BIOGRAPHICAL SKETCH

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NAME: **Liu, Ruisheng**

eRA COMMONS USER NAME (credential, e.g., agency login): **RUILIU1**

POSITION TITLE: **Professor of Physiology**

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
Jining Medical College, China	M.D.	06/1982	Medicine
Shandong Medical University, China	M.S.	06/1991	Cardiology
Uppsala University, Sweden	Ph.D.	01/2002	Physiology & Cell Biology
Henry Ford Hospital, Detroit MI	Postdoctoral	03/2006	Physiology

A. Personal Statement

The research of our laboratory has been focused on three major areas. The first area involves studying renal physiology and pathophysiology and determine the renal mechanisms of hypertension, including alterations in renal hemodynamics, sodium reabsorption and excretion and Na/K-ATPase activity, especially the significance of tubuloglomerular feedback (TGF) response in physiological and pathophysiological conditions.

The second area focuses on exploring the mechanisms and identifying potential therapeutic targets for kidney diseases,including acute kidney injury, chronic kidney disease, hypertensive kidney disease, diabetic nephropathy, and glomerulonephritis.

The third area involves utilizing solid organ transplantation models in rodents and adult Yorkshire pigs to identify novel approaches for improving donor graft function and protecting against remote organ injury after transplantation.

The techniques used in our laboratory include microperfusion of kidney tubules and arterioles *in vitro*, micropuncture *in vivo*, molecular biology, cell biology, genomic and proteomic analysis including single cell gene profiling, targeted delivery approach with nanoparticles, solid organ transplantations in rodent and swine models, synchronization modulation electric filed (SMEF), systemic hemodynamic measurement, tissue specific genetic engineering strategies, and translation approach using human samples and organs.

Experience as a Mentor: During the past years, the trainees in my laboratory have successfully obtained many research awards, including 6 summer research fellowships from APS, 4 summer research fellowships from AHA, 2 pre-doctoral awards from AHA, 3 post-doctoral fellowship awards from AHA, 2 post-doctoral awards from ASN, 1 career development award from AHA, 2 transition to independence research grants from ASN, and 3 R01 grants as ESIs from NIH.

Ongoing Research Support

R01DK138092
Liu (MPI, Contact)
NIH/NIDDK
04/01/2024—03/31/2029

Protection of donor kidney and transplanted graft function by modulating Na/K ATPase activity.
The major goal of this project is to examine the significance of SMEF on marginal organs and transplanted graft function in rodent and porcine kidney transplantation models.

R01DK134000
Liu (MPI, contact)
04/01/2023—03/31/2028
Treatment of lupus nephritis with nanoparticles that selectively target kidney glomeruli.
The major goal of this project is to develop a nanoparticle delivery system that selectively targets kidney glomeruli. The therapeutic significance of this system will be tested in a lupus mouse model.

R01DK134028
Liu (PI)
08/29/2022—04/30/2026
Tubuloglomerular feedback response in AKI to CKD transition.
The major goal of this project is to examine the significance of tubuloglomerular feedback in control of renal hemodynamics in AKI to CKD transition.

B. Positions, Scientific Appointments, and Honors

Positions:

2024 –	Director, University of South Florida (USF) - Tampa General Hospital (TGH) Transplant Research Center (UTRC), USF Health, USF, Tampa FL
2014 –	Professor, Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, USF, Tampa FL
2020 –	Co-founder, WR Biotech LLC
2010 – 2014	Associate Professor, Department of Physiology & Biophysics, Director, Renal Microcirculatory Central Laboratory, Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, Jackson MS
2008 – 2010	Assistant Professor, Department of Physiology & Biophysics, University of Mississippi Medical Center, Jackson MS
2006 – 2008	Senior Staff Investigator, Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit MI
2002 – 2006	Postdoctoral Fellow / Associate Staff Investigator, Henry Ford Hospital, Detroit MI
1998 – 2002	Ph.D. Student, Uppsala University, Uppsala Sweden
1991 – 1998	Cardiologist, Cardiology Department, Shandong Province Hospital
1988 – 1991	Fellowship, Cardiology Department, Shandong Medical University, Master's Degree Cardiology, China
1982 – 1988	Resident, Physician, Internal Medicine, Guangrao Hospital of Dongying City, China

Scientific Appointments:

2021 – 2023	Member, PBKD study section/NIH
2019 –	Member, Editorial Board of Kidney360, American Society of Nephrology
2016 –	Member, Editorial Board of *Hypertension*
2018 – 2022	Co-Chair/Chair, Awards Committee of Water & Electrolyte Hemostasis Section (WEH) of the American Physiological Society (APS)
2018 – 2022	Member, Steering Committee of WEH/APS
03/2018	Reviewer, Special Emphasis Panel ZRG1 DKUS, NIH/NIDDK
10/2018	Reviewer, CSR Anonymization Study, NIH
11/2018	Reviewer, Special Emphasis Panel ZRG1 DKUS-L (11)B, NIH/NIDDK
2015 – 2021	Member, Grant Review Committee, American Society of Nephrology
2015 – 2020	Ad hoc reviewer, NIH KMBD study section
2014 – 2016	Member, Cardiorenal 1 grant review committee, American Heart Association
2013 –	Member, Editorial Board of *American Journal of Physiology – Renal Physiology*

2012 – Fellow, American Heart Association (FAHA)
2012 – Fellow, American Society of Nephrology (FASN)
2003 – Member, American Physiological Society
2001 – Member, American Society of Nephrology
1998 – Member, American Heart Association

Honors:

2009 Excellence in Research Gold Award, University of Mississippi Medical Center
2005 Young Investigator Award, Inter-American Hypertension Society
2004 New Investigator Award for U.S. Fellows, American Heart Association
2003 New Investigator Travel Award, American Heart Association

C. Contributions to Science

We have published **31** research papers in peer-reviewed journals during the past **5** years.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/16a3itF7dCOAL/bibliography/public/

1. **Identifications of isoforms of NAD(P)H oxidase and NOS1 splice variants in the macula densa. Physiological significance of TGF responsiveness in long-term control of sodium excretion and blood pressure:** We identified the isoforms of NAD(P)H oxidase that expressed in the macula densa are NOX2 and NOX4 with laser capture microdissection and real time PCR. We found that increases of tubular NaCl enhances superoxide (O-) generation from NOX2 in the macula densa. In Ang II-induced hypertension, both NOX2 and NOX4 contribute to the O-2 generation by the macula densa. NOX2 and NOX4 are activated by intracellular pH in a Rac dependent pathway.

   We identified the α and β splice variants of NOS1 are expressed in the macula densa. We demonstrated that NOS1β is the primary splice variant that contributeto the NO generation by the macula densa. To determine the in vivo physiological role of NOS1β and TGF, we generated a macula densa specific NOS1 knockout mouse strain. These KO mice have enhanced TGF responsiveness. In response to acute slat loading, GFR response and salt-water excretionare impaired in the KO mice compared with the controls. These KO mice develop salt-sensitive hypertension following a high salt diet and gestational hypertension during pregnancy.
   a. Zhang R, Harding P, Garvin JL, Juncos R, Peterson E, Luis A. Juncos LA, **Liu R**. Isoforms andfunctions of NAD(P)H oxidase at the macula densa. *Hypertension* 53,556-563,2009
   b. Lu D, Fu Y, Lopez-Ruiz AF, Zhang R, Juncos R, Liu H, Manning RD Jr, Juncos LA, **Liu R**. Saltsensitive splice variant of nNOS expressed in the macula densa cells. PMCID: PMC2886819, *Am J Physiol Renal Physiol.* 298,F1465-1471,2010
   c. Lu Y, Wei J, Stec DE, Roman RJ, Ge Y, Cheng L, Liu EY, Zhang J, Hansen PBL, Fan F, Song J,Juncos LA, Wang L, Pollock, J, Huang PL, Fu Y, Wang S, **Liu R**. Macula densa NOS1β protects againstsalt-sensitive hypertension. PMCID: PMC4978040, *J Am Soc Nephrol.* 27, 2346-2356, 2016
   d. Wei J, Zhang J, Jiang S, Xu L, Qu L, Pang B, Jiang K, Wang L, Intapad S, Buggs J, Cheng F, Mohapatra S, Juncos LA, Osborn JL, Granger JP, **Liu R**. Macula Densa NOS1β Modulates Renal Hemodynamics and Blood Pressure during Pregnancy: Role in Gestational Hypertension. *J Am Soc Nephrol.* 32(10):2485-2500, 2021

2. **Significance of TGF response in renal hemodynamics and kidney injury in diabetes:** We have explored the significance of renal hemodynamics in diabetes. A novel mechanism for glomerular hyperfiltration in diabetes has been identified. We found that tubular glucose activates macula densa SGLT1, which enhances NOS1 activityand NO generation (SGLT1-NOS1-TGF pathway). This mechanism increases GFR and promotes the development of glomerular hyperfiltration in type 1 and type 2 diabetes.
   a. Zhang J, Jiang S, Wei J, Yip KP, Wang L, Lai EY, **Liu R**. Glucose Dilates Renal Afferent Arteriolesvia Glucose Transporter-1. *Am J Physiol Renal Physiol.* 315, F123-F129, 2018
   b. Zhang J, Wei J, Jiang S, Xu L, Wang L, Cheng F, Buggs J, Koepsell H, Vallon V, **Liu R**. Macula densa SGLT1-NOS1-Tubuloglomerular feedback pathway, a new mechanism for glomerular hyperfiltration

during hyperglycemia. *J Am Soc Nephrol.* 30(4), 578-593,2019.

c. Zhang J, Wang X, Cui Y, Jiang S, Wei J, Chan J, Thalakola A, Le T, Xu L, Zhao L, Wang L, Jiang K, Cheng F, Patel T, Buggs J, Vallon V, **Liu R**. Knockout of Macula Densa Neuronal Nitric Oxide Synthase Increases Blood Pressure in db/db Mice. *Hypertension.*78(6):1760-1770, 2021.

d. Zhang J, Cai J, Cui Y, Jiang S, Wei J, Kim YC, Chan J, Thalakola A, Le T, Xu L, Wang L, Jiang K, Wang X, Wang H, Cheng F, Buggs J, Koepsell H, Vallon V, **Liu R**. Role of the macula densa sodium glucose cotransporter type 1-nitric oxide synthase 1-tubuloglomerular feedback pathway in diabetic hyperfiltration. *Kidney Int.* 2021 Nov 26. PubMed PMID: 34843754. [Epub ahead of print]

3. **Ischemic acute kidney injury, chronic kidney disease, and transplanted renal graft function:** We have been working on the significance of renal hemodynamics and ischemia reperfusion injury in acute kidney injury (AKI), chronic kidney disease (CKD) and AKI to CKD transition. We have performed allograft kidney transplantation in rodents, with a focus on the role of ischemia reperfusion injury on the transplanted graft function.

   a. Wang L, Song J, Wang S, Buggs J, Zhang J, Wei J, **Liu R**. Cross-sex transplantation altersgene expression and enhances inflammatory response in the transplanted kidneys. *Am J Physiol Renal Physiol.* 313, F326-F338, 2017.

   b. Wang L, Wang X, Qu HY, Jiang S, Zhang J, Buggs J, Wei J, **Liu R**. The role of kidneys in sexdifferences in Ang II-induced hypertension. *Hypertension*, 70, 1219-1227, 2017.

   c. Wang L, Wang X, Jiang S, Wei J, Buggs J, Fu L, Zhang J, **Liu R**. Graft function assessment in mouse models of single- and dual- kidney transplantation. *American journal of physiology. Renal physiology.* 315, F628-F636, 2018

   d. Zhang J, Wang X, Wei J, Wang L, Jiang S, Xu L, Qu L, Yang K, Fu L, Buggs J, Cheng F, **Liu R**. A two-stage bilateral ischemia-reperfusion injury-induced AKI to CKD transition model in mice. PMCID: PMC7528400, *Am J Physiol Renal Physiol*. 319:F304-F311, 2020.

4. **Regulation of Na^+/K^+ ATPase (Na/K pump) activity with synchronization modulation electric field (SMEF):** We have developed a novel technique named SMEF that controls the Na/K ATPase activity.

   The 2nd generation of SMEF first synchronizes the pump molecules running at the same pace, and then continuously and alternatively facilitates two ion-transports by a well-designed oscillating electric field. The SMEF can increase or decrease Na/K pump activities to pre-determined values. In kidneys, Na^+/K^+-ATPase is highly expressed on the basolateral surface in tubules. The Na^+ gradient and negative membrane potential generated by the Na/K pump are the driving force for cotransporters and antiporters in reabsorption of Na^+ and other solutes such as glucose, bicarbonate, and amino acids, as well as secretion of K^+, H^+ and phosphate. Therefore, the activities of the Na/K pumps in kidneys are essential in maintenance of electrolyte, acid-base and volume homeostasis.

   The 3rd generation of SMEF not only controls the Na/K pump activity, but also generates ATP molecules. By utilizing the intrinsic dual energy transform functions of the Na/K pumps, we specially designed the 3rd generation of SMEF to control Na/K pump activity. Meanwhile, the electric field provides adequate energy to the pump molecules so that they can synthesize one ATP molecule for each pumping cycle. Consequently, the 3rd generation of SMEF can maintain the Na/K pumping activity in situations with an insufficient or lack of ATP supply, such as in hypoxia during kidney transplantation, ischemic kidney injury, or chronic kidney disease.

   a. Chen W, Wang L, Liang P, Mast J, Clausel M, Liu C, Zhang J, Fu L, Juncos L, Buggs J, **Liu R**. Reducing ischemic kidney injury through application of a synchronization modulation electric field to maintain Na^+/K^+-ATPase functions. *Science Translational Medicine.* 9;14(635):eabj4906. doi: 10.1126/scitranslmed.abj4906, 2022

   b. Patent (pending): SYSTEM AND METHOD UTILIZING ELECTRIAL ENERGY TO FUEL AND ACTIVATE ION TRANSPORT WITHOUT CONSUPTION OF ADENOSINE TRIPHOSPHATE (ATP) MOCLECULES: CLINICAL ISCHEMIA APPLICATION ON KIDNEYS
   Inventors: Wei Chen and **Ruisheng Liu**, Filing date: March 17, 2021, Serial #: 63/162,169.

5. **Development of selective kidney glomerulus targeting nanoparticles:** Collagen IV (Col4)-α3,4 and 5 are expressed in the glomerular basement membrane (GBM), the only site in the body where Col4 has direct contact with blood via fenestrated capillary endothelium. Liposomes are one of the most widely used carriers due to their excellent biocompatibility and non-immunogenicity, but they lack stability in terms of leakage of the encapsulated contents. Tripolyphosphate (TPP) cross-linked chitosan nanoparticles are characterized by controlled release of the payload, but with limited stability in the biological fluids. By coupling Col4 binding peptides on the shell of liposomes encapsulating chitosan-TPP nanoparticles, we

have generated a glomerulus selective delivery system Col4-LC-NP with stable and sustained release of the payloads at the glomerulus capillary endothelium and GBM. This nanoparticle system loaded with different drugs would offer potent site-specific treatments with minimized systemic side effects for different glomerulopathies, In addition, this system marked with different fluorescent dyes may also serve as a new tool for evaluation of functional nephron numbers in vivo with CT or MRI scanning.

a. Patent (Pending): A METHOD OF TREATING KIDNEY DISORDERS BY GLOMERULI-TARGETED NANOTHERAPEUTICS.
Inventors: Shyam Mohapatra and **Ruisheng Liu**, Filing date: May 4, 2021, Disclosure # 21A075.