel

Specific aims: 1) To determine the mechanisms by which S-nitrosylation regulates eNOS and NO signaling in the endothelium; 2) To establish the role of Rac1 GTPase in eNOS regulation and receptor-regulated endothelial signaling pathways.

NIH P01 HL48743

5/1/05-3/31/10

"Arterial Dysfunction: Basic and Clinical Mechanisms"

Principal Investigator Thomas Michel

The major goals of this Program Project Grant are to investigate the pathophysiological mechanisms in diabetes that modify critical interactions among vascular cells leading to arterial dysfunction. TM is the Project Leader for Project 1, entitled "Insulin regulation of eNOS", with the Specific Aims: 1) Determine the relationships between diabetes, insulin signaling, and eNOS nitrosation; 2) Establish the role of caveolin in insulin-mediated signal transduction in endothelial cells and 3) Elucidate the mechanisms of cross-talk between insulin receptors and sphingosine 1-phosphate receptors in eNOS regulation and kinase activation. TM is also the Director of Core A (Administrative Core) and Co-Director of Core B (Animal models of diabetic vasculopathy).