BIOGRAPHICAL SKETCH
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NAME: Sodhi, Komal

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

POSITION TITLE: Tenure-Track Associate 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
Mahatma Gandhi Memorial Medical College, Indore, India	MBBS (M.D)	01/2000	Medicine
Jaipur Golden Hospital, New Delhi, India	D.N.B (Residency)	01/2005	Family Medicine

A. Personal Statement

I have the necessary background and preparation to be considered as a future junior investigator for this COBRE, which is focused on cellular transport physiology in obesity related disorders. My principal research focus is to investigate contributions of chronic oxidative stress and metabolic imbalance as it pertains to the development of obesity, diabetes and metabolic syndrome with associated long-term complications. In this regard, I have looked at regulation of the cellular antioxidant defense system in patho-physiological states associated with chronic redox imbalance. My experimental model systems include animal models of fatty liver, hypertension, diabetes and metabolic syndrome and in vitro models of human mesenchymal stem cells, mouse hepatocytes, endothelial cells, vascular smooth muscle cells, and mouse pre-adipocytes. It has been reported previously that oxidative stress is an important component in the activation of Na/K-ATPase-mediated Src activation that further leads to ROS amplification. In this regard, studies from our laboratory have shown that Na/K-ATPase mimetic, pNaKtide peptide, restores cellular redox balance and suppresses inflammation. We have published recently that pNaKtide suppresses oxidative stress and adipogenesis in murine adipocytes and attenuates obesity, and improves insulin sensitivity and metabolic homeostasis in mice fed a high fat diet. In this proposal we aim to demonstrate that diet-induced obesity activates Na/K-ATPase signaling which creates an inflammatory and oxidative environment conducive to the development of NAFLD. We further propose that pNaKtide inhibits Na/K-ATPase/Src activation and reduces ROS, thereby, attenuates the development of steatohepatitis and progression to hepatic fibrosis while restoring metabolic balance. Veterans are frequently obese or overweight and experience the complications of obesity, such as diabetes and NAFLD. Given this extensive prevalence of obesity, diabetes and NAFLD among the veteran population, it is pivotal that we find alternate pathways to develop new and effective therapies to curtail these pathologies. One of the goals of this project is to delineate novel signaling pathways which may lead to NASH and hepatic fibrosis. This subsequently may lead to the development of new diagnostic biomarkers and therapeutic agents for NASH and hepatic fibrosis, but may also address obesity and diabetes, as they share a common etiology. My training under Drs. Nader G. Abraham and Joseph I. Shapiro, and my subsequent work will add immeasurably to the success of this proposal. My record of success and productivity is reflected by my publications. Since my arrival to Marshall University, I have independently mentored and supervised the research work of undergraduate, graduate students and postdoctoral fellows and have designed several projects for them that are successfully accomplished and are accepted for publications in high impact journals. My greatest achievement is that my recent manuscript has been accepted for publication in SCIENCE advances journal. My research projects have been diverse and have encompassed cell culture, animal models, molecular and cell biology and organotypic cultures. I have the necessary experience and

expertise and am well prepared to successfully complete this proposal in a timely manner at Marshall University.

B. Positions and Honors

Positions and Employment

2005-2006 Attending Physician, Jaipur Golden Hospital, New Delhi, India.
2008-2010 Post Doctoral Fellow, Department of Pharmacology, New York Medical College Valhalla, NY.
2010-2012 Research Associate, Department of Physiology & Pharmacology, The University of Toledo College of Medicine, Toledo, OH
2013- 2016 Assistant Professor, Department of Pharmacology/Surgery, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV
2016- present Associate Professor, Department of Pharmacology/Surgery, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Other Experience and Professional Memberships

1995-2001 Teaching of undergraduate students during my Internship.
2002-2006 Trained medical students, residents and the graduate students in the principals and practice of medicine, family medicine and surgery.
2008-present Trained a number of fellows, graduate and undergraduate students and postdoctoral fellows in the laboratory and classroom setting.
2010-present Lectures for advanced lecture series in CVMD graduate course.

Member American Heart Association
Member The American Physiological Society, USA

Editorial Board Member Journal of Pharmacogenomics & Pharmacoproteomics
Editorial Board Member Integrative Pharmaceutical Research
Editorial Board Member Current Updates in Endocrinology and Diabetes

Invited journal reviewer
Ad hoc manuscript reviewer for the International Journal of Hypertension
Ad hoc manuscript reviewer for Evidence-Based Complementary and Alternative Medicine
Ad hoc manuscript reviewer for the Journal of Clinical & Experimental Cardiology
Ad hoc manuscript reviewer for the Journal of Prostaglandins and Other Lipid Mediators
Ad hoc manuscript reviewer for International Journal of Biological Sciences
Ad hoc manuscript reviewer for the Journal of hypertension: Open access.
Ad hoc manuscript reviewer for the PLOS ONE
Ad hoc manuscript reviewer for Cell Proliferation

C. Contribution to Science

1. Oxidative stress is known to play a role in the generation and maintenance of an obesity phenotype in both isolated adipocytes and intact animals. Because Na/K-ATPase can amplify oxidant signaling, we studied a peptide designed to inhibit this pathway, pNaKtide, as it might ameliorate an obesity phenotype. Administration of pNaKtide to murine preadipocytes attenuated oxidant stress and lipid accumulation in a dose-dependent manner. Administration of pNaKtide in wild type mice reduced body weight gain, restored systemic redox and inflammatory milieu, and, crucially, improved insulin sensitivity. Thus, the inhibition of Na/K-ATPase amplification of oxidative stress may be a novel way to combat obesity, insulin resistance, and metabolic syndrome. This work was recently published in SCIENCE advances. Recently, we demonstrated that pNaKtide improved dyslipidemia and atherosclerosis in ApoE deficient mice fed a western diet.

a. Sodhi K, Kyle Maxwell, Yanling Yan, Jiang Liu, Muhammad A. Chaudhry, Morghan Getty, Zijian Xie, Nader G. Abraham, and Joseph I. Shapiro. pNaKtide Inhibits Na/K-ATPase Reactive Oxygen Species Amplification and Attenuates Adipogenesis. SCIENCE advances. 2015 Oct 16; 1(9): e1500781. doi: 10.1126/sciadv.1500781. eCollection 2015 Oct.
b. Srikanthan K, Shapiro JI, Sodhi K. The Role of Na/K-ATPase Signaling in Oxidative Stress Related to Obesity and Cardiovascular Disease. Molecules. 2016 Sep 3;21(9). pii: E1172. doi: 10.3390/molecules21091172. PMID: 27598118
c. Liu J, Tian J, Chaudhry M, Maxwell K, Yan Y, Wang X, Shah PT, Khawaja AA, Martin R, Robinette TJ, El-Hamdani A, Dodrill MW, Sodhi K, Drummond CA, Haller ST, Kennedy DJ, Abraham NG, Xie Z, Shapiro JI.. Attenuation of Na/K-ATPase Mediated Oxidant Amplification with pNaKtide Ameliorates Experimental Uremic Cardiomyopathy. NATURE Scientific Reports. 2016 Oct 4; 6:34592.doi:10.1038/srep34592. PMID: 27698370.
d. Sodhi K, Krithika Srikanthan, Perrine Gouget, Alexandra Nichols, Amrita Mallick, Preeya T. Shah, Saroj Sigdel, Mehiar El-Hamdani, Jiang Liu, Zijian Xie, Nader G. Abraham, and Joseph I. Shapiro. pNaKtide Attenuates Steatohepatitis and Atherosclerosis by Blocking Na/K-ATPase/Reactive Oxygen Species Amplification in Mouse Models of Metabolic Syndrome. Under review in NATURE Scientific Reports.

2. In addition to my research in basic science I am also involved in clinical research. My lab conducts clinically relevant, basic science research in close collaborations with basic scientists and clinicians. I have established extensive collaborations with various departments in Marshall University School of Medicine including, cardiology, pediatrics, nephrology, family medicine, surgery and oncology. Together, research novel methodologies and pathways to target diseases are of public health concern, especially in West Virginia; these include adult and childhood obesity, non-alcoholic fatty liver disease, diabetes and metabolic syndrome, hypertension, and drug-induced oncotoxicity.
    a. Adam Shaver, Alexandra Nichols, Ellen Thompson, Amrita Mallick, Kristen Payne, Shanmuga Sundaram, Joseph I. Shapiro, Sodhi K. Role of Serum Biomarkers in Early Detection of Diabetic Cardiomyopathy. Int J Med Sci. 2016
    b. Bracero L, Feyh A, Nichols A, Srikanthan K, Latif T, Preston D, Shapiro JI, Elitsur Y, Sodhi K. Role of Serum Biomarkers in Early Detection of Non-Alcoholic Steatohepatitis and Fibrosis in West Virginian Children. Journal of Clinical and Cellular Immunology.
    c. Feyh A, Bracero L, Lakhani HV, Santhanam P, Shapiro JI, Khitan Z, Sodhi K. Role of Dietary Components in Modulating Hypertension. J Clin Exp Cardiolog.
    d. Krithika Srikanthan, Andrew Feyh, Haresh Visweshwar, Shapiro JI, Sodhi K. Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population. Int J Med Sci.
    e. Yoram Elitsur, Deborah L Preston, Alexandra Nichols, Morghan Getty, Sodhi K. Insulin resistance is a key factor in the development of metabolic and inflammatory biomarkers in obese children. Pediatric Obesity.

3. One of my major research interests is the role that heme oxygenase (HO) plays in ameliorating obesity, hypertension, diabetes, and other features of metabolic syndrome. HO converts the pro-oxidant heme molecule into carbon monoxide and the antioxidant biliverdin. This research has focused on the oxidative stress-induced inflammatory processes that leads to adipocyte dysfunction, vascular dysfunction and altered metabolic profile, and the effect that HO-1 exerts on attenuating these processes. The research has also investigated novel treatment strategies involving HO upregulation, including lentiviral-mediated HO-1 gene therapy and CoPP-induced HO upregulation in various animal models treated with high fat/fructose diets and several in vitro models to attenuate metabolic imbalance. We believe, that HO represents a promising treatment pathway for the pro-oxidant and inflammatory processes that drive features of metabolic syndrome.
    a. Inoue K, Sodhi K, Puri N, Gotlinger KH, Cao J, Rezzani R, Falck JR, Abraham NG, Laniado-Schwartzman M. Endothelial-specific CYP4A2 overexpression leads to renal injury and hypertension via increased production of 20-HETE. American journal of physiology. Renal physiology. 2009; 297(4):F875-84. PMID: 19675180
    b. Sodhi K, Inoue K, Gotlinger KH, Canestraro M, Vanella L, Kim DH, Manthati VL, Koduru SR, Falck JR, Schwartzman ML, Abraham NG. Epoxyeicosatrienoic acid agonist rescues the metabolic

syndrome phenotype of HO-2-null mice. J Pharmacol Exp Ther. 2009 Dec;331(3):906-16. doi: 10.1124/jpet.109.157545. Epub 2009 Aug 28.

c. 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 (Dallas, Tex.: 1979). 2010; 56(5):871-8. NIHMSID: NIHMS252932 PMID: 20837888

d. Hinds,Jr. TD**,** Sodhi K, Meadows C, Fedorova L, Puri N, Kim DH, Peterson SJ, Shapiro J, Abraham NG, Kappas A. Increased HO-1 levels ameliorate fatty liver development through a reduction of heme and recruitment of FGF21. Obesity. Both Authors contributed equally.

e. Cao J, Sodhi K, Inoue K, Quilley J, Rezzani R, Rodella L, Vanella L, Germinario L, Stec DE, Abraham NG, Kappas A. 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. doi: 10.1089/hum.2010.059. Epub 2011 Jan 27. Both Authors contributed equally.

f. Cao J, Inoue K, Sodhi K, Puri N, Peterson SJ, Rezzani R, Abraham NG. High-fat diet exacerbates renal dysfunction in SHR: reversal by induction of HO-1-adiponectin axis. Obesity (Silver Spring). 2012 May;20(5):945-53. doi: 10.1038/oby.2011.365. Epub 2011 Dec 22. PubMed PMID: 22193921 (paid access 03/13/2013.

g. Vanella L, Kim DH, Sodhi K, Barbagallo I, Burgess AP, Falck JR, Schwartzman ML, Abraham NG. Crosstalk between EET and HO-1 downregulates Bach1 and adipogenic marker expression in mesenchymal stem cell derived adipocytes. Prostaglandins & other lipid mediators. 2011; 96(1-4):54-62. PMID: 21821145

h. Sodhi K, Hilgefort J, Banks G, Gilliam C, Stevens S, Getty M, Ansinelli H, Abraham NG, Shapiro JI, Khitan Z. Uric Acid-Induced Adipocyte Dysfunction is Attenuated by HO-1 Upregulation: Potential Role of Antioxidant Therapy to Target Obesity. Stem Cells International 2015.

i. Sodhi K, Puri N, Hyun Kim D, Hinds TD Jr, Stechschulte LA, Favero G, Rodella L, Shapiro JI, Jude D, Abraham NG. PPAR-delta binding to heme oxygenase 1 promoter prevents angiotensin II induced adipocyte dysfunction in goldblatt hypertensive rats. Int J Obes (Lond). 2013 Jun 19. doi: 10.1038/ijo.2013.116. PMID:23779049

j. Puri N, Zhang F, Monu SR, Sodhi K, Bellner L, Lamon BD, Zhang Y, Abraham NG,Nasjletti A. Antioxidants condition pleiotropic vascular responses to exogenous H(2)O(2): role of modulation of vascular TP receptors and the heme oxygenase system. Antioxid Redox Signal. 2013 Feb 10;18(5):471-80. doi: 10.1089/ars.2012.4587. Epub 2012 Sep 28. PubMed PMID: 22867102; PubMed Central PMCID: PMC3545357.

k. Khitan Z, Harsh M, Sodhi K, Shapiro JI, Abraham NG. HO-1 Upregulation Attenuates Adipocyte Dysfunction, Obesity, and Isoprostane Levels in Mice Fed High Fructose Diets. J Nutr Metab. 2014;2014:980547. PMCID: PMC4175747F

4. The SIRT1 deacetylase enzyme plays important role in cellular metabolism and cell cycle progression, and its activity can be related to cell differentiation and metabolic function. One of my major research interests involves the role SIRT1 plays on adipocyte function and hepatic lipid accumulation, which are two major aspects of metabolic syndrome. The study has indicated that SIRT-1 inhibits differentiation and proliferation of pre-adipocytes, an effect that is dependent upon antioxidant status. Our research demonstrated that SIRT1 activity increases in the presence of high antioxidant status, represented in one study by tempol treatment, and decreases in the presence of low antioxidant status, represented by heme. Additionally, we showed that HO activity, by reducing intracellular heme, results in upregulation of SIRT1 activity, which may provide an explanation to how HO, via SIRT1, can protect against facets of metabolic syndrome.

   a. Puri N, Sodhi K, Haarstad M, Kim DH, Bohinc S, Foglio E, Favero G, Abraham NG. Heme induced oxidative stress attenuates sirtuin1 and enhances adipogenesis in mesenchymal stem cells and mouse pre-adipocytes. J Cell Biochem. 2012 Jun;113(6):1926-35. doi: 10.1002/jcb.24061. PubMed PMID: 22234917; PubMed Central PMCID: PMC3360793.

   b. Sodhi K, Puri N, Favero G, Stevens S, Meadows C, Abraham NG, Rezzani R, Ansinelli H, Lebovics E, Shapiro JI. Fructose Mediated Non-Alcoholic Fatty Liver Is Attenuated by HO-1-SIRT1 Module in Murine Hepatocytes and Mice Fed a High Fructose Diet. PLoS One. 2015 Jun 22 10(6): e0128648.

doi: 10.1371/journal.pone.0128648. PubMed PMID: 26098879; PubMed Central PMCID: PMC4476565.

5. An equally exciting focus of my research entails examining HO-dependent regulation of eicosanoids and their physiological effects, particularly in the vasculature and perivascular adipocytes. I have studied the interaction between EET and HO-1 in regulation of vascular function. The central hypothesis focuses on heme oxygenase (the most potent anti- oxidant gene in human body)-adiponectin-EET plays an essential role in vascular function.

a. Sodhi K, Puri N, Inoue K, Falck JR, Schwartzman ML, Abraham NG. EET agonist prevents adiposity and vascular dysfunction in rats fed a high fat diet via a decrease in Bach 1 and an increase in HO-1 levels. Prostaglandinsn Other Lipid Mediat. 2012 Aug;98(3-4):133-42. doi: 10.1016/j.prostaglandins.2011.12.004. Epub 2011 Dec 24. PubMed PMID: 22209722; PubMed Central PMCID: PMC3449325.

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. doi: 10.1161/HYPERTENSIONAHA.110.154559. Epub 2010 Sep 13. PubMed PMID: 20837888; PubMed Central PMCID: PMC2995375.

c. Nader G. Abraham, Sodhi K, Silvis A, Vanella L, Favero G, Rezzani R, Zeldin D, 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. MS ID: HYPE201403884D. Both Authors contributed equally.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/14Ksgxpnz9lks/bibliography/48327596/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Marshall University Startup Fund: Marshall University Research Corporation 2013-present

Marshall University: Department of Surgery Research Fund Sodhi (PI) 2015-2016
Study of phenotypic alterations in obese and diabetic West Virginian population

The Edwards Foundation, Inc. Cancer Research Fund Sodhi (PI) 2015-2017
Creating biomarker panel for early detection of chemotherapy related metabolic dysfunction in West Virginian Patients