BIOGRAPHICAL SKETCH

NAME: David G. Harrison	POSITION TITLE Bernard Marcus Professor of Medicine
eRA COMMONS USER NAME: DHARRISON	

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
Oklahoma State University, Stillwater, OK	B.S.	1970	Physiology
University of Oklahoma, Oklahoma City, OK	M.D.	1974	Medicine

A. Positions and Honors: Positions and Employment:

1974 - 1975 **Medical Intern,** Duke University Medical Center, Durham, NC.
1974 - 1977 **Medical Resident,** Duke University Medical Center, Durham, NC.
1977 - 1979 **Cardiology Fellow**, Duke University Medical Center, Durham, NC.
1979 - 1980 **Clinical Instructor in Medicine**, Univ. of N.C. Sch. of Med., Affil. Hospital, Charlotte, NC
1980 - 1982 **Research Fellowship**, Cardiovascular Center, Univ. of Iowa, Iowa City, IA.
1982 - 1987 **Assistant Professor,** University of Iowa, Dept. of Internal Med., Iowa City, IA.
1987 - 1990 **Associate Professor,** University of Iowa, Iowa City, IA.
1990 - 2001 **Professor of Medicine**, Div of Cardiology, Emory Univ. Sch. of Med., Atlanta, GA.
2000 - present **Director**, Division of Cardiology, Emory University School of Medicine, Atlanta, GA
2001 – present **Bernard Marcus Professor of Medicine**, Div. of Cardiology, Emory Univ. Sch. of Medicine

Honors, Awards, and Service:

1977 Haskel Schiff Award for Outstanding Medical House Officer, Duke Univ. Dept. of Med.
1980 Outstanding Attending, Dept of Med, Charlotte Memorial Hospital
1980 Individual National Research Service Award, Natl Institute of Health
1982-1987 Clinical Investigator Award, National Institutes of Health
1987-1992 Established Investigator, American Heart Association
1995 George E. Brown Memorial Lecturer, American Heart Assn. 68th Scientific Sessions
1998 Wellcome Visiting Professor in the Basic Medical Sciences, New York Medical College
2001 Pfizer Visiting Professorship, Temple University, Philadelphia
2001 Robert Furchgott Lecture for the 8th Symposium on Mechanisms of Vasodilatation, Boston, MA
2002 Robert M. Berne Distinguished Lecturer, APS Cardiovascular Section, New Orleans, LA
2004 Novartis Award for Hypertension Research, AHA Council for High Blood Pressure, Chicago

B. Selected peer-reviewed publications (selected from over 160):

13. Freiman PC, Mitchell GG, Heistad DD, Armstrong ML, **Harrison DG**. Atherosclerosis Impairs Endothelium-Dependent Vascular Relaxation to Acetylcholine and Thrombin in Primates. *Circ Res* 1986;58:783-9.
17. **Harrison DG**, Armstrong ML, Freiman PC, Heistad DD. Restoration of Endothelium-Dependent Relaxation by Dietary Treatment of Atherosclerosis. *J Clin Invest* 1987;80:1808-11.
35. Myers PR, Minor RL Jr, Guerra R Jr, Bates JN, **Harrison DG**. Vasorelaxant Properties of the Endothelium-Derived Relaxing Factor More Closely Resemble S-Nitrosocysteine than Nitric Oxide. *Nature* 1990;345:161-3.
39. Minor RL Jr, Myers PR, Guerra R Jr, Bates JN, **Harrison DG**. Diet-Induced Atherosclerosis Increases the Release of Nitrogen Oxides from Rabbit Aorta. *J Clin Invest* 1990;86:2109-16.
52. Mügge A, Elwell JH, Peterson TE, Hofmeyer TG, Heistad DD, **Harrison DG**. Chronic Treatment with Polyethylene-Glycolated Superoxide Dismutase Partially Restores Endothelium-Dependent Vascular Relaxations in Cholesterol-Fed Rabbits. *Circ Res* 1991;69:1293-300.
61. Nishida K, **Harrison DG**, Navas JP, Fisher AA, Dockery SP, Uematsu M, Nerem RM, Alexander RW, Murphy TJ. Molecular Cloning and Characterization of the Constitutive Bovine Aortic Endothelial Cell Nitric Oxide Synthase. *J Clin Invest* 1992;90:2092-6.
66. Ohara Y, Peterson TE, **Harrison DG**. Hypercholesterolemia Increases Endothelial Superoxide Anion Production. *J Clin Invest* 1993;91:2546-51.
73. Münzel T, Sayegh H, Freeman BA, Tarpey MM, **Harrison, DG**. Evidence for Enhanced Vascular Superoxide Anion Production in Nitrate Tolerance: A Novel Mechanism Underlying Tolerance and Cross Tolerance. *J Clin Invest* 1995;95:187-94.
86. Rajagopalan S, Kurz S, Münzel T,Tarpey M, Freeman B, Griendling KK, **Harrison DG**. Angiotensin II Mediated Hypertension in the Rat Increases Vascular Superoxide Production via Membrane NADH/NADPH Oxidase Activation: Contribution to Alterations of Vasomotor Tone. *J Clin Invest* 1996;97:1916-23.

96. Bech Laursen J, Rajagopalan S, Tarpey M, Freeman B, **Harrison DG**. A Role of Superoxide in Angiotensin II – but not Catecholamine-induced Hypertension. *Circulation* 1997;95:588-593.
119. Fukai T, Siegfried M, Ushio-Fukai M, Cheng Y, Kojda G, **Harrison DG**. Regulation of Extracellular Superoxide Dismutase by Nitric Oxide and Exercise Training. *J Clin Invest* 2000;105:1631-1639.
122. Bech Laursen J, Somers M, Kurz S, McCann L, Warnholtz A, Freeman BA, Tarpey M, Fukai T, **Harrison DG**. Endothelial Regulation of Vasomotion in Apo(E)-deficient Mice: Implications for Interactions Between Peroxynitrite and Tetrahydrobiopterin. *Circ*ulation 2001;103:1282-1288.
128. Davis ME, Cai H, Drummond GR, **Harrison DG**. Shear Stress Regulates Endothelial Nitric Oxide Synthase Expression through c-Src by Divergent Signaling Pathways. *Circ Res* 2001;89:1073-1080.
131. Landmesser U, Cai H, Dikalov S, MccAnn L, Hwang J, Jo H, Holland SM, **Harrison DG**. Role of p47phox in Vascular Oxidative Stress and Hypertension caused by Angiotensin II. *Hypertension* 2002;40:511-515.
142. Spiekermann S, Landmesser U, Dikalov S, Bredt M, Gamez G, Tatge H, Reepschlager N, Hornig B, Drexler H, **Harrison DG**. Electron Spin Resonance Characterization of Vascular Xanthine and NAD(P)H Oxidase Activity in Patients with Coronary Artery Disease: Relation to Endothelin-dependent Vasodilation. *Circulation* 2003;107:1383-9.
143. Landmesser U, Dikalov S, Price R, McCann L, Fukai T, Holland SM, Mitch WE, **Harrison DG**. Oxidation of Tetrahydrobiopterin Leads to Uncoupling of Endothelial Cell Nitric Oxide Synthase in Hypertension: Role of the NADPH Oxidase. *J Clin Invest* 2003;111:1201-9.
145. Kuzkaya N, Weissmann N, **Harrison DG**, Dikalov S. Interactions of Peroxynitrite, Tetrahydrobiopterin, Ascorbic Acid and Thiols: Implications for Uncoupling Endothelial Nitric Oxide Synthase. *J Biol Chem* 2003;278:22546-22554.
151. Davis ME, Grumbach IM, Fukai T, Cutchins A, **Harrison DG**. Shear Stress Regulates Endothelial Nitric Oxide Synthase Promoter Activity through Nuclear Factor Kappa-B Binding. *J Biol Chem* 2004 Jan 2;279:163-8.
153. Ridker PM, Brown NJ, Vaughan DE, **Harrison DG**, Mehta JL. Established and Emerging Plasma Biomarkers in the Prediction of First Atherothrombotic Events. *Circulation* 2004;109:6-19.
156. Weber DS, Rocic P, Mellis AM, Laude K, Lyle AN, **Harrison DG**, Griendling KK. Angiotensin II-induced Hypertrophy is Potentiated in Mice Overexpressing p22phox in Vascular Smooth Muscle. *Am J Physiol Heart Circ Physiol* 2005;288:H37-42.
157. Laude K, Cai H, Fink B, Hoch N, Weber DS, McCann L, Kojda G, Fukai T, Schmidt HH, Dikalov S, Ramasamy R, Gamez G, Griendling KK, **Harrison DG**. Hemodynamic and Biochemical Adaptations to Vascular Smooth Muscle Overexpression of p22phox in Mice. *Am J Physiol Heart Circ Physiol* 2005;288:H7-H12.
158. Abramson JL, Hooper WC, Jones DP, Ashfaz CS, Rhodes SD, Weintraub WS, **Harrison DG**, Quyyumi AA, Vaccarino V. Association Between Novel Oxidative Stress Markers and C-reactive Protein Among Adults Without Clinical Coronary Heart Disease. *Atherosclerosis* 2005;178:115-21.
159. Lauer N, Suvorava T, Ruther U, Jacob R, Meyer W. Harrison DG, Kojda G. Critical Involvement of Hydrogen Peroxide in Exercise-induced Upregulation of Endothelial NO Synthase. Cardiovasc Res 2005;65:254-262.
160. Jeney V, Itoh S, Wendt M, Gradek Q, Ushio-Fukai M, Harrison DG, Fukai T. Role of Antioxidant-1 in Extracellular Superoxide Dismutase Function and Expression. Circ Res 2005;96:723-729.
161. Weber M, Hagedorn CH, Harrison DG, Searles CD. Laminar Shear Stress and 3' Polyadenylation of eNOS mRNA. Circ Res 2005;96:1161-8.
162. McNally JS, Saxena A, Cai H, Dikalov S, Harrison DG. Regulation os Xanthine Oxidoreductase Protein Expression by Hydrogen Peroxide and Calcium. ATVB 2005;25:1623-8.
163. Kuzkaya N, Weissman N, Harrison DG, Dikalov S. Interactions of Peroxynitrite with Uric Acid in the Presence of Ascorbate and Thiols: Implications for Uncoupling Endothelial Nitric Oxide Synthase. Biochem Pharmacol 2005;70:343-354.
164. Grumbach IM, Chen W, Mertens SA, Harrison DG. A Negative Feedback Mechanism Involving Nitric Oxide and Nuclear Factor Kappa-B Modulates Endothelial Nitric Oxide Synthase Transcription. J Mol Cell Cardiol 2005, in press.
165. Dudley SC, Hoch NE, McCann LA, Honeycutt C, Diamandopoulos L, Fukai T, Harrison DG, Dikalov SI, Langberg J. Atrial Fibrillation Increases Production of Superoxide by the Left Atrium and Left Atrial Appendage: Role of the NADPH and Xanthine Oxidases. Circulation, 2005, in press.

C. Active Research Support:

Regulation of Vascular Function by the Endothelium
Principal Investigator: David G. Harrison
Agency: National Institutes of Health
Type: RO1 HL39006 Period: 06/01/91-11/30/06
The major goals of this project are: 1) to determine if the NADH/NADPH oxidase is responsible for producing kindling radicals that result in uncoupling eNOS in DOCA-salt hypertension; to define abnormalities of tetrahydrobioptrin biosynthesis that may occur in DOCA-salt hypertension; to determine if endothelial derived H_2O_2 leads to hypertrophy and remodeling of the adjacent vascular smooth muscle in DOCA-salt hypertension; and to determine the mechanism by which oscillatory shear increases production of reactive oxygen species in endothelial cells.

Molecular Control of Vascular Function by Oxidant Stress
Principal Investigator: David G. Harrison
Agency: National Institutes of Health
Type: P01 HL58000 Period: 5/1/03-4/30/08
Project 2: Phenotypic Consequences of Vascular Oxidant Stress (Project Leader)
The major goals of this project are: 1) to examine the effect of overexpression of p22phox on vascular function
and hemodynamics in transgenic mice; 2) to decrease expression of p22phox to determine the role of this protein in total vascular ·O2 production and the effect of angiotensin II on vascular function; 3) to determine the role of NO· in the blood pressure lowering effect of superoxide dismutase in angiotensin II-induced hypertension; 4) to examine the role of reactive oxygen species in regulation of MMP activity and expression in vitro; 5) to examine mechanisms underlying increased MMP activity in rats made hypertensive by chronic angiotensin II treatment.

Molecular Control of Vascular Function by Oxidant Stress (Administrative Core)
Principal Investigator: David G. Harrison
Agency: National Institutes of Health
Type: P01 HL58000 Period: 5/1/03-4/30/08
Dr. Harrison is the Core Leader for this portion of the Program Project Grant.

Research Training in Academic Cardiology
Principal Investigator: David Harrison
Agency: National Institutes of Health
Type: T32 HL07745 Period: 7/1/04 - 6/30/09
This is an institutional research service award to train cardiology fellows.

Modulation of Vascular Function by Reactive Oxygen Species
Principal Investigator: Kathy K. Griendling
Project 3: Regulation of eNOS Expression by NFκB, Shear Stress, and Exercise
Project 3 Principal Investigator: David G. Harrison
Agency: National Institutes of Health
Type: P01HL075209 Period: 12/01/03-11/30/08
The major goals of this project are: 1) to examine molecular signals responsible for activation of NFκB in response to shear; 2) to examine the hypothesis that NO production in response to shear provides a negative feedback to inhibit NFκB-binding to the eNOS promoter, inhibiting eNOS promoter activity and reducing eNOS transcription; 3) to determine if NFκB is activated in vivo during exercise training, if its activation is modulated by NO and if NFκB activation mediates the increase in eNOS expression during exercise; and 4) to determine if an absence of NO promotes vascular inflammation during exercise.

Nanotechnology: Detection & Analysis of Plaque Formation
Principal Investigator: Gang Bao, Ph.D.
Agency: National Institutes of Health
Type: U01HL080711 Period: 05/01/05-04/30/10

Project 1: PIs: David Harrison and Gang Bao
Design, Development and Optimization of Nanostructured Probes for Specific Detection of mRNA in Living Cells to Study Molecular Mechanisms of Atherogenesis
The major goals of this project are to develop dual FRET molecular beacons with high sensitivity, stability and signal-to-background ratio and explore the use of new fluorophores; to determine the expression level and subcellular localization of mRNAs such as eNOS mRNA. We will also study the changes of the Poly-A tail of eNOS mRNA in endothelial cells in response to shear stress; and to determine the changes in expression level of stress-sensitive genes such as Caveolin-1 in response to pro-atherogenic oscillatory shear and anti-atherogenic laminar shear stress.

Project 5: PIs: David Harrison and Xiaoping Hu
LDL and Chymase-based contrast agent for in vivo plaque detection
The major goals of this project are to develop LDL-based contrast agent for the early detection of vulnerable plaques and perform in vivo testing of LDL-probe accumulation in vulnerable plaques; and to develop Chymase-activated MRI probes for the detection of vulnerable plaques.

Project 6: PIs: David Harrison and Gang Bao
Activatable Probes for Sensitive Detection of Oxidative Stress in Living Cells
The major goals of this project are to develop activatable molecular probes with different reporting strategies and perform solution studies to determine detection sensitivity and signal-to-background ratio; and to validate the detection sensitivity and specificity of oxidative stress in living cells.

Post-transcriptional Regulation of Endothelial NO Synthase
Principal Investigator: Charles Searles Co-Investigator: David Harrison
Agency: National Institutes of Health
Type: R01HL077274 Period: 4/1/05-3/31/10
The major goals of this project are: 1) to determine if shear stress-induced eNOS 3' polyadenylation occurs in the nucleus or in the cytoplasm; 2) to address the possibility that shear stress may lead to inhibition of the deadenylation process; 3) to examine mechanisms responsible for the data suggesting ahat HMG CoA reductase inhibitors also increase eNOS 3' poly(A) tail processing; and 4) to determine if shear stress associated with exercise training modulates eNOS 3' polyadenylation in vivo.

Pending:

Fish Oil Supplements and Vascular Disease
Principal Investigator: Mushtaq Ahmad Co-Investigator: David G. Harrison
Agency: National Institutes of Health
Type: R01 Period: 7/1/2006-6/30/2011
The goals of this project are: to characterize the mechanism by which DHA/EPA inhibit Rac1 activation; to characterize the mechanisms underlying DHA/EPA activation of Akt/PKB and define the manner in which it antagonizes endothelial cells activation and VCAM-1 expression by TNF; and to characterize the effects of converting endogenous omega-6 into omega-3 fatty acids on the development of hypertension and atherosclerosis by expressing transgene desaturase enzyme from C elegans in mice.

Overlap:

None.