

T.H.K.C.E.

TULANE HYPERTENSION AND RENAL CENTER OF EXCELLENCE Fall 2019 Volume 18.

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NEW DIRECTOR OF THRCE



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New Director Of THRCE

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Jia L. Zhuo, MD, PhD, will join as the new Director of Tulane Hypertension and Renal Center of excellence beginning February 2020. Dr. Zhuo, will be moving from the University of Mississippi Medical Center in Jackson, Mississippi where he was a tenured Professor in the Department of Pharmacology and Toxicology, and Director of the Receptor and Signal Transduction Laboratory. Dr. Zhuo has over 30 years' of sponsored

research experience on the roles of endocrine, paracrine, and intracrine angiotensin II in the kidney and hypertension. He has authored more than 110 peer-reviewed articles and book chapters. Dr. Zhuo is a Fellow of the American Association for the Advancement of Science (AAAS), American Heart Association (AHA), and American Society of Nephrology (ASN). He is also a permanent member for NIH/Center for Scientific Review Hypertension and Microcirculation Study Section. His research is currently supported by grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of General Medical Sciences (NIGMS), and National Heart, Lung, and Blood Institute.

TULANE PHYSICIANS RECIPIENTS OF THE JAMES B. HERRICK AWARD

Dr. Paul Whelton and Dr. Keith Ferdinand, two Tulane physicians affiliated with the Tulane Hypertension and Renal Center of excellence, were recipients of the prestigious James B. Herrick Award for their outstanding contribution to the field of cardiology and cardiovascular research. The nationally recognized honor was presented during the Council on Clinical Cardiology Annual Dinner and Business Meeting at the 2019 AHA Scientific Sessions held at the Pennsylvania Convention Center on November 17, 2019.

THRCE CO-Sponsors 2020 Mayerson DiLuzio Lecture



News

Bina Joe, PhD, FAHA, FAPS, Distinguished University Professor & Chair, and Founding Executive Director for the Center for Hypertension and Precision Medicine at the Toledo University in Ohio has been selected to present the coveted 2020 Mayerson-DiLuzio Lectureship at Tulane University for her outstanding research and studies in hypertension. She will present her lecture on March 23, 2020.

Dr. Joe received a National level Research Fellowship from the Council for Scientific and Industrial Research in India and obtained her Ph.D. in Biochemistry from the University of

Mysore in 1996. After a brief postdoctoral position at the Indian Institute of Science, she worked in AstraZeneca India before moving to NIH as an International Fogarty Research Scholar. There she began working on the genetics of complex diseases using rat models. In 2001, Dr. Joe was appointed as an Assistant Professor and rose to the rank of full Professor in 2008. She became Chair of the Department in 2015 and in 2017 was honored with the Distinguished University Professorship.

Dr. Joe's research on the genetics of hypertension is funded through multiple grants from the National Heart Lung and Blood Institute. She works predominantly with the Dahl Salt-sensitive (S) and Dahl Salt-resistant (R) rats that were inbred at her Institution by her predecessor Prof. Rapp. Through sustained substitution mapping and systems biology approaches, Dr. Joe's laboratory has identified multiple genomic loci linked to hypertension. Her most recent work has identified that variants of genes linked to hypertension in rats that are also genetically associated with human essential hypertension. Dr. Joe continues to serve as a member of several NIH study sections since 2005. She has also served as an International reviewer for the Medical Research Council of UK, the Czech Republic and the WELLCOME trust. In 2010, she was honored with the Young Scholar's Award from the American Society of Hypertension. In 2012, Dr. Joe became the founding Director of the Center for Hypertension and Personalized Medicine at the University of Toledo College of Medicine and Life Sciences in Toledo, OH, USA. Dr. Joe is also head the Program in Physiological Genomics within the Center which is focused on understanding the genetic components of pathophysiological conditions of the cardiovascular system.

The Mayerson-DiLuzio Lectureship was established in 1990 to honor the memories of Drs. Hyman S. Mayerson and Nicholas R. Di Luzio, who presided as Chairmen of the Tulane Physiology Department.

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Kidney disease is a non-communicable disease (NCD) and currently affects around 850 million people worldwide. One in ten adults has chronic kidney disease (CKD). CKD is an ever-growing global burden that is now projected to become the 5th most common cause of premature deaths by 2040. Kidney disease can be prevented and progression to end-stage kidney disease can be delayed with appropriate access to basic diagnostics and early treatment, however globally, and especially in the poorest countries, sufficient access to information, education, and awareness about kidney disease as well as CKD screening, management and treatment is still lacking. The 2020 World Kidney Day will be held on March 12 and runs a global health communication campaign that focus on "Prevention" with the theme: Kidney Health for Everyone Everywhere – from Prevention to Detection and Equitable Access to Care. The goal is to globally share kidney health awareness on the importance of preventive interventions to avert the onset and progression of CKD, and provide kidney health information and tools to allow people establish healthy life-styles and lead healthier lives.

IN HONOR OF WKD, THRCE HAS SCHEDULED TWO SPECIAL EVENTS ON MARCH 12TH



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• During the World Kidney Day, the THRCE, the Department of Physiology, the Department of Medicine (Section of Nephrology), and the National Kidney Foundation of Louisiana, will conduct a "**Tulane WKD Health Screening Fair**" in the Lobby of Tulane University Hospital and Clinics. This free program will be held from 9am until 3pm, and is designed to screen people at risk for CKD and promote CKD awareness among the public. Participants will be screened for blood pressure & the risk for developing kidney disease.

• At 4pm, a **Special WKD THRCE Seminar** will be presented by the new Director of THRCE, Dr. Jia L. Zhuo. The Special Seminar will be held in the Pharmacology Conference room, 4700, at Tulane University, School of Medicine.

HONORS & RECOGNITION AWARDED TO THRCE AFFILIATED INVESTIGATORS

Patrice Delafontaine, MD:

• Executive Dean at Tulane University School of Medicine, was appointed as Adjunct Professor in the Department of Physiology in July 2019.

Andrei Derbenev, PhD:

- Appointed Directorship of the Neuroscience PhD Program at the Tulane Brain Institute from July 2019.
- Awarded the Tulane Brain Institute Marko Spark Innovation Research Fund.

Kathleen Hering-Smith, PhD:

• Along with co-investigators, Drs. Batuman, Abdulnour-Nakhoul, and Nakhoul, received an equipment grant from the Tulane Research Advisory Committee to purchase an EVOS Imaging System.

Jean-Pyo Lee, PhD:

- Participated, on December 10, in a Podcast for the American Journal of Physiology (AJP)-Heart Circulatory Physiology as a scientific expert in the field, "Angiogenic Exosomes from Vascular Progenitor Cells."
- Participated in an NIH Study section in Chicago, IL in October 2019.
- Selected as the Star Reviewer by the Editor of the AJP-Heart and Circulatory Physiology.
- On June 27, was highlighted in "Tulane Today" for receiving a \$2.4 million R01 grant from NINDS.
- Participated in an NIH study section in Washington, DC in June 2019.
- Selected as Abstract Reviewer for the 2019 International Stroke Conference.
- Selected as Guest Editor for Experimental Neurology.
- Editorial board member of "AJP-Heart Circulation Physiology" Journal.

Kenneth D. Mitchell, PhD:

• Nominated for the 2019 Owl Club's "Best Phase 1 Course" Award.

Honors & Recognition Awarded to THRCE Affiliated Investigators, continued...

Dewan S. A. Majid, MD, PhD:

- Recipient of the Marquis Who's Who's "Albert Nelson Marquis Lifetime Achievement" Award.
- Served as a Research Faculty for LBRN (Louisiana Biomedical Research Network) Program. He mentored the LBRN Summer Research Scholar, Ms. Chikaodil Osuji, who is an undergraduate student from Southern University of New Orleans. LBRN Summer Research Program is supported by NIH/National Institute of General Medical Sciences (NIGMS)'s IDeA Networks of Biomedical Research Excellence.
- Awarded the Carol Lavin Bernick grant in June 2019.
- Awarded Pilot Project grant by the Research Advisory Committee of the Tulane School of Medicine.

Nazih Nakhoul, PhD:

• Along with co-investigators, Drs. Batuman, Abdulnour-Nakhoul, and Hering-Smith, received an equipment grant from the Tulane Research Advisory Committee to purchase an EVOS Imaging System.

L. Gabriel Navar, PhD:

- Selected by the American Physiological Society as the 4th recipient of the "A. Clifford Barger Underrepresented Minority Mentorship Award" that will be presented at the EB 2020 meeting scheduled for April 4-7 in San Diego.
- Recipient of the Marquis Who's Who's "Albert Nelson Marquis Lifetime Achievement" Award.
- Hosted the IASH Executive Committee Meeting held in Tulane University on September 4, 2019.
- Presented, "Purinergic P2X receptor & angiotensin AT1 receptor interactions in the regulation of preglomerular renal microcirculation in angiotensin II dependent hypertension" at the APS/ASN Conference on Renal Function in Health and Disease held in Charlottesville, VA in June 2019.
- Awarded a Carol Lavin Bernick grant in June 2019.
- Presented the IASH Symposium titled, "The intratubular intracellular renin-angiotensin system in hypertension and diabetes" and "Augmentation of intrarenal angiotensinogen in hypertension and diabetes" on May 2019 at the 2nd Pan American Physiological Sciences Congress held in Havana, Cuba.

Honors & Recognition Awarded to THRCE Affiliated Investigators, continued...

- Co-chaired the Symposium: Novel Thoughts Open New Windows into the Function of the Intrarenal Renin-Angiotensin System in Cardiovascular Diseases, at the 2nd Pan American Physiological Sciences Congress.
- The Department's "Physiology Course" was nominated for the 2019 Owl Club's "Best Phase 1 course" Award.

Kailash N. Pandey, PhD:

- Attended the Council of Basic Cardiovascular Sciences, American Heart Association meeting in Boston, held in July 2019.
- Awarded a Carol Lavin Bernick grant in June 2019.
- Presented on April 24, 2019, "The recent developments in the field of molecular signaling mechanisms of natriuretic peptides and their receptor systems in the health and disease," at the Department of Microbiology in Gargi College in Delhi, India. Gargi College is affiliated to Delhi University.

Minolfa C. Prieto, MD, PhD:

- Awarded a Pilot Project grant by the Dean's research awards Committee of the Tulane School of Medicine.
- Presented on May 2019, "Recent advances in the biology of the RAS in the distal nephron in hypertension" & "Impact of the interactions of renin, prorenin receptor, and soluble prorenin receptor in cardiovascular diseases" at 2nd Pan American Physiological Sciences Congress held in Havana, Cuba.
- Co-chaired a session at the 2nd Pan American Physiological Sciences Congress titled, Novel Thoughts Open New Windows into the Function of the Intrarenal Renin-Angiotensin System in Cardiovascular Diseases.

Ryosuke Sato, PhD:

- Awarded a Pilot Project grant by the Research Advisory Committee of Tulane School of Medicine.
- Received an equipment award from the Tulane Research Advisory Committee to purchase a Biorad Chemidoc Imaging instrument for the Molecular and Imaging Core of THRCE.

Weijian Shao, PhD:

• Received the service award for his 20 years of service at Tulane.

Honors & Recognition Awarded to THRCE Affiliated Investigators, continued...

T. Cooper Woods, PhD:

• Nominated for the 2019 Owl Club's "Best Phase 1 Professor" Award.

Andrea Zsombok, PhD:

- Invited as keynote speaker at the upcoming 2020 Experimental Biology Meeting that will be held in San Diego, California in April 2020. The talk, "Hypothalamic preautonomic neurons in diabetes" is scheduled to be presented in the session: "New advance in autonomic control of metabolic homeostasis."
- Awarded the Tulane Brain Institute Marko Spark Innovation Research Fund.
- Co-authored a paper with Dr. Eric Lazartigues that was featured as a "High Impact Paper" in Hypertension's Summer Collection. The paper was titled, "Activation of ADAM17 (A Disintegrin and Metalloprotease 17) on Glutamatergic Neurons Selectively Promotes Sympathoexcitation."
- Nominated for the 2019 Owl Club's "Best Phase 1 CBL Facilitator" Award.

Undergraduate, Graduate, & Postdoctoral Fellows:

- Postdoctoral Fellow, Dr. Supaporn (Tom) Kulthinee (Mentor: Dr. Navar):
 - Awarded the Kidney Council New Investigator Travel Award and the Paul Dudley White International Scholar Award for her abstract, "Purinergic P2X receptors and AT1 receptors share post-receptor signaling pathways regulating renal afferent arterioles in angiotensin II dependent hypertension" that she presented on September at the 2019 AHA Hypertension Scientific Sessions held at the New Orleans Marriott.
- Postdoctoral Fellow, Dr. Bruna Visniauskas (Mentor: Dr. Prieto):
 - Presented her abstract, "The Association between Plasma Soluble Prorenin Receptor and Renin Activity Renin Emphasizes the Effects of Angiotensin System Activation on Cardiovascular Complications in Women with Type
 2 Diabetes" for which she was awarded both the AHA Kidney Council New Investigator Travel Award and the Paul Dudley White International Scholar Award. The presentation was held at the 2019 AHA Hypertension Sessions held in New Orleans.
- Graduate student, Owen Richfield (Mentor: Dr. LG Navar):
 - Presented, "Shear stress is normalized while hoop stress is elevated in the

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Honors & Recognition Awarded to THRCE Affiliated Investigators, continued...

diabetic rat glomerulus: A Modeling Study" at the APS/ASN Conference on Renal Function in Health and Disease held in Charlottesville, VA in June 2019.

- Chaired a session at the 2019 APS Meeting on Interface of Math Models and Experimental Biology: Role of the Microvasculature Conference held in Scottsdale, AZ on September 13, 2019. The session was title, Structural adaptation and angiogenesis in microcirculatory pathways. During the session he also presented, "Glomerular capillary shear stress and hoop stress are significantly elevated in 5/6-nephrectomy: A modeling study."
- Undergraduate student, Jennifer Hong (Mentor, Dr. Prieto):
 - Selected First place winner for the SSCI Young Investigator Award for her abstract entitled: "Soluble Prorenin receptor (sPRR) is Associated with Type 2 Diabetes in Women."

UPCOMING MEETINGS & EVENTS:

• Southern Regional Meeting 2020 of the Joint Society Members (SSCI, SAFMR, SSGIM, SSPR, APA, ASN)

~ New Orleans, LA, February 13-15, 2020.

- 19th Annual SSCI Nephrology Young Investigator's Forum
 ~ New Orleans, LA, February 12, 2020.
- Tulane WKD Health Screening Fair
 ~ Lobby of Tulane University Hospital and Clinics, NOLA, March 12, 2020.
- Special WKD THRCE Seminar
 ~ Tulane University Pharmacology Conference room, NOLA, March 12, 2020.
- Tulane University 31st Annual Health Sciences Research Days
 ~ New Orleans, Louisiana, March 11-12, 2020.
- Distinguished Mayerson-DiLuzio Lectureship
 ~ Department of Physiology, Tulane University, NOLA, March 23, 2020.
- 2020 Experimental Biology Meeting
 ~ San Diego, CA, April 4-7, 2020.
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2019 Student Research Program

Each year meritorious Medical, Graduate, and Undergraduate Research Students are selected to work with faculty researchers affiliated with the Tulane Hypertension & Renal Center of Excellence. Students selected are exposed to the valuable nature of a career path in research. While most students work during the summer, some continue their research experience beyond their summer break and into their next academic year.

The following students selected for the 2019 Student Research Program received sponsored stipend during the 8 to 10 weeks they worked:

MEDICAL STUDENTS:

Sponsor: ASPIRE grant award

- **Annie Bell** Mentor: Dr. Gabriel Navar (Additional support: Bourgeois Award)
- Mardeen Karim Mentor: Dr. Olan Jackson-Weaver
- Stephanie McNamara
 Mentor: Mentor: Dr. Andrea Zsombok

Sponsor: DeBakey Scholar

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- **Alexander Cao** Mentor: Dr. Hongju Wu
- Anna Hodges Mentor: Dr. Solange Abdulnour-Nakhoul

Sponsor: Warren R. Bourgeois III, M.D. and Usha Ramadhyani Bourgeois, M.D. Student Research Endowed Fund

- **Stacy Yanofsky** *Mentor: Dr. Ryosuke Sato (Additional support: Departmental Research Grant)*
- Annie Bell Mentor: Dr. Gabriel Navar (Additional support: ASPIRE Grant Award) Mentor: Dr. Solange Abdulnour-Nakhoul

UNDERGRADUATE STUDENT:

Sponsor: Louisiana Biomedical Research Network

Chikaodilil Osuji Mentor: Dr. Dewan S. A. Majid Student: Southern University of New Orleans

The following graduate and undergraduate students volunteered with Tulane faculties as research investigators to acquire valuable research experiences and skills. Although their time was volunteered, their research study was supported by their mentor.

GRADUATE STUDENT:

Valeria Noguera Mentor: Dr. Kailash Pandey (MS student in Structural and Cellular Biology)

UNDERGRADUATE STUDENTS:

- Robert Drury Mentor: Dr. Olan Jackson-Weaver
- Maribeth Harlan Mentor: Dr. Olan Jackson-Weaver (Started July 2019)
- Jacob Packer Mentor: Dr. Olan Jackson-Weaver
- Mark Legendre Mentor: Dr. Olan Jackson-Weaver Student: University of Notre Dame
- Rudy Neustadt Mentor: Drs. T. Cooper Woods

THRCE SPONSORED PRESENTATIONS

Speakers who present a THRCE Seminar-sponsored presentation are asked to provide a brief summary of their talk that we can share with our newsletter audience. From May through December 2019, the following speakers presented THRCE-sponsored seminars:



News

LEIF OXBURGH, PHD

Professor of Medicine, Cell, Molecular & Developmental Biology, Tufts University School of Medicine, Scientific Director & Vice President for Basic & Clinical Research The Rogosin Institute, New York, NY.

Dr. Leif Oxburgh presented the Kathy Newman Pediatrics Research Seminar that was sponsored by both THRCE and the Department of Pediatrics. The talk, "Understanding the Niche that Controls Nephron Specification" was presented on May 16th 2019.

SUMMARY OF PRESENTATION:

The kidney provides several physiological functions essential to the survival of mammals: in addition to its role as an excretory organ, it controls blood pressure and the production of red blood cells. Consequences of loss of function are therefore multifaceted and severe, frequently requiring replacement therapy in the form of dialysis and/or transplantation. Although the kidney is endowed with a tremendous surplus capacity, and the ability to regenerate following acute injury, kidney disease resulting in functional impairment is very common. The research by Dr. Oxburgh and his study group focuses on understanding the complex series of control mechanisms governing embryonic development of this organ, and on reproducing these events in culture with the goal of generating new kidney tissue from stem cells. Bone Morphogenetic Protein (BMP) signaling is central to both of these processes, and in ongoing studies using primary cell culture, genetic models, and disease models his group is exploring how this signaling pathway acts in the fetal kidney and in human kidney tissue derived from pluripotent stem cells.



SNEZANA PETROVIĆ, MD, PHD, FASN

Assistant Professor, Department of Internal Medicine, Section on Gerontology and Geriatrics, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC.

On Thursday June 13th 2019, the Dean's Office of Tulane School of Medicine and THRCE Co-Sponsored a presentation by Dr. Snežana Petrović titled "Dietary acid load, kidney function and disability in older adults: Current evidence and future directions."

SUMMARY OF PRESENTATION:

Effective, well-tolerated, and inexpensive interventions are needed to reduce disability among older adults given that 40% of adults >65 years of age report one or more limitations in an activity of daily living that decreases quality of life and increases health care costs in this population. Oral bicarbonate supplementation is potentially one such intervention based on evidence that titrating diet-dependent metabolic acid load with bicarbonate may improve physical function, slow progression of chronic kidney disease (CKD), and ameliorate high risk of disability associated with CKD. Dr. Petrović's presentation reviewed the link between diet-dependent metabolic acid load, kidney disease, and disability. Pre-requisites for broader testing of oral bicarbonate supplementation as an intervention that may ameliorate/prevent aging-associated decline in kidney function and mobility disability was discussed at the seminar.



KRISZTIAN STADLER, PHD Associate Professor Oxidative Stress & Disease Laboratory Pennington Biomedical Research Center Baton Rouge, LA

"Mitochondrial substrate overload and chronic kidney disease" was presented at the Physiology Seminar Series by Dr. Krisztian Stadler. The presentation was held on Monday, June 24th, 2019 and was co-sponsored by THRCE and the Department of Physiology.

SUMMARY OF PRESENTATION:

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Diabetic kidney disease (DKD) is one of the most devastating complications of diabetes. Treatment options are limited and many of the patients develop end-stage renal disease requiring costly dialysis which is also detrimental to their life quality. The kidney is a very complex organ consisting of at least 16 different cell types. An important question therefore is: Which cell type(s) is/are the primary target(s) in metabolic disease? So far, the majority of research focused on the glomeruli and podocytes, suggesting that DKD is primarily a glomerular disease. In his seminar, Dr Stadler detailed new research from his laboratory supporting the notion that DKD can also originate from tubular abnormalities. Proximal tubular epithelial cells are highly energy demanding. Such energy need is covered mostly from mitochondrial fatty acid oxidation. It is suggested, but not entirely clear whether derailments in fatty acid metabolism and mitochondrial dysfunction are forerunners of tubular damage. Dr Stadler's laboratory modeled substrate excess and mitochondrial overload - an important aspect of metabolic disease and diabetes - by creating mice lacking the enzyme carnitine acetyl-transferase (CrAT) in the PTC, thus limiting a primary mechanism to export carbons under conditions of substrate excess. Mice developed tubular disease and interestingly, secondary glomerulosclerosis. This was accompanied by increased levels of apoptosis, increased oxidative stress and abnormal profiles of fatty acid, amino acid and carbohydrate metabolism. Primary PTCs isolated from the knockout mice displayed energy deficit and impaired respiration before the onset of pathology. Next

generation sequencing analysis from cortices at different time points revealed dysregulation of genes related to mitochondrial function, suggesting mitochondrial respiratory abnormalities as one potential underlying mechanism. In summary, Dr Stadler concluded that these findings support the hypothesis that derailments of mitochondrial substrate metabolism may be causative to kidney disease. The results also suggest that tubular injury may be a primary event in diabetes, raising the possibility that focusing on normalizing tubular cell metabolism could be an important preventative strategy.



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DULCE CASARINI, PHD Professor, Department of Medicine, Discipline of Nephrology Escola Paulista De Medicina Universidade Federal de São Paulo São Paulo, Brazil.

Dr. Dulce Casarini presented, "Association between 90 kDa N-domain ACE and presence of arterial hypertension," at the Physiology Seminar that was co-sponsored by THRCE and the Department of Physiology. The presentation was held on Monday, September 9th, 2019.

SUMMARY OF PRESENTATION:

Hypertension is a worldwide public health problem and the Renin Angiotensin System (RAS) has been a focus of researchers in the area of hypertension. To identify the components involved in the onset of hypertension and the involvement of angiotensin converting enzyme (ACE) in this problem, RAS has been the object of many studies. ACE converts angiotensin I into angiotensin II, a potent vasoconstrictor. Studies by Dr. Casarini's research group suggested the association of ACE isoforms, especially the 90 kDa N-domain isoform, with hypertension. The objective of their study was to investigate the association between ACE isoforms and the presence of arterial hypertension in the second phase of the prospective study (MONICA Project) in the population of Vitória - ES, Brazil. The demographic, clinical and biochemical parameters of 220 individuals were evaluated. Urine

samples collected with inhibitors were concentrated and ACE isoforms were identified by the Western Blotting technique. The groups were classified as Group 1 (presence of isoforms with 65, 90 and 190 KDa); Group 2 (65 and 90 kDa N-domain isoforms) and Group 3 (65 and 190 kDa isoforms). The results showed a high prevalence of the 90 kDa isoform with a higher incidence of hypertension (higher in Group 2) after five years of segment. The groups containing 90 kDa N-domain isoform showed higher systolic and diastolic pressure profiles in the second phase and the frequency of normotensives expressing the isoforms with 65 and 190 kDa was higher than that the hypertensive ones. Loss of isoform expression at 190 kDa increases the chances of developing hypertension as well as family history of hypertension. The results suggest the 90-kDa N-domain isoform as a possible biological marker of hypertension, which confirms the results obtained in the first phase of the study. The association of the presence of this isoform with environmental and metabolic factors may contribute to the development of this disease, emphasizing the importance of this isoform as a biological marker of hypertension.

As a marker for diagnosis, prognosis and appropriate treatment, it may have a potential for modifying the evolution of renal and cardiovascular diseases, which will allow preventive treatment of patients, thus preventing the worsening of the disease or preventing the onset of the disease associated with the stimulus quality of life.



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IAN SMYTH, PHD

Professor & Deputy Head (Research), Department of Anatomy and Developmental Biology Co-Head, Development and Stem Cells Program Monash Biomedicine Discovery Institute, Monash University Melbourne, Victoria, Australia.

Dr. Ian Smythe presented the Kathy Newman Pediatrics Research Seminar on Thursday October 31st. The presentation, "Making your Kidneys & Keeping them Happy – Understanding the Development & Homeostasis of the Renal Collecting Duct System," was co-Sponsored by THRCE and the Department of Pediatrics.

SUMMARY OF PRESENTATION:

Kidney development is driven by the outgrowth and branching of the ureteric bud, a structure fated to form the urine collecting duct system. The tubules built by the ureteric bud are also the site of cyst formation in patients suffering from polycystic kidney disease (PKD). Dr. Smythe's research group have profiled the morphogenetic development of the renal collecting ducts and studied how this process integrates with other cell populations to build the kidney. Using the mouse as a model, they have shown that the basic architecture of the kidney is established early on in development but that nephron formation occurs later in this process. A major focus of these studies was to attempt to model this process mathematically and to understand how it contributes to establishing the normal complement of nephrons. Using a number of different mathematical approaches they were able to show that while branching morphogenesis in the kidney was not completely stereotyped, an underlying pattern characterizes this process and is likely driven by the interaction between cells at the tips of the branching UB structure. These interactions serve to suppress branching events in neighboring tips. Taken together, this suggests an overarching developmental program which regulates normal renal development and specifies nephron endowment in the organ.

While the collecting duct system is required to build a normal kidney, several key cell signaling molecules are necessary to maintain it after birth - many of which are perturbed in patients with PKD. One of these is Aurora Kinase A, a multifunctional mitotic kinase. Dr. Smythe's laboratory have shown that genetic deletion (but not drug based kinase inhibition) of this protein is able to prevent the development of renal cysts in a mouse model of a recessive human ciliopathy known as Joubert Syndrome. The mechanism for this suppression appears to be through AKT signaling, as suppression of cyst growth can also be achieved by AKT inhibition. This work identifies a new pathway important for the development of renal cysts. Whether this also includes common diseases such as autosomal dominant PKD remains the subject of ongoing investigation.

Recent Publications

Includes publications that acknowledges either COBRE grant, THRCE center, or one of the center's CORE facilities.

- Bullen AL, Katz R, Lee AK, Anderson CAM, Cheung AK, Garimella PS, Jotwani V, Haley WE, Ishani A, Lash JP, Neyra JA, Punzi H, Rastogi A, Riessen E, Malhotra R, Parikh CR, Rocco MV, Wall BM, Bhatt UY, Shlipak MG, Ix JH, Estrella MM. The SPRINT trial suggests that markers of tubule cell function in the urine associate with risk of subsequent acute kidney injury while injury markers elevate after the injury. *Kidney Int.* 2019 Aug;96(2):470-479. doi: 10.1016/j.kint.2019.03.024. PMID: 31262489/PMCID: PMC6650383.
- Cargill K, Hemker SL, Clugston A, Murali A, Mukherjee E, Liu J, Bushnell D, Bodnar AJ, Saifudeen Z, Ho J, Bates CM, Kostka D, Goetzman ES, Sims-Lucas S. Von Hippel-Lindau Acts as a Metabolic Switch Controlling Nephron Progenitor Differentiation. J Am Soc Nephrol. 2019 Jul;30(7):1192-1205. doi: 10.1681/ ASN.2018111170. PMID: 31142573/PMCID: PMC6622426.
- Franco M, Pérez-Méndez O, Kulthinee S, Navar LG. Integration of purinergic and angiotensin II receptor function in renal vascular responses and renal injury in angiotensin II-dependent hypertension. *Purinergic Signal*. 2019 Jun;15(2):277-285. doi: 10.1007/s11302-019-09662-5. PMID: 31183668/PMCID: PMC6635571.
- Foy CG, Newman JC, Berlowitz DR, Russell LP, Kimmel PL, Wadley VG, Thomas HN, Lerner AJ, Riley WT; SPRINT Study Research Group. Blood Pressure, Sexual Activity, and Erectile Function in Hypertensive Men: Baseline Findings from the Systolic Blood Pressure Intervention Trial (SPRINT). *J Sex Med.* 2019 Feb;16(2):235-247. doi: 10.1016/j.jsxm.2018.12.007. PMID: 30655182/PMCID: PMC6444897.
- Gonsalez SR, Cortês AL, Silva RCD, Lowe J, Prieto MC, Silva Lara LD. Acute kidney injury overview: From basic findings to new prevention and therapy strategies. *Pharmacol Ther.* 2019 Aug;200:1-12. doi: 10.1016/j.pharmthera.2019.04.001. *Epub* 2019 Apr 6. Review. PMID: 30959059.
- Jotwani VK, Lee AK, Estrella MM, Katz R, Garimella PS, Malhotra R, Rifkin DE, Ambrosius W, Freedman BI, Cheung AK, Raphael KL, Drawz P, Neyra JA, Oparil S, Punzi H, Shlipak MG, Ix JH; for the SPRINT Research Group. Urinary Biomarkers of Tubular Damage Are Associated with Mortality but Not Cardiovascular Risk among Systolic Blood Pressure Intervention Trial Participants with Chronic Kidney Disease. *Am J Nephrol.* 2019;49(5):346-355. *doi:* 10.1159/000499531. PMID:30939472/PMCID: PMC6491265.
- Kemp BA, Howell NL, Keller SR, Gildea JJ, Shao W, Navar LG, Carey RM.. Defective Renal Angiotensin III and AT2 Receptor Signaling in Prehypertensive Spontaneously Hypertensive Rats. J Am Heart Assoc. 2019 May 7;8(9):e012016. doi: 10.1161/JAHA.119.012016. PMID: 31039659/PMCID: PMC6512109.

- Lee AK, Katz R, Jotwani V, Garimella PS, Ambrosius WT, Cheung AK, Gren LH, Neyra JA, Punzi H, Raphael KL, Shlipak MG, Ix JH. Distinct Dimensions of Kidney Health and Risk of Cardiovascular Disease, Heart Failure, and Mortality. *Hypertension*. 2019 Oct;74(4):872-879. doi: 10.1161/HYPERTENSIONAHA.119.13339. *Epub* 2019 Aug 5. PMID: 31378102/PMCID: PMC6739187.
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- Castillo A, Talwar S, Abdel-Mageed AB, Ekpo PE, Majid DSA. Nitric Oxide Inhibition Enhances the Protein Expression of TNF-α Receptor Type 1 in Cultured M -1 Cells With Characteristics of Renal Collecting Duct Epithelium. *Hypertension*, 2019;74:AP2039.
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APS/ASN Renal Summer Conference: Control of Renal Function in Health & Disease, Jun. 23-27 / Charlottesville, VA

- Kulthinee S, Shao W, Brand G, Franco M, Navar LG. Purinergic P2X receptor and angiotensin AT1 receptor interactions in the regulation of preglomerular renal microcirculation in angiotensin II dependent hypertension. #12.4.
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AHA Hypertension 2019 Scientific Sessions, Sept. 5–7 / New Orleans, LA

- Egan B, Li J, Sutherland S, Jones D, Hong Y, Ferdinand K, Sinopoli A. Life's Simple 7 for Cardiovascular and Total Health: How are we doing? P2060.
- **Gogulamudi VR, Mani I, Subramanian U, Pandey KN.** Genetic Disruption of Npr1 Depletes T Regulatory Cells and Provokes High Levels of Proinflammatory Cytokines and Fibrosis in the Kidneys of Female Mutant Mice. P2045.
- Gonzalez AA, Reyes C. (Pro)Renin Receptor-Dependent Induction of Pro-Fibrotic Factors is Mediated by COX-2/EP4/NOX-4/Smad Pathway in Mouse Renal Collecting Duct Cell. P2019.
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- Singh P, Dutta SR, Malik KU. Cytochrome P450 1b1-Dependent Sex Differences in Norepinephrine-Induced Hypertension. P170.
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CORE Facilities & Services

Tulane Hypertension and Renal Center of Excellence (THRCE) houses two research core facilities that were developed during COBRE phases I, II, and III and are now maintained and supported by the Department of Physiology and revenues for services performed. These core facilities are essential for the support of basic, clinical, and translational research in hypertension and renal biology and provide unique research opportunities for emerging leaders by establishing an enriched environment in which to develop investigators in both clinical and basic hypertension research. The resources and services provided by the Center's COBRE Core facilities can be utilized by both COBRE and other investigators within Tulane and other institutions for hypertension, cardiovascular and renal research. The two research Core facilities are:

- The Molecular, Imaging, and Analytical Core: Serves as the resource for instruments and equipment needed to perform advanced molecular biology, semi-quantitative immuno-histochemistry and bio-analytical experiments.
- Mouse Phenotyping Research Core (MPRC): Contains resources to support high-tech data collection capabilities that are unique in the State of Louisiana and essential to research requiring the utilization of an array of methodologies to perform measurements of cardiovascular, blood pressure and renal function in mice.

Other activities of the Center include the sponsorship of local and regional meetings on hypertension and public education programs to increase awareness of the dangers of hypertension.

T.H.R.C.E.



Tulane Hypertension & Renal Center of Excellence (THRCE) will appreciate any support for the continual development of the center and its CORE Facilities, the publication of the THRCE newsletters, and the support of the THRCE bi-weekly seminars series. All donations to the center and its activities are considered tax-deductible.

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