BIOGRAPHICAL SKETCH
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NAME: Shapiro, Joseph I

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

POSITION TITLE: Dean

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

A. Personal Statement

As Dean of the Joan C Edwards School of Medicine (JCESOM) since July of 2012, I am well positioned to support and participate in this COBRE, focused on cellular transport physiology in obesity related conditions, as a member of the Internal Advisory Committee (IAC) and Executive Committee of the IAC. Prior to my position as Dean at JCESOM, 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 mechanisms by which renal disease progresses and causes cardiovascular disease. During these investigations, I have, through my collaborations with Drs. Zijian Xie, Jiang Liu, Jiang Tian, Christopher Cooper. Komal Sodhi, James Willey and Nader Abraham, become interested in the role of ROS in Na/K-ATPase signaling and the potential for this signaling process to serve as a therapeutic target in renal and cardiovascular disease. Four of my most relevant papers to this proposal would include:

1. Yan, Y, AP Shapiro, S Haller, V Katragadda, L Liu, J Tian, V Basrur, D Malhotra, Z Xie, NG Abraham, JI Shapiro and J Liu. 2013.The Involvement of Reactive Oxygen Species in a Feed-Forward Mechanism of Na/K-ATPase Mediated Signaling. J. Biol. Chem. 288:34249-58. PMID: 24121502.
2. 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. 1:e1500781. PMID: 26601314.
3. 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 PMID: 26098879
4. 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. Sci Rep. 2016 Oct 4;6:34592. doi: 10.1038/srep34592 PMID: 27698370.

I would also emphasize that I have worked closely with the members of this research team for nearly 20 years. Several of my coinvestigators have finished their training and developed independent status during this time. I

am absolutely delighted to play a coordinating role with these investigators, all of whom I have come to know very well, as well as assume overall responsibility for this exciting project.

B. Positions and Honors

Positions and Employment

1986-1991	University of Colorado: Director, Chronic Dialysis Service
1986-1987	University of Colorado: Instructor in Medicine
1987-1993	University of Colorado: Assistant Professor of Medicine
1989-1995	University of Colorado: Co-Director NMR Spectroscopy
1989-1997	University of Colorado: Co-Director Renal Transplant Physicians
1989-1993	University of Colorado: Assistant Professor of Radiology
1992-1997	Denver University: Adjunct Professor of Physics
1993-1997	University of Colorado: Associate Professor of Medicine
1993-1997	University of Colorado: Associate Professor of Radiology
1995-1997	Denver VAMC: Director, Renal Transplant Service
1996-1997	Denver VAMC: Section Head, Renal Diseases

University of Toledo (formerly Medical College of Ohio at Toledo):

1997-2012	Professor of Medicine & Physiology/Pharmacology
1997-1999	University of Toledo: Renal Division Head
1999-1999	University of Toledo: Interim Chairman of Medicine
1999-2012	University of Toledo: Chairman of Medicine
2004-2005	University of Toledo: Interim Chairman of Physiology
2006-2012	University of Toledo: Associate Dean for Business Development
2011-2012	University of Toledo Physicians, President

2012-present	Marshall University: Dean, College of Medicine
2012-present	Marshall University: Professor of Medicine

Honors:

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

C. Contribution 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.
    a. 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.
    b. 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.
    c. 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.
    d. 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.
    a. 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
    b. 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.
    c. 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.
    d. 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).
    a. 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. P MID:2301590.
    b. 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.
    c. 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.
    d. 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.

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).
    a. Xie, Z., P. Kometiani, J. Liu, J.I. Shapiro and A. Askari. 1999. Intracellular reactive oxygen species mediate the linkage of Na+/K+-ATPase to hypertrophy and its marker genes in cardiac myocytes. *J. Biol. Chem.* 274:19323-8.
    b. 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.
    c. 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.
    d. Periyasamy, S.M., Liu, J., Tanta, T., Kabak, B., Wakefield, B., Malhotra, D., Nadoor, O., Fedorova, O.V., Gunning, W,, Xie, Z., Bagrov, A.Y., and Shapiro, J.I. 2005. Salt loading induces redistribution of the plasmalemmal Na/K-ATPase proximal tubule cells. Kidney Int. 67, 1868-1877.

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.
    a. 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.
    b. 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.
    c. 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.
    d. 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.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Zm8CXC1OsuAT/bibliography/49944523/public/?sort=date&direction=ascending

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

NIH 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.

NIH 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.

Completed Research Support

NIH 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.