BIOGRAPHICAL SKETCH

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NAME: Nader G. Abraham

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

POSITION TITLE: Professor

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
Mt. Sinai School of Medicine, New York	*Ph.D.*	*06/1975*	*Biomedical Sciences*
The Rockefeller University	*Post Doc.*	*12/1976*	*Pharmacology/Metabolism*

A. Personal Statement

My long-lasting research program centers on the biochemistry, biology and functional/clinical relevance of the heme-heme oxygenase (HO) system. As a postdoctoral fellow in the laboratory of Dr. Kappas at the Rockefeller University, I purified HO from rat and human liver and characterized its catalytic properties. I continued exploring the biology of HO throughout my scientific career in a prolific research program that made seminal contributions to this field of research. For example, we were the first to demonstrate the importance of HO-1 in the cardiovascular system and to document its regulatory function on the biosynthesis of eicosanoids; specifically those derive from the cytochrome P450 (CYP) pathway. In the last decade, studies in my laboratory explored the pathophysiology aspects of the heme-HO-1 in hypertension, diabetes and the Metabolic Syndrome. I have published over 300 articles in peer-reviewed journals, authored/co-edited 9 books and hold 5 US patents. As indicated in Google Scholar, several citations of my papers were higher than 400 citation i.e., citation class along with an “h” index of 68. I have been involved in the program project from its inception. I conceived the original idea that the role of CYP-derived eicosanoids can be tested through the prism of HO and presented this finding to Dr. McGiff. This idea was the basis of the first Program Project Grant in 1985. Later, in 2000, I lent my expertise in molecular biology/gene transfer technologies and joined the Program Project Grant as leader of a new core, the Vector Core (Core C). In that capacity, I helped project leaders in the design, construction and administration of viral vector-DNA constructs as well as in interpretation and analysis of data. Throughout the life of this Program Project, I served as a collaborator/consultant on several projects and in 2010 joined as a project leader expanding my research program to include the role of EETs in the regulation of the vascular and renal cytoprotective actions of the HO system. I brought to the Program Project novel concepts and innovative approaches which explored the significance of EET-HO-1 interactions in the regulation of adipocyte-mediated protection of vascular function in obesity-induced hypertension. The current proposal builds on original findings made during the last period that are largely described in more than 70 peer-reviewed publications.

I have successfully mentored undergraduate, graduate, post-doctoral and clinical fellows and junior faculty for more than 35 years. Many of these individuals have attained positions of leadership including departmental chairs, full professorships, and chiefs of clinical departments and have achieved national and international recognition in their respective fields. I have the necessary experience and expertise as IAC to insure the success of this COBRE application, which is designed to address the high incidence of obesity and metabolic syndrome in Appalachia populations

a. Sacerdoti D, Escalante B, Abraham NG, McGiff JC, Levere RD, Schwartzman ML. Treatment with tin prevents the development of hypertension in spontaneously hypertensive rats. Science 243:388-390, 1989.
b. Levere RD, Martasek P, Escalante B, Schwartzman ML, Abraham NG. Effect of heme arginate administration on blood pressure in spontaneous hypertensive rats. J. Clin. Invest. 86:213-219, 1990

c. Kaide, J-I., Zhang, F., Wei, Y., Jiang, H., Yu, C., Wang, W., Balazy, M., Abraham, N.G., and Nasjletti, A.: Carbon monoxide of vascular origin attenuates the sensitivity of renal arterial vessels to vasoconstrictors. J. Clin. Invest. 107:1163-1171, 2001.

B. Positions and Honor

Positions and Employment:

2015-present	Professor, Department of Medicine and Pharmacology, New York Medical College, Valhalla, NY
2015-present	Professor, Joan C Edwards School of Medicine, Marshall University, WV
2012- 2014	Vice Dean for Research, Marshall University Joan C. Edwards School of Medicine, Huntington, WV
2009-2012	Professor & Chairman, Department of Physiology & Pharmacology, The University of Toledo
2009-2014	Adjunct Professor, Department of Pharmacology and Medicine, New York Medical College, Valhalla, NY
1996-2009	Professor, Director of Stem Cells/Gene Therapy, Department of Pharmacology and Medicine, New York Medical College, Valhalla. NY
1993-1996	New York University School of Medicine, Department of Medicine, NY, NY Professor full-time
1993-2014	The Rockefeller University, NY, NY, Adjunct Professor, Adjunct scientist/Dr. Kappas' Lab.
1978-1993	New York Medical College, Department of Medicine, Valhalla, NY, Assistant/Associate/Professor full-time.
1977-1978	New York University Medical Center, Department of Medicine, NY, NY, Associate Scientist full-time
1972-1975	Mt. Sinai School of Medicine, Department of Biochemistry, NY, NY Doctoral Student full-time

Honors

1981-1986	Recipient, Research Career Development Award from the National Institute of Arthritis, Metabolism and Digestive Diseases
1985	Tinsley Harrison Award for the best single cardiology manuscript published by the AMJS
1997	Honored Professorship, Japanese Society for the Promotion of Science
1997	Alma Mater Studiorum, Saecularia Nona Award, University of Bologna, Italy
2004-present	Member of NIH Panel for Excellency on Stem cells/Gene Therapy and in Molecular Hematology (DK04-015); Chairman of Renal Science Special emphasis Panel (ZRG1-RUS-E) Reviewer for PPG's of several study section
2007	Recipient of NYMC's Dean Distinguished Award; Dean Distinguished Award for Stem Cells and Diabetes, University of Catania's Dean award, Sicily; Dr David M Kovitz Lecturer Award, University of Calgary, Canada; Recipient of the Cardiovascular Distinguished Award, University of Saskatoon, Canada
2009	Honoree Doctorate in Pharmacy/Medicine, Laurea Honoris Causa, University of Catania, Italy

Other Experience Professional Memberships and Editorial Boards

1991-1997	Stem Cells
1993-2000	Blood, Experimental Hematology
1995-2000	The Society for Experimental Biology and Medicine
1995-2000	Acta Haematologica
2014-present	Member, Editorial Board, Pathology and Laboratory Medicine International
2014-present	Member, Editorial Board, Cardiology in Review (an affiliated journal of AHA)
2014-present	Member, Editorial Board, Integrated Blood Pressure Control
Reviewer	Cancer Research Therapy and Control, Journal of Biological Chemistry, Science, FASEB, American Journal of Physiology, Journal of Pharmacology and Experimental Therapeutics, Circulation, Circulation Research.

C. Contribution to Science

1. Immediately after receiving my PhD degree, my postdoctoral fellowship at the Rockefeller University focused on the purification of a human liver protein (heme oxygenase, HO-1) and its gene sequence, including the promoter region. Thereafter, I led a productive research that further characterized the biochemistry of heme oxygenase and the implication of its activity to heme and iron homeostasis and the function of hematopoietic

stem cells. We were the first to apply retroviral and adenoviral vector to deliver HO-1 to organ/specific sites to attenuate inflammation. Our work led to the discovery that the endogenous HO-1/HO-2 system serves as a major controller of renal function and vascular tone by regulating the formation of CO, a potent vasodilator. The examination of the biological function of CO led to the discovery of the role of heme arginine in lowering blood pressure as a result of the cross-talk between CO and NO which resulted in the development of a patent for arginine, an amino acid effective in lowering blood pressure in the rodent and in man. The patent royalties supported my institution and my research. This discovery was based on the seminal observation and to the landmark discovery that induction of HO-1 with SnCl2 prevents the development of hypertension (Science 1989 and J Clinical Investigation 1990). This landmark publication was the first to place HO-1 in the realm of cardiovascular disease/research.

a. Chernick RJ, Martasek P, Levere RD, Margreiter R, Abraham NG. Sensitivity of human tissue heme oxygenase to a new synthetic metalloporphyrin. Hepatology 10(3):365-369, 1989.
b. Abraham NG, da Silva J-L, Lavrovsky Y, Stoltz RA, Kappas A, Dunn MW, Laniado-Schwartzman M. Adenovirus-mediated heme oxygenase-1 (HO-1) gene transfer into rabbit ocular tissues. Invest. Ophthalmol. Vis. Sci. 36:2202-2210, 1995.
c. Johnson RA, Lavesa M, Askari B, Abraham NG, Nasjletti A. A heme oxygenase product, presumably carbon monoxide, mediates a vasodepressor function in rats. Hypertension 25:166-169, 1995.

2. **Transcriptional factors and HO-1.** We were the first to identify novel regulatory sites on the human HO-1 promoter including NFKB, AP2, SP1, TFID, OKTI and CREB. We showed that NFKB and AP2 activation is associated with the immediate response of the cell to an injury and that HO-1 acts as a defense mechanism against endothelial cell injury thus blocking inflammation and cellular damage. This key finding led to the examination of the protective effect of HO gene transfer and its overexpression against heme/hemoglobin toxicity in vascular endothelial cells, and to the recognition that HO-1 is an important tissue adaptive mechanism for moderating cell damage against injurious stimuli.

a. Lavrovsky Y, Schwartzman ML, Abraham NG. Novel regulatory sites of the human heme oxygenase-1 promoter region. Biochem.Biophys.Res.Commun. 1993 Oct 15;196(1):336-41
b. Lavrovsky Y, Schwartzman ML, Levere RD, Kappas A, Abraham NG. Identification of binding sites for transcription factors NF-kappa B and AP-2 in the promoter region of the human heme oxygenase 1 gene. Proc.Natl.Acad.Sci.U.S.A 1994 Jun 21;91(13):5987-91
c. Abraham NG, Lavrovsky Y, Schwartzman ML, Stoltz RA, Levere RD, Gerritsen ME, Shibahara S, Kappas A. Transfection of the human heme oxygenase gene into rabbit coronary microvessel endothelial cells: protective effect against heme and hemoglobin toxicity. Proc.Natl.Acad.Sci.U.S.A 1995 Jul 18;92(15):6798-802
d. Abraham NG, Junge JM, Drummond GS. Translational Significance of Heme Oxygenase in Obesity and Metabolic Syndrome. Trends Pharmacol Sci. 2015 Oct 26. pii: S0165-6147(15)00202-3. doi: 10.1016/j.tips.2015.

3. **Kidney gene targeting, hypertension and vascular function.** Based on the beneficial function of HO-1, i.e., degradation of heme, (pro-oxidant) to bilirubin “antioxidant”, CO and Fe “increase ferritin” to increase antioxidant properties, we conducted studies to assess the contribution of tissue-specific HO-1 cytoprotective properties to the pathogenesis of disease in which oxidative stress has been implicated. We demonstrated that TALH cell transfected with adenoviral-NKCC2-HO-1 gene attenuated Ang II induced DNA degradation and the decrease of GSH and cell survival, thus blocking inflammation and apoptosis. We examined the effect of lentiviral-HO-1 gene transfer by a single intra-cardiac injection to deliver viral particles in 5-day-old SHR rats. Rats expressing global human HO-1 showed a significant decrease of urinary excretion of a vasoconstrictor AA metabolite (20-HETE) and reduction in myogenic response. Delivery of human HO-1 by retroviral vectors attenuated the development of hypertension in SHR. We further showed that HO-1 gene transfer decreases oxidant production and endothelial damage and attenuated vascular complications in diabetes.

a. Sabaawy HE, Zhang F, Nguyen X, Elhosseiny A, Nasjletti A, Schwartzman M, Dennery P, Kappas A, Abraham NG. Human heme oxygenase-1 gene transfer lowers blood pressure and promotes growth in spontaneously hypertensive rats. Hypertension 2001 Aug;38(2):210-5
b. Quan S, Yang L, Shenouda S, Schwartzman ML, Nasjletti A, Goodman AI, Abraham NG. Expression of human heme oxygenase-1 in the thick ascending limb attenuates angiotensin II-mediated increase in oxidative injury. Kidney Int. 2004 May;65(5):1628-39

c. Abraham NG, Kushida T, McClung J, Weiss M, Quan S, Lafaro R, Darzynkiewicz Z, Wolin M. Heme oxygenase-1 attenuates glucose-mediated cell growth arrest and apoptosis in human microvessel endothelial cells. Circ.Res. 2003 Sep 19;93(6):507-14
d. Di Noia MA, Van DS, Palmieri F, Yang LM, Quan S, Goodman AI, Abraham NG. Heme oxygenase-1 enhances renal mitochondrial transport carriers and cytochrome C oxidase activity in experimental diabetes. J Biol.Chem. 2006 Jun 9;281(23):15687-93

4. **HO-1/EET and Metabolic Syndrome / Diabetes.** HO acts as a molecular "switch" to genetically reprogram adipocyte stem cells and subsequently, vascular endothelium through activation of a unique signaling cascade that results in the amplification of protective circuits and provides resistance to vascular dysfunction. Increased HO-1 expression provides protection for stem cell function and, decreases adiposity. HO-1 also serves as the mediator of cross-talk between adipose tissue and the vasculature. Our studies demonstrated that HO-1 expression in pericardial tissue provides protection to heart function and attenuates myocardial infarction (MI) and heart failure. Both human and animal models of diabetes and obesity were utilized to examine the use of stem cell intervention and gene therapy to amplify HO-1 levels. Additionally, our research approach proved to be a powerful tool in the identification of novel biomarkers for cardiovascular and metabolic disease (e.g. circulating endothelial cells and progenitor stem cells [EPCs] for better prognosis). We believe that the effect of anti-diabetic drugs alone, or in combination with antioxidant genes, have a differential impact on stem cell function and vascular disease. We showed an independent role of HO-1 and HO-2 in vascular protection and adiposity. For example, deletion of HO-2, increased obesity and decreased EET, this can be rescued by pharmacological upregulation of HO-1, signifying the role of both HO-1/-2 in adipocyte/vascular protection by regulating the EET-adiponectin-pAMPK signaling pathway.

a. Burgess A, Li M, Vanella L, Kim DH, Rezzani R, Rodella L, Sodhi K, Canestraro M, Martasek P, Peterson SJ, et al. Adipocyte heme oxygenase-1 induction attenuates metabolic syndrome in both male and female obese mice. Hypertension 2010 Dec;56(6):1124-30
b. Nicolai A, Li M, Kim DH, Peterson SJ, Vanella L, Positano V, Gastaldelli A, Rezzani R, Rodella LF, Drummond G, et al. Heme oxygenase-1 induction remodels adipose tissue and improves insulin sensitivity in obesity-induced diabetic rats. Hypertension 2009 Mar;53(3):508-15. PMCID:PMC2745551
c. Li M, Kim DH, Tsenovoy PL, Peterson SJ, Rezzani R, Rodella LF, Aronow WS, Ikehara S, Abraham NG. Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. Diabetes 2008 Jun;57(6):1526-35
d. Sodhi K, Inoue K, Gotlinger KH, Canestraro M, Vanella L, Kim DH, Manthati VL, Koduru SR, Falck JR, Schwartzman ML, et al. Epoxyeicosatrienoic acid agonist rescues the metabolic syndrome phenotype of HO-2-null mice. J.Pharmacol.Exp.Ther. 2009 Dec;331(3):906-16. PMCID:PMC2784709

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5. **HO-1/EET Gene Targeting to EC / Adipocytes**. Specific targeting of the adipocyte-specific vector, (LV-aP2-HO-1), elicited a chronic state of endothelium protection with sustained elevated levels of the EET-adiponectin-pAMPK-signaling pathway and amelioration of obesity-mediated hypertension. The permanent expression of HO-1, using an endothelial-specific promoter (LV-VECAD-HO-1), attenuated Ang II-induced hypertension but failed however to reduce blood pressure in obese mice. While targeting CYP-A4A2 increased hypertension. Targeting endothelial cells with CYP2J2, i.e., increased vascular EET, resulted in decreased obesity induced blood pressure in WT mice, while targeting HO-1 in the vascular system failed to decrease blood pressure in obese mice. It is not clear why LV-VECAD-HO-1 reduces Ang II-induced hypertension but not obesity while targeting vessels with 2J2 increases vascular EET protecting against obesity-induced hypertension. Currently, experiments are being performed to understand how adipocytes cross talk to vascular systems to modulate the levels of EET-HO-1-adiponectin to control the endothelial and adipocyte phenotype in relation to obesity and hypertension.

a. Cao J, Peterson SJ, Sodhi K, Vanella L, Barbagallo I, Rodella LF, Schwartzman ML, Abraham NG, Kappas A. Heme oxygenase gene targeting to adipocytes attenuates adiposity and vascular dysfunction in mice fed a high-fat diet. Hypertension 2012 Aug;60(2):467-75. PMCID:PMC3423899
b. Sodhi K, Wu CC, Cheng J, Gotlinger K, Inoue K, Goli M, Falck JR, Abraham NG, Schwartzman ML. CYP4A2-induced hypertension is 20-hydroxyeicosatetraenoic acid- and angiotensin II-dependent. Hypertension 2010 Nov;56(5):871-8. PMCID:PMC2995375
c. Cao J, Sodhi K, Inoue K, Quilley J, Rezzani R, Rodella L, Vanella L, Germinario L, Stec DE, Abraham NG, et al. Lentiviral-human heme oxygenase targeting endothelium improved vascular function in

angiotensin II animal model of hypertension. Hum.Gene Ther. 2011 Mar;22(3):271-82. PMCID:PMC3057195

d. Abraham NG, Sodhi K, Silvis AM, Vanella L, Favero G, Rezzani R, Lee C, Zeldin DC, Schwartzman ML. CYP2J2 targeting to endothelial cells attenuates adiposity and vascular dysfunction in mice fed a high-fat diet by reprogramming adipocyte phenotype. Hypertension 2014 Dec;64(6):1352-61. PMCID:PMC4230994

Complete List of Published Work in My Bibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/nader.abraham.1/bibliography/40704217/public/?sort=date&direction=descending

D. RESEARCH SUPPORT

Ongoing Research Support

5PO1 HL34300 Schwartzman, M. (PI) 9/01/05-8/31/15
Hormonal Regulation of Blood Pressure
Core C: Gene Transfer Core
Role: Core Leader
The objective of the Core C gene transfer is to provide the resources and expertise for the efficient generation of recombinant expression vectors and viruses genes for *in vitro* and *in vivo* studies proposed by the project investigators.

P01HL34300-26 Schwartzman (PI) 4/1/2011 – 3/31/2016
Hormonal Regulation of Blood Pressure
Project 3: HO-EET Regulation of Adipocyte Vascular Interactions Abraham (PI)

The goal of this project is to determine whether the cellular and molecular mechanisms governing adipocyte-vascular interactions will lead to the development of therapeutic strategies to fight vascular dysfunction and hypertension seen in obesity.

R01HL111877-04 Vazquez (PI) 12/15/2011-11/30/2015
Role of TRPC3 channels in molecular and cellular events of atherogenesis

Pending

P01HL34300-26 Schwartzman (PI) 6/1/2016 – 3/31/2021
Hormonal Regulation of Blood Pressure
Project 3: HO-EET Regulation of Adipocyte Vascular Interactions Abraham (PI)

Completed During the Last 3 Years:

RO1DK56601 Abraham (PI) 4/1/2010-03/30/15
Heme Oxygenase Regulation of Eicosanoid Biosynthesis
The goal of this project is to determine the molecular mechanism(s) whereby upregulation of vascular endothelial HO-1 ameliorates obesity-induced vascular dysfunction and to elucidate the role HO-1 interactions with cytoprotective pathways, including cytochrome P450-derived eicosanoids, EC-SOD and adiponectin-pAMPK signaling.