As I write this message, the phrase, “Time flies like an arrow, and the sun and the moon come and go like shuttles,” comes to mind as I think how quickly the last six months have passed! On the behalf of the Tulane Hypertension and Renal Center of Excellence (THRCE), it is my pleasure to present the 2021 Winter issue of the THRCE Newsletter that highlights some of center’s ongoing research, education, and training activities in the hypertension and kidney research during the second half of the past year, 2021. During that period, our faculty members, postdoctoral fellows, and graduate students continued to adapt to the enormous challenges of the ongoing COVID-19 pandemic and the disruption caused by Hurricane Ida and the subsequent city-wide power outrages. Despite these challenges, we were able to carry out our research and training activities with perseverance and professionalism. One of the most significant news is that the Office of Research held the first Tulane University Research, Scholarship and Artistic Achievement Awards Ceremony on Thursday, November 4, 2021, to honor outstanding Tulane scholars and recognize their exceptional research activities. Dr. L. Gabriel Navar, Chairman of the Department of Physiology and the THRCE’s Previous Director, was recognized with a 2021 Research Hall of Fame Award. This prestigious award recognizes Dr. Navar for his exceptional lifetime contributions to advancing hypertension and kidney research over his academic career. We are very proud of our own Gabby! In the presence of continued travel restrictions, THRCE was able to run a robust Frontiers in Hypertension and Kidney Research Seminar Series by inviting many nationally recognized scientists to give zoom presentations. We would like to thank all speakers for sharing their new hypotheses or ideas, new experimental approaches and models, and new insights in their research with our faculty, postdoctoral fellows, graduate students, and Seminar participants from around the world. The Frontiers in Hypertension and Kidney Research Seminar Series play a key role in updating and promoting the THRCE’s research and training programs. The other highlights in this newsletter include that Dr. Navar, Dr. Zhuo, and Dr. Prieto were invited to give lectures at the XIII International Symposium on Vasoactive Peptides Virtual Meeting on October 10-15, 2021, organized by Dr. Robson Santos, MD, PhD, and more than 10 of our researchers presented their recent research at...
the 2021 AHA Council for Hypertension Research Meeting between September 27-29, 2021, as well as at the APS 7th Conferences on New Trends in Sex and Gender Medicine that was held October 19-22, 2021. Finally, Dr. Chih-Hong Wang, an Assistant Professor and THRCE affiliate, left Tulane to accept a position in the pharmaceutical industry and we wish him great success in his future endeavors. Overall, I would like to thank all members of the THRCE for their dedication and perseverance to their research work, and wish everyone a safe, healthy, and productive 2022.

Sincerely,

Zhuo, Jia, M.D, Ph.D.
Director, Tulane Hypertension & Renal Center of Excellence
Professor, Department of Physiology & Medicine

Honors and Recognition

Jia L. Zhuo, MD, PhD:
- Invited to serve as a mentor for the NIH Faculty Institutional Recruitment for Sustainable Transformation (FIRST) Program. This mentored career development program aims to recruit a critical mass of diverse early career faculty to the university with a focus on inclusive excellence.
- Appointed Reviewer Editor on the Editorial Board of Frontiers in Physiology, Renal and Epithelial Physiology Section.
- Invited to serve as the Chair, NIH/NHLBI/CSR Special Review Panel ZRG1 VH-D02.

L. Gabriel Navar, PhD:
- Appointed Associate Editor on the Editorial Board of Renal and Epithelial Physiology (specialty section of Frontiers in Physiology).
- Appointment as Senior Advisory Editor to the new Editorial Board of Hypertension under their new editor, Dr. Rhian Touyz.
- One of four recipients who received the 2021 Research Hall of Fame award from Tulane University presented at the first Tulane University Research, Scholarship and Artistic Achievement Awards Ceremony on November 4, 2021. The prestigious lifetime achievement award recognizes a nationally and internationally renowned scholar/investigator who has made substantial contributions to advancing knowledge over his/her academic career.
Prasad V.G. Katakam, MD, PhD, Associate Professor of Pharmacology at Tulane University, the School of Medicine, presented, “Novel Effects of Nitric Oxide Synthase Inhibition on Mitochondrial Respiration,” on July 8th, 2021.

**Summary of presentation:**

Nitric oxide synthase (NOS) is an enzyme that produces nitric oxide under physiological conditions and superoxide under pathological states such as stroke and diabetes. There are distinct variants of NOS in endothelial cells and neurons that have been shown to exert diverse effects on brain injury following stroke. We examined the impact of simultaneous inhibition of all variants of NOS on cellular injury caused by oxygen-glucose deprivation (anoxic injury). Nitric oxide has been widely reported to negatively regulate mitochondrial respiration. Interestingly, we found that NOS inhibition in neurons under normoxic conditions enhanced mitochondrial respiration in neurons but not in brain microvascular endothelial cells. In addition, we observed that NOS inhibition was protective against anoxic injury in both brain microvascular endothelial cells and neurons. This cytoprotective effect of NOS inhibition was accompanied by reducing oxidative stress and recovering mitochondrial membrane potential. Notably, NOS inhibition had diverse effects on mitochondrial respiration under normoxic conditions in endothelial cells and neurons but identical effects when treated for short duration (8-9 hours). However, longer exposure (28 hours) to NOS inhibition elicited distinctly different effects on mitochondrial respiration in endothelial cells and neurons. Longer exposure to NOS inhibition recovered the mitochondrial respiration in neurons following anoxic injury but endothelial mitochondrial respiration remained depressed. Thus, our studies have uncovered novel effects of NOS inhibition on mitochondrial respiration that are dependent on normoxia/anoxia or endothelial cells/neurons or short/long duration of treatment.

Ben Fogelgren, PhD, Associate Professor in the Department of Anatomy, Biochemistry, & Physiology at John A. Burns School of Medicine in the University of Hawaii at Manoa, Honolulu, HI, presented, “Urothelial dysfunction as a cause for congenital ureteropelvic obstruction and nephropathy,” on September 16th, 2021. This seminar was the “Kathy Newman Lecture,” which was jointly hosted with the Department of Pediatrics.

**Summary of presentation:**

Congenital obstructive nephropathy (CON), the most common cause of chronic kidney disease and end stage renal disease in children, is caused by obstruction of the urinary tract during fetal development. Most often, this obstruction occurs at the ureteropelvic junction (UPJ), where the renal pelvis connects to the ureter. Despite the high medical burden, there is a poor understanding of the molecular and genetic causes of UPJ obstructions, with very few animal models. For the past decade, Dr. Fogelgren has studied the role of the eight-protein exocyst trafficking complex in kidney development, physiology, and disease. To facilitate in vivo studies of the exocyst during mammalian development, he generated a novel
conditional knockout mouse for a central exocyst subunit Exoc5 using Cre-lox transgenic technology. Surprisingly, targeted deletion of Exoc5 in ureteric bud-derived epithelia caused in utero bilateral UPJ obstructions with hydronephrosis, complete anuria, and neonatal lethality. In these mutant mice, the ureter urothelium fails to differentiate a superficial layer between gestational day 16.5 (E16.5) and E17.5. This leads to urothelial cell death and a leaky urothelial barrier against urine, with an increase in TGFβ1 expression and mesenchymal cell proliferation. By E18.5, the ureter lumen at the UPJ is obliterated due to stromal remodeling and overgrowth of fibroblastic cells. Further studies have shown exocyst disruption in urothelial cells disrupts autophagy, which triggers conserved cell stress pathways and non-apoptotic cell death. This model lends support to the hypothesis that a significant portion of human UPJ obstructions arise due to a dysfunctional urothelial barrier.

Youhua Liu, PhD, Professor of Pathology and UPMC Endowed Chair in Tissue Biology at the University of Pittsburgh Medical Center, (UPMC), presented, “Tough neighborhood: Tissue microenvironment and kidney fibrosis,” on September 30th, 2021.

**Summary of presentation:**
Irrespective of the initial cause, kidney fibrosis is considered to be the final common pathway in the evolution of virtually all types of chronic kidney disease (CKD). At present, no treatment is specifically targeted against kidney fibrosis. Studies show that renal fibrotic lesions are neither uniform nor at random across the kidney parenchyma. Rather, it initiates at certain focal sites, in which the fibrogenic niche is formed and provides a unique microenvironment that promotes fibroblast activation in a spatially defined fashion. The fibrogenic niche is orchestrated by a specialized extracellular matrix network, consisting of structurally unrelated, de novo-induced matricellular proteins such as tenascin-C and fibrillin-1. Participants of the presentation will appreciate recent advances on molecular dissection of the fibrogenic niche and understand the mechanism underlying its action. Remedies disrupting the formation of the fibrogenic niche could be a novel strategy for the therapy of fibrotic diseases.

Sarah Lindsey, PhD, Associate Professor and the Dr. Barbara S. Beckman Professorship in Pharmacology, at Tulane University, School of Medicine, presented, “Postmenopausal Cardiovascular Disease: Chasing a Moving Target,” on October 14th, 2021.

**Summary of presentation:**
Favorable cardiovascular effects of estrogen are found in observational studies with younger and healthier women, while randomized clinical trials failed to find favorable effects in older women many years past menopause. Many factors may contribute to the lack of cardiovascular protection, including biological aging, underlying disease, and endocrine disruptors. Moreover, recent clinical findings suggest that cardiovascular risk factors may be unique in postmenopausal women. We assessed the impact of estrogen loss, aging,
endocrine disruption, and hypertension on estrogen receptor expression and the vascular response to exogenous estrogen in female mice. We found that estrogen loss induces arterial stiffening before increases in blood pressure, which may be used as a better indicator of cardiovascular risk in postmenopausal women. We also found that aging, the endocrine disruptor Bisphenol A, and hypertension induced by angiotensin II all significantly downregulate estrogen receptors and decrease the vasodilatory response to estrogen. In conclusion, there are many factors which may influence the cardiovascular response to menopausal hormone therapy. Only after understanding the impact of the environment can we effectively prevent postmenopausal cardiovascular disease and extend life in aging women.

Sergey Dikalov, PhD, presented on November 11th 2021, “Mitochondrial Oxidative Stress and Sirtuin 3 in Hypertension and Vascular Diseases.” Dr. Dikalov is Associate Professor and Director of Free Radicals in Medicine Core in the Vanderbilt University Medical Center, Nashville, Tennessee.

**Summary of Presentation:**

Hypertension remains a major health problem in Western Societies, and blood pressure is poorly controlled in a third of patients despite use of multiple drugs. Mitochondrial dysfunction contributes to hypertension and mitochondria-targeted agents can potentially improve treatment of hypertension. Hypertension is a multifactorial disorder and oxidative stress is increased in multiple organs in hypertension. Oxidative stress contributes to hypertension by increasing sympathetic outflow, promoting kidney dysfunction, and increasing systemic vascular resistance. Meanwhile, common antioxidants, like ascorbate and vitamin E, are ineffective in the treatment of cardiovascular diseases and hypertension, and in some studies, worsen the outcome. Intrinsic enzymatic antioxidants are much more effective against oxidative stress compared with low molecular weight antioxidants, but these intrinsic antioxidants can be inactivated in hypertension. Dr. Dikalov and colleagues have found that essential hypertension is associated with inactivation of a key mitochondrial antioxidant, superoxide dismutase 2 (SOD2), by acetylation of lysine residues at the catalytic center due to reduced activity of mitochondrial deacetylase Sirtuin 3 (Sirt3). However the precise mechanism of Sirt3 inactivation and molecular consequences of SOD2 inhibition are not clear.

Dr. Dikalov reported that Sirt3 level is decreased in arterioles from human subjects with essential hypertension compared to normotensive subjects, and this is accompanied by alterations in vascular metabolic, inflammatory and cell-senescence pathways similar to Sirt3 depleted mice. Furthermore, Sirt3 overexpression prevents vascular oxidative stress and attenuates hypertension in angiotensin II and DOCA-salt mouse models while Sirt3 depletion accelerates vascular inflammation, vascular aging and age-dependent hypertension. Finally, Sirt3 overexpression inhibits vascular hypertrophy, protects endothelial barrier function, prevents end-organ inflammation and preserves endothelial-dependent relaxation. Interestingly, oxidative stress is associated with formation of highly reactive and harmful lipid peroxidation products isolevuglandins. Scavenging of mitochondrial isolevuglandins improves kidney mitochondrial function and improves vascular function by rescuing Sirt3 activity. These data support the therapeutic potential of targeting Sirt3 activity in hypertensive end-organ dysfunction.
Robert S Hoover MD, Professor of Medicine and Physiology, the Dr. A. Rudolph and Ruth Ryder Huberwald Chair of Deming Department of Medicine, and Chief of Section of Nephrology and Hypertension at Tulane University School of Medicine presented, “NCC AND ENaC: Facebook Friends or Linked (In) Together (and other stories of sodium transport),” on December 9th, 2021.

**Summary of Presentation:**
This seminar discussed the association between two key sodium transporters in the distal nephron: NCC and ENaC. Work examining the effect of diet on hypertension and NCC was also presented. Future directions/new projects was discussed as well.

**Publications**


Heart disease is the No. 1 killer worldwide, and stroke ranks second globally. Even when those conditions don’t result in death, they can cause disability and diminish quality of life. The Tulane Hypertension and Renal Center of Excellence and the Department of Physiology jointly participated as one of 12 teams under the Tulane Health Banner in the 2021 American Heart Association (AHA) Heart Walk. The AHA Heart Walk raises critical funds that is reinvested locally and around the globe to support cardiovascular medical research, educate consumers on healthy living, and foster appropriate cardiac care in an effort to reduce disability and deaths caused by cardiovascular disease and stroke. Over the years, the American Heart Association has invested over $4 billion in heart and stroke research worldwide.

With just 24 registered walkers, Tulane University was able to raise $8,685 for the 2021 AHA Heart-Walk. Most of the funds raised in the New Orleans AHA Heart Walk is reinvested back into the local community to fund research and other public education programs in Louisiana. The 2021 AHA Heart Walk was held at the Lasalle Park on 6600 Airline Drive, Metairie, Louisiana on Saturday, November 20, 2021.

**Publications Cont...**


Wang C, Zhuo JL, Li X. A Significant Anemic Phenotype In Ren1c−/− Mice Due To Impaired Erythropoiesis And Epo Production. Abstract P248.

Navar LG. Urinary Angiotensinogen excretion as a reflection of intrarenal RAS activity in Hypertension and Diabetes and sex associated differences. Invited Oral Presentation.


Leite APO, Li XC, Zhuo JL. Sex differences in angiotensin II-induced hypertension and kidney injury: role of AT1α receptors in the proximal tubules of the kidney.

Pemberton E, Shao W, Katsurada A, Bell A, Navar LG. Sex-dependent differences in hypertension and urinary angiotensinogen excretion in 2-kidney 1-clip (2K1C) Goldblatt hypertensive rats are mitigated in ovariectomized rats.
Your support is welcome

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

CORE Facilities & Services

Tulane Hypertension and Renal Center of Excellence (THRCE) houses 2 research core facilities that were developed during COBRE phases I, II, and III. These are now maintained and supported by THRCE and fees collected from the usage of some CORE facility services. The 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 the clinical and basic hypertension research. The resources and services provided by the Center’s Core facilities can be utilized by investigators within Tulane and other institutions for hypertension, cardiovascular and renal research. The 2 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 the biweekly THRCE meetings, and the participation in public education programs and events such as the AHA Heart Walk and National Kidney Day to increase public awareness of the dangers of hypertension and its complications.

Upcoming Meetings & Events

2022 Southern Regional Meeting

World Kidney Day 2022
~ Tulane University: April 20-21, 2022

European Society of Hypertension 2022
~ Athens, Greece: June 17-20, 2022

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During COVID-19 restrictions: Zoom meetings will replace in-person meetings and are scheduled alternative Thursdays from 12 noon till 1 PM.