BIOGRAPHICAL SKETCH

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NAME: Zhen Wang

eRA COMMONS USER NAME (credential, e.g., agency login): zhenwang3

POSITION TITLE: Assistant 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
Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	B.S.	06/1999	Medicine
Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China	M.S.	06/2004	Pharmacology
University of Arkansas for Medical Sciences, Little Rock, AR	Ph.D.	07/2012	Pharmacology
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS	Postdoctoral Fellow	01/2014	Physiology

A. Personal Statement

My major research interest is to understand the pathophysiology of diabetic cardiovascular diseases and to determine the molecular mechanisms of target organ injury induced by diabetes, hypertension, and obesity. My early research project was to study the mechanism of renal microcirculatory failure during sepsis-induced acute kidney injury. My research was extended to a broader area in my postdoctoral training to reveal how the CNS leptin signaling pathway differentially regulates blood pressure and metabolism in obesity. My academic training and research experiences have provided an excellent background in multiple biological disciplines, including molecular biology, pharmacology, and physiology. During my postdoctoral training, I developed my own project that was funded by NIDDK for a K99/R00 grant to examine the synergistic interactions of hypertension and diabetes in promoting kidney injury.

During the last few years as a PI, my research focused on investigating how ER stress and mitochondrial dysfunction contribute to hypertensive-diabetic induced target organ injury, including nephropathy, cardiomyopathy, and neuropathy. We developed reliable surgery techniques to establish a unique diabetic-hypertensive animal model in both rats and mice. We also generated a new TRPC6 flox mouse strain to delete the TRPC6 gene with specific Cre expression in different tissues. Most importantly, comprehensive experimental methods have been established that allow us to examine physiological functions, such as GFR, cardiac systolic and diastolic function, and whole-body metabolic profiles, as well as to explore detailed molecular mechanisms such as TRPC6 activation, mitochondrial function, mitochondrial DNA variants, and cellular stress response in both *in vivo* and *in vitro* studies. Our compelling preliminary data indicate that global knockout of TRPC6 protects against diabetic-hypertensive glomerular injury. Therefore, in the current application, we will use novel genetically engineered mouse models and pharmacological interventions to examine whether overactivation of TRPC6 mediates mitochondrial injury and apoptosis in podocytes that contribute to the renal injury in kidneys exposed to diabetes+hypertension. The results from this proposal will advance our understanding of the

pathogenesis of diabetic nephropathy, and may provide a new therapeutic target to prevent/halt progressive CKD.

Ongoing and recently completed projects:

P20GM10435 (COBRE pilot grant) John Hall (PI) 07/01/2019

Title: Role of TRPC6 channels in mediating cardiac injury in hypertension combined with diabetes

4R00DK113280-02 Zhen Wang (PI) 08/01/2018 - 07/31/2022

Title: Synergistic interactions of hypertension and diabetes in promoting kidney injury.

K99DK113280-01 Zhen Wang (PI) 05/15/2017 - 05/14/2018

Title: Synergistic interactions of hypertension and diabetes in promoting kidney injury.

B. Positions, Scientific Appointments, and Honors

Positions and Employment

ACTIVITY/ OCCUPATION	START DATE MM/YYYY	END DATE MM/YYYY	FIELD	INSTITUTION/ COMPANY
Medical Technologist	06/1999	03/2001	Pathology	Landing Early Cancer Diagnosis Center
Research Assistant	6/2005	6/2007	Molecular Biology	Cardiology Division, Department of Internal Medicine, University of Arkansas for Medical Sciences
Instructor	01/2014	07/2018	Physiology	Department of Physiology and Biophysics, University of Mississippi Medical Center,
Assistant Professor	08/2018	Present	Physiology	Department of Physiology and Biophysics, University of Mississippi Medical Center,

Other Experiences and Professional Memberships

2008-2012 American Society for Pharmacology and Experimental Therapeutics
2012- American Heart Association
2012- American Physiological Society

Academic and Professional Honors

2014 Showcase presentation in the KCVD Young Investigator Symposium, ASN, Kidney Week, 2014
2015 APS Caroline tum Suden/Francis A. Hellebrandt Professional Opportunity Award, Experimental Biology, 2015
2017 Trustmark Postdoctoral Publication Award, School of Graduate Studies in the Hearth Sciences

C. Contributions to Science

1. Early career: My graduate research was focused on understanding the biochemical and physiological mechanisms triggered by sepsis that lead to cellular injury and organ failure in animal models of sepsis-induced acute kidney injury. I found that the development of oxidative stress in the peritubular capillary

microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. I also reported new therapeutic approaches to prevent sepsis-induced renal injury by targeting Sphingosine-1-Phosphate receptor 1 and mitochondrial-generated ROS production. During my Ph.D. studies, I developed a new technique with intravital video microscopy to assess mitochondrial oxidant production and measure peritubular capillary perfusion *in vivo.* I also learned techniques for measuring renal blood flow, glomerular filtration rate in the mouse, and immunohistochemistry/immunofluorescence techniques.

1. **Zhen Wang**, Christan Herzog, Gur P. Kaushal, Neriman Gokden, Philip R. Mayeux. Actinonin, a meprin A inhibitor, protects the renal microcirculation during sepsis. *Shock.* 2011 Feb;35(2):141-147.
2. Joseph H. Holthoff, **Zhen Wang**, Kathryn A. Seely, Neriman Gokden, Philip R. Mayeux. Resveratrol improves renal microcirculation, protects the tubular epithelium and prolongs survival in a mouse model of sepsis-induced acute kidney injury. *Kidney Int*. 2012 Feb;81(4):370-378.
3. **Zhen Wang**, Joseph H. Holthoff, Kathryn A. Seely, Horace J. Spencer, III, Neriman Gokden, Philip R. Mayeux. Development of oxidative stress in the peritubular capillary microenvironment mediates sepsis-induced renal microcirculatory failure and acute kidney injury. *Am J Pathol.* 2012 Feb;180(2):505-516.
4. **Zhen Wang**, Clark R. Sims, Naeem K. Patil, Neriman Gokden and Philip R. Mayeux. Pharmacological Targeting of Sphingosine-1-Phosphate Receptor 1 Improves the Renal Microcirculation During Sepsis in the Mouse. *J Pharmacol Exp Ther.* 2015 January:352:61–66.

2. Postdoctoral/ Instructor Training: During my postdoctoral period, my project was to examine the role of negative regulators of leptin signaling (SOCS3) in modulating leptin's metabolic and cardiovascular functions in POMC neurons. I found that selective deletion of SOCS3 in POMC neurons amplifies the blood pressue response to a high-fat diet and acute stress but has minimal effects on metabolic functions. From this project, I gained more experience in animal surgical procedures and measuring cardiac-renal function.

1. Nicola Aberdein, Robert J Dambrino, Jussara M. do Carmo, **Zhen Wang**, Laura E Mitchell, Heather A Drummond, and John E. Hall. Role of PTP1B in POMC neurons during chronic high-fat diet: sex differences in regulation of liver lipids and glucose tolerance. *Am J Physiol-Regulatory, Integrative and Comparative Physiology*. 2018; Mar 1;314(3):R478-R488
2. Jussara M. do Carmo, Alexandre A. da Silva, John Nathan Freeman, **Zhen Wang**, Sydney P. Moak, Michael W. Hankins, Heather A. Drummond, John E. Hall. Neuronal SOCS3 (Suppressor of Cytokine Signaling 3) Role in Modulating Chronic Metabolic and Cardiovascular Effects of Leptin. *Hypertension*. 2018; 71:00-00
3. **Zhen Wang**, Jussara M. do Carmo, Alexandre A. da Silva, Kandice C. Bailey, Nicola Aberdein, Sydney P. Moak, and John E. Hall. Role of SOCS3 in POMC Neurons in Metabolic and Cardiovascular Regulation. *Am J Physiol-Regulatory, Integrative and Comparative Physiology.* 2019; 316: R338–R351.

3. Junior faculty: My current research projects focused on investigating the molecular mechanisms of hypertensive-diabetic induced target organ injury. I found that hypertension interacts synergistically with diabetes to promote renal injury by initiating a positive feedback loop including mitochondrial dysfunction, ER stress, and oxidative stress. I also found that deletion of TRPC6 markedly attenuated renal dysfunction and reduced apoptotic cell injury in glomeruli exposed to hyperglycemia and high blood pressure. I am now extending my research to a more broad area to investigate the role of TRPC6 channels in mediating metabolic abnormality in multiple organs, including kidney, heart, and brain, in diabetes, hypertension and obesity.

1. **Zhen Wang**, Jussara M. do Carmo, Nicola Aberdein, Xinchun Zhou, Jan M. Williams, Alexandre A. da Silva, John E. Hall. Synergistic Interaction of Hypertension and Diabetes in Promoting Kidney Injury and the Role of Endoplasmic Reticulum Stress. *Hypertension.* 2017; May;69(5):879-891.
2. John Hall, Jussara do Carmo, Alexandre da Silva, **Zhen Wang**, and Michael Hall. Obesity, kidney dysfunction and hypertension: mechanistic links. *Nature Reviews Nephrology.* 2019; 15(6):367-385.
3. **Zhen Wang**, Jussara M. do Carmo, Alexandre A. da Silva, Yiling Fu and John E. Hall. Mechanisms of synergistic interactions of diabetes and hypertension in chronic kidney disease: role of mitochondrial dysfunction and ER stress. *Current Hypertension Reports.* 2020. Feb 3;22(2):15.

4. Shashank Shekhar, Yedan Liu, Shaoxun Wang, Huawei Zhang, Xing Fang, Jin Zhang, Letao Fan, Baoying Zheng, Richard J Roman**, Zhen Wang**, Fan Fan, George W Booz. Novel Mechanistic Insights and Potential Therapeutic Impact of TRPC6 in Neurovascular Coupling and Ischemic Stroke. *Int J Mol Sci.* 2021 Feb 19;22(4):2074
5. Jussara M. do Carmo, Ana C. M. Omoto, Xuemei Dai, Sydney P. Moak, Gabriela S. Mega, Xuan Li, **Zhen Wang**, Alan J. Mouton, John E. Hall, and Alexandre A. da Silva. Sex differences in the impact of parental obesity on offspring cardiac SIRT3 expression, mitochondrial efficiency and diastolic function early in life. *Am J Physiol-Heart Circ Physiol*. 2021 Sep 1;321(3):H485-H495.
6. **Zhen Wang,** Jussara M. do Carmo, Alexandre A. da Silva, Yiling Fu, Lance T. Jaynes, Jaylan Sears, Xuan Li, Alan Mouton, Ana Carolina M. Omoto, , and John E. Hall. Transient receptor potential cation channel 6 (TRPC6) deficiency leads to obesity and metabolic dysfunction. *Am J Physiol-Regu.* Revision
7. **Zhen Wang**, Yiling Fu, Jussara M. do Carmo, Alexandre A. da Silva, Xuan Li, Alan Mouton, Ana Carolina M. Omoto, Jaylan Sears, and John E. Hall. Transient receptor potential cation channel 6 contributes to kidney injury induced by diabetes and hypertension. *Am J Physiol Renal Physiol.* 2022 Jan 1;322(1):F76-F88..

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1497cnWDxtw/bibliography/40776773/public/?sort=date&direction=ascending