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NAME Joseph I. Shapiro, M.D.	POSITION TITLE Dean, Joan C. Edwards School of Medicine Professor of Medicine Marshall University
eRA COMMONS USER NAME (credential, e.g., agency login)	

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
University of Pennsylvania, Philadelphia, PA	BA	1972-76	Mathematics
UMDNJ-College of Medicine, Newark, NJ	MD	1976-80	Medicine
Georgetown University, Washington, DC		1980-83	Internal Medicine
University of Colorado, Denver, CO		1983-87	Nephrology

A. Personal Statement

I have been the Dean of the Joan C Edwards School of Medicine (JCESOM) since July of 2012. Prior to this position, I served as Chairman of Medicine at the University of Toledo for nearly 14 years. Despite these administrative positions, I have been an active researcher for my entire career. My research has focused on the intersection between kidney and cardiovascular disease, and I have been active in both bench and clinical research. In particular, I have participated as the enrollment chairman for the CORAL trial which has recently been concluded, and I remain extremely interested Na/K-ATPase signaling and its relevance to disease. My 4 most relevant papers to this COBRE application are:

1. Tian, J, S Haller, S Periyasamy, P Brewster, H Zhang, OV Fedorova, Z Xie, AY Bagrov, JI Shapiro and CJ Cooper. 2010. Renal ischemia regulates marinobufagenin release in humans. 56:914-9. PMID:20823380.
2. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, Prince MR, Lewis EF, Tuttle KR, Shapiro JI, Rundback JH, Massaro JM, D'Agostino RB, and Dworkin LD. 2014. Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. N.Engl.J.Med. 370:13-22. PMID: 24245566.
3. Sodhi K, Puri N, Favero G, Stevens S, Meadows C, Abraham NG, Rezzani R, Ansinelli H, Lebovics E, Shapiro JI. 2015, 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. e0128648. PMID: 26098879.
4. Sodhi, K, K Maxwell, Y Yan, J Liu, MA Chaudhry, M Getty, Z Xie, NG Abraham and JI Shapiro. 2015. pNaKtide Inhibits Na/K-ATPase Reactive Oxygen Species Amplification and Attenuates Adipogenesis. Science Advances. e1500761. PMID: 26601314

I am absolutely delighted to work with Dr. Sundaram who has developed an exciting application which will expand our understanding of diseases that plague our Appalachian region. I will do my best to provide help in any and all aspects of the proposed projects. To be very frank, I look at the COBRE application as the very best hope this institution has of rebuilding a pipeline of competitive biomedical scientists. As I believe this is core to the noble mission of this medical school, I will do everything in my power to ensure its success.

B. Positions and Honors

Positions:

University of Colorado: Director, Chronic Dialysis Service	1986-1991.
University of Colorado: Instructor in Medicine	1986-1987.
University of Colorado: Assistant Professor of Medicine	1987-1993.
University of Colorado: Co-Director NMR Spectroscopy	1989-1995.
University of Colorado: Co-Director Renal Transplant Physicians	1989-1997.
University of Colorado: Assistant Professor of Radiology	1989-1993.
Denver University: Adjunct Professor of Physics	1992-1997.
University of Colorado: Associate Professor of Medicine	1993-1997.
University of Colorado: Associate Professor of Radiology	1993-1997.
Denver VAMC: Director, Renal Transplant Service	1995-1997.
Denver VAMC: Section Head, Renal Diseases	1996-1997.
University of Toledo (formerly Medical College of Ohio at Toledo):	
Professor of Medicine & Physiology/Pharmacology	1997-2012.
University of Toledo: Renal Division Head	1997-1999.
University of Toledo: Interim Chairman of Medicine	1999-1999.
University of Toledo: Chairman of Medicine	1999-2012.
University of Toledo: Interim Chairman of Physiology	2004-2005.
University of Toledo: Associate Dean for Business Development	2006-2012.
University of Toledo Physicians, President	2011-2012.
Marshall University: Dean, College of Medicine	2012-present
Marshall University: Professor of Medicine	2012-present

Honors:

Pi Mu Epsilon (Mathematics honor society, 1974)
Graduated University of Pa. Magna cum Laude with distinction in Mathematics (1976).
University of Medicine and Dentistry of New Jersey: Alpha Omega Alpha (1980).
Georgetown University: Dudley P. Jackson Award (1983).
NIH fellowship award (1985-87).
American Heart Clinician-Scientist Award (1988-92).
American Heart Association Established-Investigator Award (1992-97).
Western Society for Clinical Investigation (1992).
Medical College of Ohio Internal Medicine Faculty Teaching Award (1998).
Central Society for Clinical Investigation (2000)
American Society of Nephrology (1999). Chairman, Dialysis Hemodynamics Abstract Selection Committee.
American Heart Association – Hypertension Fellow (2001).
American Heart Association – Kidney Disease Fellow (2001)
Fellow of the American College of Physicians (2001).
Arnold P. Gold – Healthcare Foundation of New Jersey Humanism in Medicine Award (2002).
Mercy Health Partners-Northern Region Endowed Chair of Excellence in Internal Medicine Education (2003).
Fellow of the American Society of Nephrology (2004).
St. Vs- UT Internal Medicine Excellence in Education Award (2009).
America's Top Doctors (2009-present).
America's Best Doctors (2009-present).
Castle Connolly Top Doctors (2012-present).
Phi Kappa Phi Honor Society (2013-present).
American Physiological Society Cardiovascular Fellow (2013-present).
Laurence Chan Endowed Lectureship. 2014 (Inaugural Lecture).
Harold J. Jeghers Memorial Lecture. 2015.

C. Contributions to Science

1. In vivo NMR spectroscopy applied to models of kidney disease. My first major contribution to Science occurred as the disciple of Drs. Laurence Chan and Robert W. Schrier in the development of in vivo NMR methods for studying renal biochemistry in living animals. This work applied to models acute kidney injury, chronic renal failure (section 3), urinary obstruction and renal transplant rejection is represented below.

1. Shapiro, J.I., and L. Chan. 1987. P-31 nuclear magnetic resonance study of urinary obstruction in the rat. *J. Clin. Invest.* 80:1422-1427. PMID1422-7.
2. Nakamoto, M., J.I. Shapiro, L. Chan, and R.W. Schrier. 1987. The invitro and invivo protective effect of atriopeptin III in ischemic acute renal failure in the rat. *J. Clin. Invest.* 80:698-705. PMID: 2957391.
3. Shapiro, J.I., C.E. Haug, R. Weil,III, and L. Chan. 1988. P-31 NMR study of renal allograft rejection in the rat. *Transplant.* 45:17-21. PMID: 3680505.
4. Burke, T.J., D. Malhotra and J.I. Shapiro. 2001. Effect of enhanced oxygen release from hemoglobin with RSR13 on acute renal failure in the rat. *Kidney Int.* 60:1407-1414.PMID: 11576354.

2. Molecular mechanisms causing organ dysfunction during metabolic acidosis and treatment. In the early 1980s, concern developed that treatment of metabolic acidosis with sodium bicarbonate might be deleterious. On this background, initially working with the late Dr. Giles Filley (famed physiologist and inventor of Carbicarb), we developed strategies for the measurement of intracellular pH in isolated organs and in vivo animals as well as performed studies during experimental metabolic acidosis. We were able to determine that "paradoxical" intracellular acidosis with sodium bicarbonate occurred in vitro and in vivo, and that Carbicarb (which was designed to be CO2 neutral over a range of infusion quantities) had beneficial effects in these settings. We subsequently were able to determine the molecular mechanism by which metabolic acidosis impaired cardiac energy metabolism and function.

1. Shapiro, J.I., M. Whalen, R. Kucera, N. Kindig, G. Filley, and L. Chan. 1989. Brain pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *Am. J. Physiol.* 256:H1316-H1321. PMID:2541632
2. Shapiro, J.I.: 1990. Functional and metabolic responses of the isolated heart to acidosis: Effects of sodium bicarbonate and Carbicarb. *Am. J. Physiol.* 258:H1835-H1839. PMID: 2163220.
3. Zhou, H.Z., D. Malhotra and J.I. Shapiro: 1991. Contractile failure during metabolic acidosis: role of impaired energy metabolism. *Am. J. Physiol.* 261:H1481-H1486. PMID: 1951735.
4. Suleymanlar, G., H.Z. Zhou, M. McCormack, N. Elkins, R. Kucera, O.K. Reiss and J.I. Shapiro. 1992. Mechanisms of impaired energy metabolism during acidosis role of oxidative metabolism. *Am. J. Physiol.* 263:H1818-H1822. PMID: 1621841.

3. Oxidant stress in chronic renal failure progression. The mechanisms by which chronic kidney injury appears to inexorably progress has been an important topic for some time. We (including Drs. Laurence Chan and Robert W. Schrier) were among the first to identify that the metabolic rate of the chronic renal failure kidney was increased an uncoupled from sodium transport. We have subsequently linked this to progressive renal fibrosis and our work with the Na/K-ATPase as a signal transducer (discussed below in sections 4 and 5).

1. Shapiro, J.I., D.C.H. Harris, R.W. Schrier, and L. Chan. 1990. Attenuation of hypermetabolism in the remnant kidney by dietary phosphate restriction in the rat. *Am. J. Physiol.* 258:F183-188. PMID:2301590.
2. Shapiro, J.I., N. Elkins, G. Suleymanlar, O.K. Reiss, H. Jin, R.W. Schrier, and L. Chan. 1994. Energy metabolism in chronic renal failure. *Kidney Int.* 45:S100-105. PMID:8158875.
3. Fedorova, L, V Raju, N El-Okdi, A Shidyak, S Vetteth, D Kennedy, S Vetteth, D Giovannucci, AY Bagrov, O Fedorova, JI Shapiro and D Malhotra. 2009. Cardiotonic steroid hormone marinobufagenin induces renal fibrosis: Implications of epithelial to mesenchymal transition. *Am.J.Physiol.* 296:F922-34. PMID: 1916701.
4. Haller, ST, CA Drummond, Y Yan, J Liu, J Tian, D Malhotra and JI Shapiro. 2013. Passive immunization against marinobufagenin attenuates renal fibrosis and improves renal function in experimental renal disease. Am.J.Hyperten. 27:603-9. PMID:24014658.

Briefly describe up to five of your most significant contributions to science. For each contribution, indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in the described work. For each of these contributions, reference up to four peer-reviewed publications that are relevant to that contribution. The description of each contribution should be no longer than one half page including figures and citations. Please also provide a URL to a full list of your published work as found in a publicly available digital database such as PubMed or My Bibliography, which are maintained by the US National Library of Medicine.

4. Scaffolding function of the Na/K-ATPase and its implications toward signaling, renal salt handling and hypertension. I am extremely proud to be part of the group that delineated the Na/K-ATPase-Src-EGFR-ROS signal cascade resulting from the scaffolding function of the alpha1 subunit of the Na/K-ATPase with Src. We were the first to identify this cascade and have worked for the better part of the last 20 years to define its role in pathophysiology. I must at this point admit that my colleague, Zijian Xie, conceived of the overall scaffolding function concept whereas my personal contributions were to uncover the ligand mediated endocytosis of the Na/K-ATPase and the potential role in renal sodium transport and hypertension (where Dr. Jiang Liu, a former fellow played a critical role) as well as to delineate the implications of this signal cascade to the subject of uremic cardiomyopathy (discussed below in section 5).

1. Liu, J., S.M. Periyasamy, W. Gunning, O.V. Fedorova, A.Y. Bagrov, D. Malhotra, Z Xie, and J.I. Shapiro. 2002. Effects of cardiac glycosides on sodium pump expression and function in LLC-PK1 and MDCK cells. *Kidney Int.* 62:2118-2125. PMID: 12427136.
2. Liu, J., M. Liang, L. Liu, D. Malhotra, Z. Xie, and J.I.Shapiro. 2005. Ouabain induced endocytosis of the plasmalemmal Na/K-ATPase in LLC-PK1 cells requires caveolin-1. *Kidney Int*. 67: 1844-1854. PMID: 15840032.
3. Liu, J, Y Yang, L Liu, Z Xie, DK Malhotra, B Joe, and JI Shapiro. 2011. Impaired ouabain-induced endocytosis of the Na/K-ATPase and NHE3 in proximal tubule characterizes Dahl salt-sensitive hypertension. J. Biol. Chem. 286:22806-13. PMID: 21555512.
4. Yan Y, Shapiro AP, Haller S, Katragadda V, Liu L, Tian J, Basrur V, Malhotra D, Xie ZJ, Abraham NG, Shapiro JI, Liu J. Involvement of reactive oxygen species in a feed-forward mechanism of Na/K-ATPase mediated signal transduction. 2013. J. Biol. Chem. 288:34249-58. PMID:24121502.

5. Role of cardiotonic steroid signaling in the pathogenesis of uremic cardiomyopathy. Back in the 1960s, Neil Bricker and others postulated that a circulating inhibitor of the Na/K-ATPase might be involved in the pathogenesis of progressive renal failure (see section 3 above) and the symptom complex of uremia. Our group, working with Drs. Alexei Bagrov and Olga Fedorova, have explored the role of the Na/K-ATPase signal cascade in the pathogenesis of the cardiomyopathic aspect of uremia (uremic cardiomyopathy). In particular, we have causally linked such signaling to the cardiac fibrosis which complicates uremic cardiomyopathy. We have also explored different novel therapies of this important clinical complication of chronic renal failure.

1. Kennedy, D., E. Omran, S. M. Periyasamy, J. Nadoor, A. Priyadarshi, J.C. Willey, D. Malhotra, Z. Xie and J.I. Shapiro. 2003. Effect of chronic renal failure on cardiac contractile function, calcium cycling and gene expression of proteins important for calcium homeostasis in the rat. *J.A.S.N.* 14:90-97. PMID: 12506141.
2. Kennedy, D.J., S. Vetteth, S.M. Periyasamy, M. Kanj, L. Fedorova, S. Khouri, M. B. Kahaleh, Z. Xie, D. Malhotra, N. Kolodin, E. G. Lakatta, O.V. Fedorova, A.Y. Bagrov and J.I. Shapiro. 2006. Central role for the cardiotonic steroid, marinobufagenin, in the pathogenesis of experimental uremic cardiomyopathy. *Hypertension*. 47:488-495. PMID: 16446397.
3. Elkareh, J, SM Periyasamy, A Shidyak, S Vetteth, J Schroeder, V Raju, I Hariri, N El-Okdi, S Gupta, L Fedorova, J Liu, O Fedorova, M Kahaleh, Z Xie, D Malhotra, D Watson, A Bagrov and JI Shapiro. 2009. Marinobufagenin Induces Increases in Procollagen Expression in a Process Involving Protein Kinase C and Fli-1. *Am. J. Physiol.* 296:F1219-26. PMID: 19261738.
4. Tian, J, A Shidyak, SM Periyasamy, S Haller, S Oweis, , M Taleb, N El-Okdi, J Elkareh, S Gupta, OV Fedorova, CJ Cooper, Z Xie, D Malhotra, AY Bagrov and JI Shapiro. 2009. Spironolactone attenuates uremic cardiomyopathy by antagonizing the signaling of cardiotonic steroids through the Na/K-ATPase. Hypertension. 54:1313-20. PMID: 19884563.

D. Research Support

List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). *Begin with the projects that are most relevant to the research proposed in the application.* Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.

N.I.H. RO1 (HL109015, 2011-2015) JI Shapiro and Z Xie Co-PIs. Receptor Na/K-ATPase Antagonists As Novel Therapeutics For Renal/Cardiac Diseases. In this project which is currently in a no-cost extension, the aim are to define the potential therapeutic role of novel antagonists which we've developed to the Na/K-ATPase signal cascade in the context of experimental models of uremic cardiomyopathy. My role is as a joint PI (it is a multiple PI application) focusing in particular on the experiments utilizing animal models. There is no budgetary or scientific overlap with the current proposal.

N.I.H. RO1 (2004-2012) Cardiovascular outcomes in renal atherosclerotic lesions (CORAL). PI Christopher Cooper, M.D., HL071556, National enrollment committee chairman and site co-PI, JI Shapiro, M.D. The objective of the CORAL study was to determine whether renal arterial stenting was advantageous to patients with atheromatous renal artery stenosis. In addition to being part of the team that conceived of this study, my primary role in the project was to serve as enrollment chairman for the project. There is no budgetary or scientific overlap with the current proposal.

N.I.H. RO1 (2011-2016, 250K per year.).Na/K-ATPase reduction in renal disease-related cardiac dysfunction. PI – Jiang Tian, PhD, Co-I JI Shapiro, MD. HL105649. The aims of this project are to define the roles of cardiotonic steroid induced apoptosis and other signaling events in the pathogenesis of uremic cardiomyopathy as well as examine potential linkage of such signaling to cardiovascular outcomes in the CORAL population. My primary role with this project is to oversee the clinical-translational components as well as provide insights related to my expertise with animal models of uremic cardiomyopathy. There is no budgetary or scientific overlap with the current proposal.