



T.H.R.C.E.

TULANE HYPERTENSION AND RENAL CENTER OF EXCELLENCE

Summer 2014

Volume 13, Issue 2

Science in News: Effects of Low-Carbohydrate and Low-Fat Diets



Photo taken by Advocate news-photographer, JOHN McCUSKER.

A study by former COBRE Junior investigator, Dr. Lydia Bazzano, was highlighted in numerous local and national news media. Dr. Bazzano's COBRE study, "Effects of Low-Carbohydrate and Low-Fat Diets: A Randomized Trial" was published in the September issue of the *Annals of Internal Medicine* and since then has generated a lot of national interest. The news was highlighted in the *New York Times*, *USA Today*, *Time* magazine, *NPR*, *Huffington Post*, amongst many others! The picture above left was published in the "The Advocate" (*Tyler Bridges* [Sept. 11, 2014]. *Low-carb study draws spotlight to low-profile Tulane professor. The Advocate*. Retrieved from <http://theadvocate.com/>). You may access the scientific publication at: <http://annals.org/article.aspx?articleid=1900694>.

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COBRE AWARDS 3 PILOT PROJECT GRANTS

Each year, COBRE provide three pilot projects grants of \$45,000 to support scientific research related to hypertension. The pilot project awards provide one year research opportunities for novel, innovative, highly competitive meritorious projects with high likelihood for garnering extramural research support. Projects that address important and significant issues related to the broad area encompassed by hypertension, renal and cardiovascular research are considered. Applications are subjected to a rigorous internal and external review process to ensure that funds are provided only to highly meritorious pilot projects that are likely to lead to extramural research support and will stimulate multidisciplinary collaborative interactions. This year's Pilot Project award recipients are Drs. Woods, Chen and Kumar:

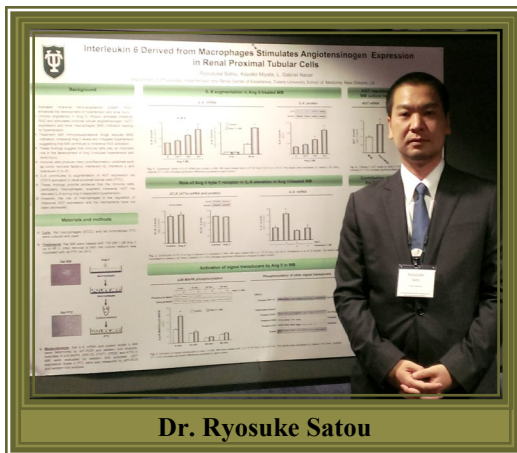
- **Pilot Project 1:** *Non-coding RNA in Diabetes mediated Enhanced Intimal Thickening during Early Atherosclerotic Plaque Development.*
PI: T. Cooper Woods, PhD, Department of Physiology.
- **Pilot Project 2:** *Histone Deacetylases 1 and 2 in Kidney Development.*
PI: Shaowei Chen, MD, PhD, Division of Pediatric Nephrology, Dept. of Pediatric.
- **Pilot Project 3:** *Estrogen-dependent activation of guanylyl cyclase/ natriuretic peptide receptor A gene expression via estrogen receptors ER_α and ER_β.*
PI: Prerna Kumar, PhD, Department of Physiology.

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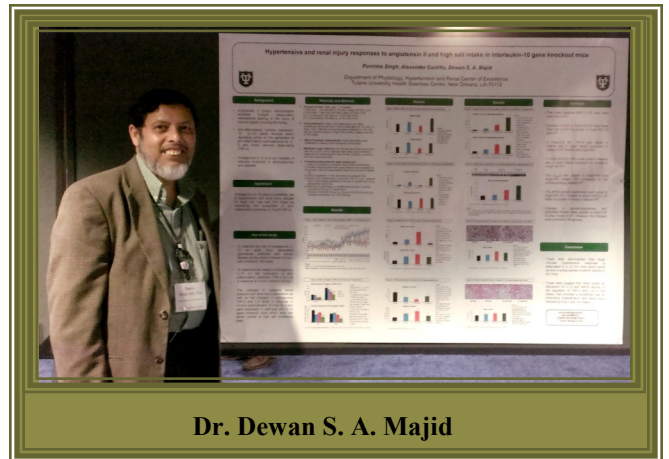
NIH, NIGMS FIFTH BIENNIAL NATIONAL IDEA SYMPOSIUM

Tulane COBRE Investigators participated in the 2014 NIH, NIGMS National IDeA Symposium of Biomedical Research Excellence. The meeting was held in Washington DC between June 16 - 18, 2014. Abstracts were presented by Drs. Dewan Majid, Ryosuke Sato, and Lee Murfee. THRCE Senior Program Coordinator, Nina Majid, presented a poster about COBRE III Translational Research in Hypertension & Renal Biology program and how it had benefited Tulane investigators and the THRCE Center. For further details on the poster presentations, please refer to page 16.

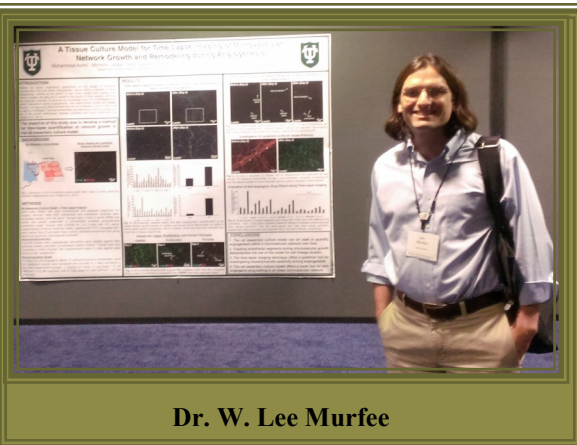
NISBRE is the National IDeA Symposium for Biomedical Excellence that showcases the scientific and training accomplishments of the IDeA program of NIGMS. IDeA develops scientific centers of excellence and trains biomedical scientists in the IDeA eligible states. The IDeA program consists of two different programs, the COBRE and INBRE. The Core facilities and affiliates of THRCE are supported by the NIGMS IDeA COBRE program.



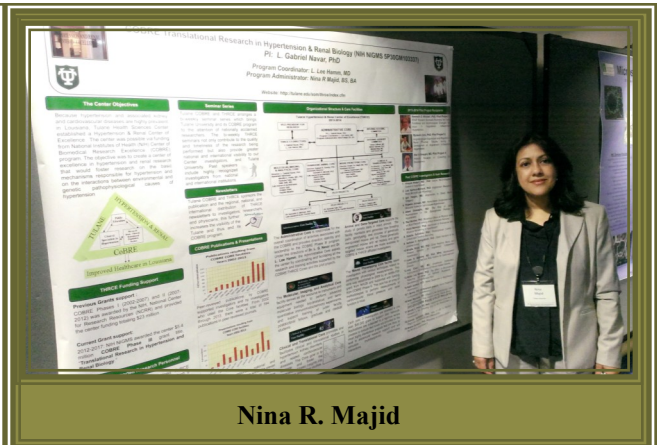
Dr. Ryosuke Satou



Dr. Dewan S. A. Majid



Dr. W. Lee Murfee



Nina R. Majid



National Institute of General Medical Sciences

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HONORS & RECOGNITION AWARDED TO THREE AFFILIATED INVESTIGATORS

Shaowei Chen, MD, PhD :

- Awarded one of three COBRE Phase III Pilot Project Award.

Andrei Derbenev, PhD:

- Hosted a visiting high school research student, Ivan Prisyazhnyuk, from King's School Canterbury, UK.

Kathleen Hering-Smith, PhD:

- A paper, "Localization of the calcium-regulated citrate transport process in proximal tubule cells. Urolithiasis," was listed as a Key Scientific Article in July's Global Medical Discovery.
- On June 8, 2014, was invited to the Pharmacology Department at LSUHSC in Shreveport as external expert reviewer on the committee for a PhD candidate, Ms. Corie Robinson. Dr. Hering-Smith also presented a seminar during her visit.



Prerna Kumar, PhD :

- Awarded one of three COBRE Phase III Pilot Project Award.

Dewan S. A. Majid, MD, PhD:

- Served as "Editor-in-Chief" for the Journal featuring the "Annual International Conference on Advanced Research: Physiology" held in July, 2014 in Singapore.
- Awarded Pilot Bridge Award from Tulane University, SOM Research Pilot Program.

Solange Abdunour-Nakhoul, PhD:

- Awarded a 4 year, VA Merit grant for the research, "Acid-Base and Ammonia Transport in the Collecting Duct." 2012-2016.

L. Gabriel Navar, PhD:

- Named the "Robert M. Hearin Distinguished Lecturer," by the University of Mississippi Medical Center, Jackson, MS., on May 15, 2014.
- Selected onto the Editorial Board: Enliven: Nephrology and Renal Studies, 2014
- Invited to Chair the Tulane SOM 2014 Research Advisory Committee.
- Awarded Year-3 of the NIH/NIGMS CoBRE III Grant (5P30GM103337-03) for the period 08/01/2014 - 07/31/2015.

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

Kailash N. Pandey, PhD:

- Edited a book that was published in June 2014, titled, "Natriuretic Peptides: Physiology, Molecular Biology, and Clinical Implications." It provides current knowledge and recent developments to navigate cellular, molecular, and clinical aspects of natriuretic peptides and their receptors in health and disease.
- Received a plaque for a presentations he gave in India.

Minolfa C. Prieto, MD, PhD:

- Promoted to Associate Professor effective July 1, 2014.
- Awarded 5-year, NIH/RO1 award for her study, "Impact of renin and prorenin receptor interaction in the collecting duct on blood pressure."
- Awarded an APS NIDDK Minority Travel Fellowship Award to attend the 1st Pan-American Meeting of Physiology, held at the Falls of Igazu, Brazil.
- Appointed to serve for a 3-year term on the APS Council Awards Committee beginning January 1, 2015.
- Selected as Member of the Steering Committee of the Physiological Group of the APS-Newsletter Editor Chair.
- Selected as Member of the Organizer Committee of the 2014 Inter-American Society of Hypertension Meeting, held in Salvador do Bahia, Brazil.
- Appointed to the Hypertension and Microcirculation Study Section for NIH.

Ryosuke Sato, PhD:

- Awarded the "Young Investigator Award," at the 2014 IDeA symposium in DC.

T. Cooper Woods, PhD :

- Awarded one of three COBRE Phase III Pilot Project Award.

Andrea Zsombok, PhD:

- Awarded 5-year, NIH/RO1 grant for her study, "TRPV1-dependent autonomic control in diabetes."
- Awarded Pilot Project grant from Tulane University, SOM Research Pilot Program.

Graduate & Post-doctoral fellows:

- Tolga Caner (Mentor: Dr. Nakhoul) defended his PhD thesis titled, "Mechanisms of Ammonia & Ammonium Transport by Rhesus Associated Glycoproteins," in Aug 2014.
- Medical Student, Catherine Howard received the 2014 Mayerson Award during the 2014 Commencement Ceremony when she received an M.D and a Ph.D. in Physiology.
- Medical Students, Laleh Bahrami, James O'Hare, and Carolyn Campbell all received the Nicholas R. DiLuzio Award.
- Medical student, David (Matt) McLellan was the Inaugural Recipient of the 2014 Bourgeois Student Research Award.

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2014 New Orleans Heart Walk

THRCE is participating in the New Orleans Heart Walk benefiting the American Heart Association (AHA). Cardiovascular diseases or stroke have or will somehow affect many of our friends, family members and/or co-workers. The funds raised will be used for critical research and education on cardiovascular diseases. **Please support the 2014 AHA fundraiser by:**

1. Making a secure, online, tax-deductible donation by visiting the page, <http://neworleansheartwalk.kintera.org/ninamajid> and clicking on the "Give Now" link.
2. **Volunteering your time and join in the walk!** The 2014 Heart Walk is happening Saturday, November 15 at LaSalle Park. It's a fun filled event and it's for a good cause.

The money raised often helps right here in the Tulane community! Tulane School of Medicine Hypertension and Renal Center of Excellence centralizes and coordinates Tulane research activities related to cardiovascular, kidney, and hypertension diseases. The center houses a state-of-the-art Molecular, Imaging, and Analytical Core, the Animal and Gene-Targeted Core, the Mouse Phenotyping core, and the Clinical & Translational Core facilities. The center is composed of faculty from multi-disciplinary fields that are specifically dedicated to investigative efforts, patient care, and public education in the crucial areas of hypertension and kidney diseases. Funds raised by the American Heart Association have over the years helped to support our faculty, and helped support this exceptional research center at Tulane. Your help raising funds for the AHA may directly come back and support research, patient care, and educational programs at Tulane.



2013 Heart Walk: Participant walkers from the various TSOM teams. Over 70 members were recruited as walkers at the 2013 Heart Walk.



MARCH 12, 2015 IS WORLD KIDNEY DAY!

"Kidney Health for All" is the theme for the 2015 World Kidney Day (WKD). Within both higher and lower income countries there are communities that are at greater risk than others because of their ethnic origin, socioeconomic status and/or where they live. WKD is a global health campaign that aims to raise awareness of the importance of our kidneys to our overall health, and to reduce the frequency and impact of kidney disease and its associated health problems. Taking steps to live a healthy lifestyle clearly helps to reduce risk, and early detection and treatment can slow or prevent the progression of Chronic Kidney Disease (CKD), and reduce the increased incidence of associated cardiovascular disease. WKD is a joint initiative of the International Society of Nephrology (ISN) and the International Federation of Kidney Foundations (IFKF). More information on WKD can be accessed at: <http://www.worldkidneyday.org/#sthash.G9pW6Ivp.dpuf>.

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SCIENCE IN NEWS: BLOOD PRESSURE INCREASES WITH SODIUM INTAKE

In a study of 102,216 adults from 18 countries, researchers found that increasing sodium intake directly increases blood pressure, particularly among individuals with hypertension and amongst older people, according to a new report in *The New England Journal of Medicine* (2014;371:601-611).

Researchers found that each 1-gram increment in sodium excretion was associated with a 2.11 mmHg increment in systolic blood pressure (SBP) and a 0.78 mmHg increment in diastolic blood pressure (DBP). The association was most pronounced among subjects with a sodium excretion greater than 5 grams per day. In these individuals, each 1-gram increment in sodium excretion was associated with a 2.58 mmHg increment in SBP. The effect of sodium on blood-pressure is further pronounced amongst individuals with hypertension than those without hypertension, and amongst those aged 55 years and older.

Potassium excretion was inversely associated with SBP, significantly more so in individuals with hypertension than in those without it. Each 1-gram increment in potassium excretion per day was associated with a 0.75 mmHg decrement in SBP and a 0.06 mmHg decrement in DBP. The investigators used fasting morning urine specimens to estimate 24-hour sodium and potassium excretion, and used these estimates as surrogates for sodium and potassium intake.

Source: <http://www.renalandurologynews.com/blood-pressure-increases-along-with-sodium-intake/article/366216/>

THRCE Welcomes 2014 Summer Students

The Tulane Hypertension & Renal Center of Excellence was pleased to host Medical and Undergraduate Summer Research Students. For 8 to 10 weeks, Summer Research Students work with Center researchers. The Medical and Undergraduate summer students are exposed to the nature of a career path in research and have the opportunity to attend the THRCE events and Seminars.

Sponsor: AHA Summer Fellowship Program

- **Courtney Enix**
Mentor: Dr. Andrea Zsombok
- **Mariana Zapata**
Mentor: Dr. T. Cooper Woods
- **Nora Haney**
Mentor: Dr. Kenneth D. Mitchell
- **Ryan O'Leary**
Mentor: Dr. Ryosuke Sato

Sponsor: Bourgeois Medical Research Award

- **David (Matt) McLellan**
Mentor: Dr. Minolfa Prieto

Sponsor: Federal Summer Aid (Military)

- **Oliver Gentile**
Mentor: Dr. Minolfa Prieto

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THRCE SPONSORED LOCAL, NATIONAL & INTERNATIONAL SPEAKERS

THRCE sponsors bi-weekly seminars by scheduling nationally and internationally recognized investigators and clinicians in the field of hypertension research, treatment and education. From May through August, 2014, the center hosted the following speakers to present THRCE seminars:



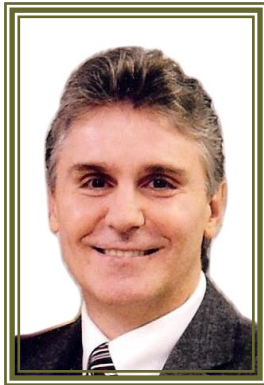
- **Alicia McDonough, PhD**
Professor, Cell & Neurobiology
Keck School of Medicine, University of South California,,
Los Angeles, CA.

The Department of Physiology and THRCE jointly sponsored a seminar by Dr. Alicia McDonough. Her talk, "Integrated regulation of sodium transporters along the nephron by Angiotensin II and blood pressure," was presented on Monday, May 19, 2014.

Summary: By matching output to input, the kidneys control the set point for body fluid sodium and volume as well as potassium. Regulation of renal transporter activity is the final step in homeostatic control of these variables. According to Guyton, the kidneys should have the capacity to excrete enough sodium and volume to normalize blood pressure in the face of increased salt intake. Likewise, the kidneys have an enormous capacity to secrete potassium to maintain precise control of this cation that controls membrane potential. Thus, both hypertension and hyperkalemia can be characterized as failures of renal compensation. Normal renal control of sodium and potassium requires integration of transporter regulation all along the nephron, including regulation of abundance, trafficking to the plasma membrane, phosphorylation and proteolytic processing. For example, during AngII hypertension sodium transporters are activated in the distal nephron (cNKCC, NCC, ENaC) which, via the resultant hypertension, drives inactivation of transporters in the proximal nephron (NHE3, NaPi2, mTALH) in order to match Na⁺ output to input- at the expense of elevated pressure. During AngII hypertension there is inflammation, cytokine release and activation of intrarenal AngII accumulation that critically influence the transporter activation and/or the

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blunting of the proximal transporter responses. Interestingly, blood pressure (BP) rises as dietary K⁺/Na⁺ ratio falls, e.g. when people move from isolated to industrialized societies. An explanation may lie in the observation that a K⁺ rich diet, or a simple small rise in plasma [K⁺], inactivates the distal tubule Na-Cl-cotransporter. This drives more Na⁺ downstream for reabsorption by the epithelial sodium channel which creates a negative luminal potential that stimulates K⁺ secretion. Sex specific transporter abundance and regulation by potassium may help explain the lower blood pressures in females. Further focus on the integrated responses of renal Na⁺ and K⁺ transporters along the nephron will likely help us understand and treat hypertension and hyperkalemia.



- **Daniel R. Kapusta, PhD**

*Professor and Director, LSUHSC Cardiovascular CoBRE Program,
Department of Pharmacology,
LSU Health Sciences Center,
New Orleans, LA.*

Dr. Kapusta presented, “Radiofrequency ablation of the renal nerves & Management of Resistant Hypertension: Ongoing studies using the Spontaneously Hypertensive Rat,” at the June 5th THRCE Seminar.

Summary: Hypertension is a major global public health concern. Despite the availability of numerous safe and effective antihypertensive medications, the percentage of patients achieving desired target blood pressure control is still below 50%. A patient is classified as having ‘resistant hypertension’ when their systolic blood pressure (SBP) remains ≥ 160 mmHg while taking three or more anti-hypertensive medications, one of which is a diuretic, at the highest tolerated doses. It is well known that the renal afferent and efferent nerves participate in the regulation of blood pressure in health and disease. Based on this knowledge it has been recently demonstrated that percutaneous catheter based radiofrequency ablation of renal arteries (RF-ABL) decreases blood pressure in patients with drug-resistant hypertension, with the hypotensive response being sustained for years following a single treatment. Despite these exciting findings, the underlying mechanism(s) by which RF-ABL decreases blood pressure in patients with resistant

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hypertension remains unclear. To investigate this question we developed an approach in which to study the effects of RF-ABL in spontaneously hypertensive rats (SHR), an animal model of neurogenic hypertension. For these studies blood pressure was continuously measured (telemetry) in 20-week old male SHR before (1 week) and after either sham or bilateral RF-ABL of the renal arteries (external vascular application of the RF probe). In these studies, we observed that RF-ABL (but not the sham procedure) produced a significant decrease in blood pressure that was sustained for 2 months (longer time points not studied); the decrease in blood pressure in SHR ranged from ~ -10 to -25 mmHg, which was similar to that produced by RF-ABL in humans. In these and related studies using spectral analysis of blood pressure variability and administration of a ganglionic blocker, we demonstrated that RF-ABL significantly decreased sympathetic outflow. Further, the kidney norepinephrine content (a marker of the degree of renal nerve destruction) was markedly decreased at 8 weeks in these RF-ABL SHR compared to levels in sham SHR. While it is known that the renal nerves participate in the renal handling of water and sodium, our studies demonstrated that RF-ABL did not produce a sustained reduction in blood pressure in SHR via altering daily sodium or water balance. It is recognized that SHR have an enhanced urinary excretion of angiotensinogen (a marker of heightened kidney angiotensin II activity), however, studies in collaboration with Dr. Navar's group failed to show that the sustained reduction in blood pressure produced by RF-ABL was due to an alteration in plasma renin activity, kidney renin content or urinary angiotensinogen levels. From these studies, our long-term objective is to continue to use this SHR model to further investigate how RF-ABL of the renal nerves can lead to global changes in central efferent sympathetic outflow to the periphery (vasculature, heart and kidneys) and consequently decrease blood pressure in neurogenic (and resistant) hypertension.



- **Prasad V.G. Katakam, MD, PhD**
*Assistant Professor, Department of Pharmacology,
Tulane School of Medicine, New Orleans, LA.*

Dr. Katakam presented, "Uncoupling of Nitric Oxide Synthase and Insulin Resistance," at the May 22nd THRCE Seminar.

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Summary: Nitric oxide synthase (NOS) is an enzyme that catalyzes formation of nitric oxide (NO). However, under certain pathological states, NOS catalyzes generation of superoxide instead of NO, a condition referred to as 'NO Uncoupling'. Dr. Katakam's previous studies demonstrated that insulin promotes uncoupling of NOS isoforms in cerebral arteries of Zucker obese(ZO) rat, a model of insulin resistance and type 2 diabetes. In addition, he also observed that cerebral arteries of Zucker obese rats also display impaired mitochondrial mediated vasodilation. His goal is to examine the role of NOS uncoupling in vascular dysfunction following hypoxic injury and determine the relationship between NOS uncoupling and mitochondrial function in health and disease states. His preliminary findings observed that preempting NOS uncoupling affords protection against hypoxia-reoxygenation injury in brain microvascular endothelial cells. This may be related to a decrease in interorganelle communication between endoplasmic reticulum and mitochondria. Importantly, he and his research team has observed that insulin is protective against hypoxic injury in phenotypically normal endothelial cells and arteries by reducing NOS uncoupling. However, insulin loses its ability to prevent NOS uncoupling and protect arteries against hypoxic injury in insulin resistant rats. His long term objective is to provide mechanistic basis for potential adverse actions of insulin in insulin resistant state.



- **Keith C. Ferdinand, MD**
Professor of Clinical Medicine
Tulane University School of Medicine, New Orleans, LA.
Chair, National Forum for Heart Disease & Stroke Prevention.

Dr. Keith C. Ferdinand, MD, presented a synopsis and review of the new hypertension guideline reports at the July 17, 2014 THRCE Seminar.

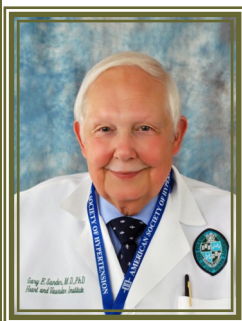
Summary: Dr. Ferdinand, Professor of Clinical Medicine, discussed the 2013-2014 multiple guidelines on the treatment of hypertension. There was a specific focus on areas of controversy and concern. The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) is the last, and apparently final, true recommendations for management of hypertension supported and endorsed by the National Heart, Lung, and Blood Institute (NHLBI). Based on strict adherence to evidence-based medicine, the Joint

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National Committee-8 Panel (JNC-8P), not endorsed by NHLBI, recommended a major change by defining, for those 60 years old and above to have a SBP >150 mm Hg threshold for initiating antihypertensive drug treatment and a treatment goal SBP of <150 mm Hg.

The controversial paper from members appointed to JNC-8 panel has led to robust discussion and debate. Dr. Ferdinand was one of the authors of a recent State-of-the-Art Review of the pitfalls in the new report from the JNC-8 panel in the July Journal of the American College of Cardiology

In addition, the American Heart Association (AHA), the American College of Cardiology (ACC), and the Centers for Disease Control and Prevention (CDC) jointly published a brief focused advisory and concise algorithm for management of hypertension(3), maintaining the goal for treatment of adult hypertension was a systolic blood pressure (SBP) <140 mm Hg and diastolic blood pressure (DBP) <90 mm Hg. This recommendation also had been reflected in the European Society of Hypertension /European Society of Cardiology Guideline that preceded both of the U.S. documents. There is also the International Hypertension Society and the American Society of Hypertension guideline. The Association of Black Cardiologists (ABC) and other specialists and other concerned clinicians and specialists in the treatment of hypertension have published editorials on the potential harm or short-comings of the JNC8 panel's stance, especially in consideration of potential harm to women and African-Americans. The new hypertension recommendations may harm all patients age 60 years and older, but it disproportionately affects women since there are so many more women in this age demographic with high blood pressure (BP) and blacks, because African Americans are such high risk.



- **Gary E. Sander, MD**
*Professor of Clinical Medicine
 Tulane University School of Medicine,
 New Orleans, LA.*

On July 31st, 2014, Dr. Sander presented “**Management of Hypertension in July 2014: Controversy and Progress.**”

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Summary: In trying to understand hypertension, it is first necessary to understand that blood pressure (BP) is only a biomarker that may signal the presence of hypertension as a cardiovascular disease. Blood pressure is the force necessary to insure adequate organ; hence BP increases in the presence of endothelial dysfunction and loss of normal vaso-relaxation. Confusion over BP thresholds at which to begin treatment and targets of treatment have become increasingly controversial due to the lack of definitive evidence that aggressive BP lowering better reduces the cardiovascular event rate (other than for stroke) than does more modest treatment (<140/90 mmHg for most individuals), and what should be the threshold for subjects over 60 years of age. Existing data show that risk of development of cardiovascular events is lowest for subjects with BP <115/75, and that the event rate doubles for each increase of 20 mmHg systolic BP and 10 mm Hg diastolic BP. Unfortunately, reduction in existing elevated BP does not follow the same pattern, but even as little as 2-3 mmHg of systolic and diastolic BP reductions significantly reduce the incidence of ischemic heart disease, heart failure, and stroke. Although the report of the JNC-8 committee suggested that, for subjects over age 60, a BP of 150/90 mmHg should be the threshold to begin treatment, this threshold has not been accepted by groups such as the American Heart Association and the American College of Cardiology. Several recent developments in hypertension research have exciting potential to offer new treatment options. The hormone aldosterone contributes to the development of hypertension and tissue fibrosis; it has now been shown that the aldosterone receptor is present on vascular smooth muscle and may function as an important BP regulator. This would explain the observed benefit of drugs such as spironolactone that can significantly improve BP control even in the absence of aldosterone excess. Yet another study has demonstrated that the antibiotic minocycline can significantly reduce BP by inhibiting angiotensin activation in the brain. Other studies are demonstrating that BP as routinely measured in the doctor's office poorly reflects the presence of hypertensive disease; improvements in monitoring include 24 hour ambulatory BP monitoring, and non-invasive measurements of central (aortic) BP, augmentation index, and pulse wave velocity.



- **Ryosuke Sato, PhD**
*Instructor, Department of Physiology
Tulane University School of Medicine,
New Orleans, LA.*

On August 14, **Dr. Ryosuke Sato** presented a seminar titled “**Pro-inflammatory cytokines derived from immune cells regulate angiotensinogen expression in renal proximal tubular cells.**”

Summary: Inappropriate activation of intrarenal renin-angiotensin system (RAS) is a major contributor to the development of hypertension and kidney injury. Intrarenal angiotensinogen (AGT) regulation is a key contributor to the hypertensive process. In the kidney, AGT is mainly produced in renal proximal tubular cells (PTC). Recent studies and our preliminary studies provide novel evidence that proximal tubular AGT protein consists of kidney AGT and internalized plasma AGT, and that the S1, S2, and S3 segments of proximal tubules have diverse AGT regulating systems via AGT internalization and synthesis. Thus, characterizing AGT regulation in each segment is required to elucidate the mechanisms of intrarenal RAS activation and its subsequent renal actions. However, the lack of available experimental tools has precluded an accurate, direct evaluation of the distribution and regulation of AGT expression in the individual segments of the proximal tubule. Furthermore, although studies have suggested the importance of immune cells and the immune cell-derived interleukin 6 (IL-6) in intrarenal RAS activation and the development of hypertension and kidney injury, the link between the immune cells-IL-6 axis and intrarenal RAS activation is still unclear. Therefore, Dr. Sato hypothesizes that AGT synthesis is stimulated in a segment-specific manner in the proximal tubule via angiotensin II (Ang II)-induced IL-6 derived from immune cells, which is the primary mechanism underlying elevated intrarenal AGT levels during Ang II-dependent hypertension.

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- **Ihor V. Yosypiv, MD.**

*Associate Professor, Department of Pediatrics,
Chief, Div. of Pediatric Nephrology,
Tulane University School of Medicine,
New Orleans, LA.*

On August 28th, 2014 **Dr. Ihor Yosypiv** presented **“Prorenin Receptor Regulates Nephron Induction During Mouse Kidney Development.”**

Summary: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), including renal hypoplasia/hypodysplasia (RHD), account for a majority of children with end-stage-renal disease requiring dialysis and renal transplantation. Fine balance of self-renewal and differentiation of nephron progenitors into nephrons determines the final number of nephrons, the structural and functional units of the kidney. Congenital reduction of nephron number, a condition called RHD, is associated with subsequent hypertension and chronic kidney disease in humans. Dr. Yosypiv’s laboratory is interested in the basic mechanisms which control differentiation of nephron progenitors, a group of “stem-like” cells. Dr. Yosypiv and his research group has demonstrated that conditional deletion of the prorenin receptor (PRR) in nephron progenitors and their derivatives in mice disrupts molecular programming of nephrogenesis ultimately resulting in congenital RHD. The long-term goal of Dr. Yosypiv’s research is to identify deleterious mutations of the PRR gene in humans with CAKUT and to develop novel therapies that can be applied to the study of nephron regeneration strategies in CAKUT.

Recent Publications

Bazzano LA, Hu T, Reynolds K, Yao L, Bunol C, Liu Y, Chen CS, Klag MJ, Whelton PK, He J. Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med.* 2014 Sep 2;161(5):309-18. doi: 10.7326/M14-0180. PMID: 25178568.

Coleman CB, Lightell DJ Jr, Moss SC, Bates M, Parrino PE, Woods TC. Elevation of miR-221 and -222 in the internal mammary arteries of diabetic subjects and normalization with metformin. *Mol Cell Endocrinol.* 2013 Jul 15;374(1-2):125-9. PMID: 23648338. PMCID: PMC3684440.

Chi, YW, Woods, TC. Clinical risk factors to predict deep venous thrombosis post-endovenous laser ablation of saphenous veins. *Phlebology.* 2014 Apr;29(3):150-3. PMID: 23434616.

Dobrowolski L, Kuczeriszka M, Castillo A, Majid DS, Navar LG. Role of atrial natriuretic peptide in mediating the blood pressure-independent natriuresis elicited by systemic inhibition of nitric oxide. *Pflugers Arch.* 2014 Jun 24. [Epub ahead of print]. PMID: 24953240.

Gonzalez AA, Green T, Luffman C, Bourgeois CR, Gabriel Navar L, Prieto MC. Renal medullary cyclooxygenase-2 and (pro)renin receptor expression during angiotensin II-dependent hypertension. *Am J Physiol Renal Physiol.* 2014 Oct 15;307(8):F962-70. PMID: 25143455.

Gonzalez AA, Womack JP, Liu L, Seth DM, Prieto MC. Angiotensin II Increases the Expression of (Pro)Renin Receptor During Low-Salt Conditions. *Am J Med Sci.* 2014 Sep 23. [Epub ahead of print]. PMID: 25250989.

Gong Y, Yu M, Yang J, Gonzales E, Perez R, Hou M, Tripathi P, Hering-Smith KS, Hamm LL, Hou J. The Cap1-claudin-4 regulatory pathway is important for renal chloride reabsorption and blood pressure regulation. *Proc Natl Acad Sci U S A.* 2014 Aug 25. [Epub ahead of print]. PMID: 25157135.

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Hering-Smith KS, Mao W, Schiro FR, Coleman-Barnett J, Pajor AM, Hamm LL. Localization of the calcium-regulated citrate transport process in proximal tubule cells. *Urolithiasis.* 2014 Jun;42(3):209-19. PMID: 24652587. PMCID: PMC4106718.

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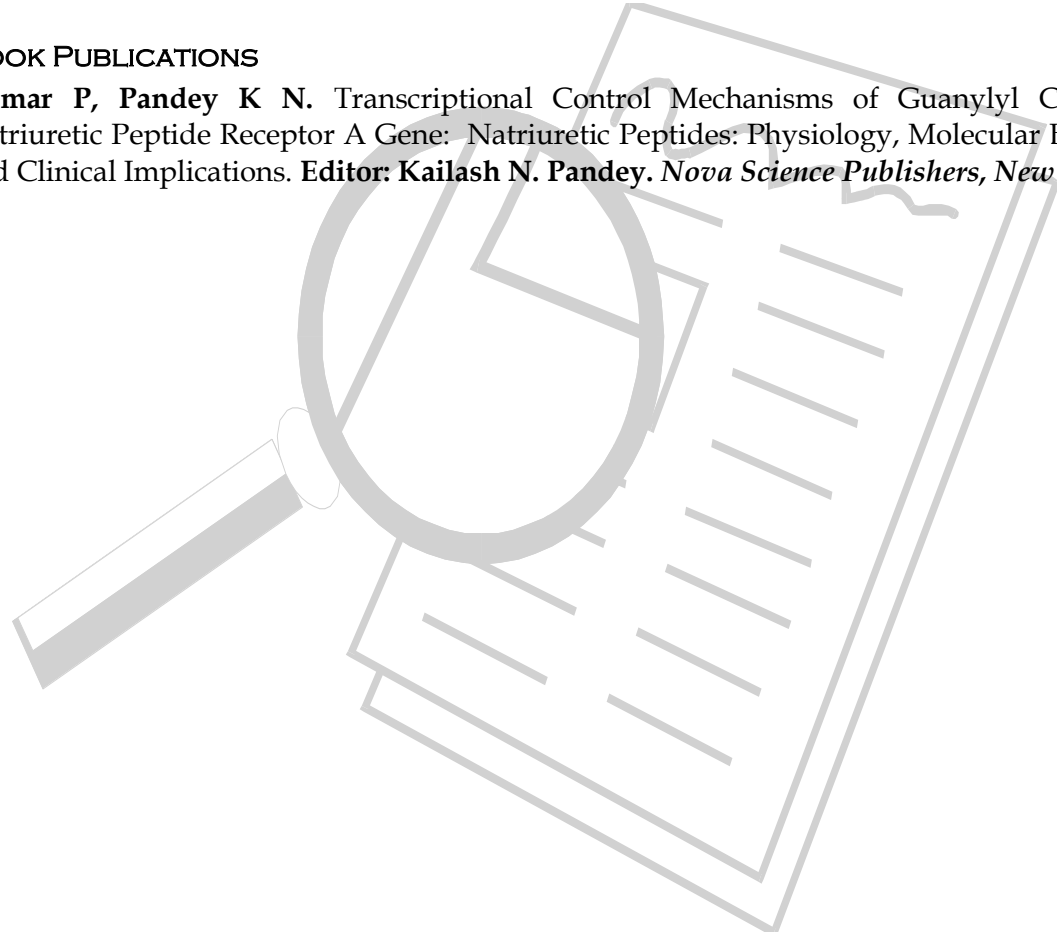
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Yan L, Yao X, Bachvarov D, Saifudeen Z, El-Dahr SS. Genome-wide analysis of gestational gene-environment interactions in the developing kidney. *Physiol Genomics*. 2014 Sep 1;46(17):655-70. Epub 2014 Jul 8. PMID: 25005792. PMCID: PMC4154247.

BOOK PUBLICATIONS

Kumar P, Pandey K N. Transcriptional Control Mechanisms of Guanylyl Cyclase/ Natriuretic Peptide Receptor A Gene: Natriuretic Peptides: Physiology, Molecular Biology, and Clinical Implications. **Editor: Kailash N. Pandey.** *Nova Science Publishers, New York.*



From May through August, 2014 investigators and physicians affiliated with T.H.R.C.E. participated in many regional, national, & international meetings.

Arteriosclerosis, Thrombosis, and Vascular Biology 2014 Scientific Sessions. May 1-3, 2014

- Bazan H, Lightell DJ, Sternbergh WC, Woods TC. Recently Ruptured Carotid Plaques Have Increased Levels Of circularRNA-16, which Negatively Regulates The Pro-proliferative And Antiapoptotic microRNA-221: A Novel Mediator Of Carotid Plaque Rupture.

World Congress of Cardiology Scientific Sessions, Melbourne, Australia, May 4-7, 2014

- Mills KT, Appel LJ, Chen J, Delafontaine P, Kusek J, Ojo AO, Rahman M, Townsend RR, Yang W, He J. Urinary sodium and potassium excretion and cardiovascular diseases in patients with chronic kidney disease: The chronic renal insufficiency cohort study. WCC14-ABS-1232.

Biology of Genomes meeting “The Biology of Genomes” Cold Spring Harbor, NY. May 6-10, 2014

- Xue C, Raveendran M, Fawcett G, White S, Rio Deiros D, Harris RA, Dahdouli M, Salerno W, Johnson Z, Vallender E, Wiseman R, Kubisch HM, Cox L, Kanthaswamy S, Smith, DG, Ferguson B, Muzny D, Gibbs RA, Yu F, Rogers J. Whole genome sequencing of 152 rhesus macaques reveals substantial polymorphism, complex demographic history and significant variability in ENCODE annotated sequences.

2014 Vascular Annual Meeting June 5-7, 2014

- Bazan H, Lightell DJ, Sternbergh WC, Woods TC. CircularRNA-16 in acutely asymptomatic carotid plaques: A novel mediator of carotid plaque rupture.

ESH-ISH Joint meeting, Athens, Greece June 13-16, 2014

- Navar LG, Shao W, Prieto MC, Katsurada A, Mitchell KD. Increased urinary angiotensinogen in the non-clipped kidneys of 2-kidney 1-clip hypertensive rats.

Continued...

***NIH/NIGMS Fifth Biennial National IDeA Symposium
Washington, DC, June 16 - 18, 2014***

- **Majid, Nina R.** COBRE Translational Research in Hypertension & Renal Biology
- **Murfee, Walter.** The effect of Aging on Microvascular Density and Angiogenesis.
- **Murfee, Walter.** A tissue culture model for time-lapse imaging of microvascular network growth and remodeling during angiogenesis.
- **Purnima Singh, Alex Castillo, Dewan S. A. Majid.** Hypertensive and renal injury responses to angiotensin II and high salt intake in interleukin-10 gene knockout mice. *Highlighted Poster*
- **Ryosuke Satou.** IL-6 derived from macrophages stimulates angiotensinogen in renal proximal tubular cells.

***Society for the Study of Ingestive Behavior, Seattle, WA, July
29-Aug 2, 2014***

- Gao H, Anwar IJ, Satou R, Krantz AM, Zsombok A, Derbenev AV. TRPA1 regulates neurons of the DMV. P151.
- Anwar IJ, Miyata K, Zsombok A. Olanzapine alters neuronal activity in the dorsal motor nucleus of the vagus. P148.

THRCE investigators and physicians were invited to lecture at various national and international events.

Hering-Smith, Kathleen:

- Presented, "Citrate: A Tale of Two Transporters," on June 9, 2014 at the Pharmacology Department at LSUHSC in Shreveport, Louisiana.

Navar, L. Gabriel:

- "Intrarenal Renin-Angiotensin System in Hypertension." Presented as the "Robert M. Hearin Distinguished Lecturer" on May 15, 2014 at the University of Mississippi, Medical Center, Jackson, MS.
- "Increased uAGT in non-clipped kidney of 2K1C hypertensive rats," at the Joint Meeting of the European Society of Hypertension (ESH) and the International Society of Hypertension (ISH) held in Athens, Greece on June 14, 2014.
- Chaired Workshop, "Hypertension and the Kidney," on June 15, 2014 at the ESH-ISH Hypertension Meeting in Athens, Greece.
- "Intrarenal/Intratubular Renin-Angiotensin System in Hypertension and Diabetes," on July 30, 2013 at the Seminar for Section of Endocrinology, Department of Medicine, Tulane SOM.
- "Activation of the Tubular Renin-Angiotensin System in Hypertension," on August 8, 2014 at the III International Symposium of the Renin Angiotensin System (RAS): Understanding Systemic, Intracellular and Tissue RAS. The meeting was held at Sao Paulo, Brazil. Also served as Co-Chair.
- Served as Chair and Lecturer, at the XXII Congress of the Brazilian Society of Hypertension/XX Scientific Sessions of the Interamerican Society of Hypertension, held in Salvador-Bahia, Brazil. Presented, "The Kidney and Hypertension," on August 15.

Pandey, Kailash N:

- "Natriuretic Peptides and their Receptors: Physiology, Molecular Biology, and Clinical Implications," on Mar 5, 2014 at the Department of Endocrinology, All India Institute of Medical Sciences, New Delhi, India.
- "Advances and Novel Concepts in the Field of Cellular and Molecular Biology of Natriuretic Peptides and their Receptors in Cardiovascular Regulation and Function," on May 8, at the Indian Institute of Informatics Technology,

Continued...

Allahabad, India.

- “Transcriptional Regulation & Function of Guanylyl Cyclase/Natriuretic Peptide Recepto-A,” on May 15, 2014 at the Amity University Institute of Pharmacy, in Noida-New Delhi, India.
- Presented a Plenary Session talk, “Genetic disruption of Npr1 upregulates cardiac expression of proinflammatory mediators” and Chaired the session, “Genetic Aspects of Cardiovascular Disease/Stem Cell and Gene Therapy,” on July, 2014 at the International Academy of Cardiology Annual Scientific Session -19th World Congress on Heart Disease, in Boston, MA.

Prieto, Minolfa C:

- “Renin and prorenin receptor” on August 8, 2014 at the 3rd International Symposium of the Renin Angiotensin System (RAS): Understanding Systemic, intracellular and tissue RAS. The meeting was held in Sao Paulo, Brazil. She also served as Co-Chair at the meeting.
- “Role of renin and prorenin receptor in the collecting duct in hypertension” at the XXII Congress of the Brazilian Society of Hypertension, Salvador-Bahia, Brazil on August 15, 2014.

Calendar of Events

THRCE Seminars

May 8, 2014

**No THRCE seminar due to scheduling conflict with
the Center for Aging Seminar Series**

The presentation for the Center for Aging Seminar Series is by Judy Delp (Associate Professor, Department of Physiology and Functional Genomics, University of Florida)

May 19, 2014 **

**Joint Seminar:
THRCE & Department of Physiology**

Alicia McDonough, PhD
Professor, Cell and Neurobiology
Keck School of Medicine University of South California, Los Angeles, CA.
*"Integrated regulation of sodium transporters along the nephron by
Angiotensin II and blood pressure."*

May 22, 2014

Prasad V.G. Katakam, MD, PhD
Assistant Professor, Department of Pharmacology,
Tulane School of Medicine, New Orleans, LA.
"Uncoupling of Nitric Oxide Synthase and Insulin Resistance."

June 5, 2014

Daniel R. Kapusta, PhD,
Professor of Pharmacology,
PI and Director, COBRE Cardiovascular Research Program,
LSU Health Sciences Center, New Orleans, LA.
*"Radiofrequency ablation of the renal nerves & Management of
Resistant Hypertension: Ongoing studies using the Spontaneously Hypertensive Rat."*

June 19, 2014

NO MEETING
NIH, NIGMS Fifth Biennial National IDeA Symposium
Washington, DC, June 16 - 18, 2014

June 30, 2014 **

**Joint Seminar:
THRCE & Department of Physiology**

Richard J. Roman, PhD
Professor and Chair, Department of Pharmacology and Toxicology,
University of Mississippi Medical Center, Jackson, MS.
"CYP450 Eicosanoids, Hypertension and Renal and Cerebral End Organ Damage."

July 3, 2014

NO MEETING
4th of July Holiday
Happy Independence Day!

July 17, 2014

Keith C. Ferdinand, MD
Chair, National Forum for Heart Disease & Stroke Prevention
Professor of Clinical Medicine
Tulane University School of Medicine, New Orleans, LA.
"Discussion Topic: The new blood pressure (BP) guidelines."

Calendar of Events

Continued...

July 31, 2014

Gary Sander, MD

Professor of Clinical Medicine

Tulane University School of Medicine, New Orleans, LA.

"Management of Hypertension in July 2014: Controversy and Progress."

August 14, 2014

Ryosuke Sato, PhD

Instructor, Department of Physiology,

Tulane University School of Medicine, New Orleans, LA.

"Pro-inflammatory cytokines derived from immune cells regulate angiotensinogen expression in renal proximal tubular cells."

August 28, 2014

Ihor V. Yosypiv, MD,

Associate Professor of Pediatrics, Department of Pediatrics,

Chief, Division of Pediatric Nephrology,

Tulane University School of Medicine, New Orleans, LA.

"Prorenin receptor regulates nephron induction during mouse kidney development."

September 11, 2014

NO MEETING

High Blood Pressure Research 2014 Scientific Sessions

San Francisco, California, Sept. 9-12, 2014

September 25, 2014

Sean P. Didion, PhD

Associate Professor, Departments of Pharmacology & Neurology

Director, MD/PhD Program,

The University of Mississippi Medical Center, Jackson, MS.

"Inflammation, Endothelial Dysfunction, and Angiotensin II."

October 9, 2014

No THRCE seminar due to scheduling conflict with the Tulane Diabetes Research Program special lecture

Speaker: C Ronald Kahn, MD Joslin Diabetes Center and Harvard Medical School

Lecture: Genes environment interactions in the pathogenesis of diabetes and metabolic syndrome

October 23, 2014

Kenneth D. Mitchell, PhD

Professor, Department of Physiology,

Tulane University School of Medicine, New Orleans, LA.

"Renal Derangements in ANG II-Dependent Hypertension: Role of PDG."

November 6, 2014

Aaron S. Dumont, MD

Charles B. Wilson Professor & Chairman, Department of Neurosurgery,

Tulane University School of Medicine, New Orleans, LA.

"Inflammation and Cerebral Aneurysms."

November 20, 2014

Wenzheng Zhang, PhD

Associate Professor, Department of Internal Medicine,

Division of Renal Diseases and Hypertension,

University of Texas Medical School, Houston, TX.

TBA

Conferences are held alternative Thursdays at 4:00pm in the Tulane Medical School, Pharmacology Library, Room 4700

*** Denotes the seminar date is not our normally scheduled day.*

CORE Facilities & Services

National Institute of
General Medical Sciences



Tulane Hypertension and Renal Center of Excellence (THRCE) houses 4 research core facilities that were developed during COBRE phases I and II and are now maintained and supported by a COBRE Phase III grant awarded by the NIH/NIGMS. 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 in hypertension 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 COBRE Core facilities can be utilized by both COBRE and other investigators within Tulane and other institutions for hypertension, cardiovascular and renal research. The 4 research Core facilities are:

- **The Molecular, Imaging, and Analytical Core:** This facility serves as the resource for instruments and equipment needed to perform advanced molecular biology, semi-quantitative immuno-histochemistry and bio-analytical experiments.
- **Animal and Gene-Targeted Core:** This facility maintains and generates new breeding pairs, does genotyping, and maintains colonies of genetically manipulated mice and rats.
- **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.
- **Clinical and Translational Core:** Promotes and facilitates clinical and translational studies in hypertension, kidney disorders, and related cardiovascular diseases.

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. For further information regarding the Core Facilities, please access <http://tulane.edu/som/thrce/>.

T.H.R.C.E.

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

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www.som.tulane.edu/centprog/htn/

The directors invite faculty members interested in participating in the activities of the T.H.R.C.E. to submit your name, phone number, fax number, and e-mail address to the Program Coordinator, Nina Majid by e-mail at htnctr@tulane.edu or regular mail to the address provided. Also, please forward all information (awards, publications, presentations and other news items) to this email address for inclusion in the next newsletter.