Tulane Hypertension and Renal Center of Excellence

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Tulane University
SCHOOL OF MEDICINE

A Message from the Director

Welcome to the Fall 2022 Newsletter of the Tulane Hypertension and Renal Center of Excellence (THRCE)! In this edition, we are delighted to share the latest developments and accomplishments of our faculty members and trainees in hypertension and kidney research and training. We are excited to announce two important updates at the THRCE during the second half of 2022. Firstly, our inaugural THRCE director, Dr. L. Gabriel Navar, has stepped down as the Chairman of the Department of Physiology after leading the department and THRCE's prominent hypertension and kidney research for 34 years. He has returned to his full-time faculty research on intratubular renin-angiotensin system and hypertension and is still working with great passion and energy. Secondly, we are thrilled to welcome our new Department of Physiology Chair, Dr. Heddwen Brooks, Ph.D., who joined us on November 1, 2022. Dr. Brooks brings with her a wealth of experience and expertise in sex differences, aquaporin biology, and kidney medulla physiology, as well as the vision, energy, and leadership needed to further advance hypertension and kidney research at Tulane.

We are also proud to highlight the recent achievements of two of our outstanding faculty members. Dr. Kailash N. Pandey was recognized with the prestigious Lewis K. Dahl Memorial Lectureship Award at the 2022 American Heart Association Council on Hypertension Research Conference in September 2022. This honor recognizes Dr. Pandey's pioneering work on salt, the kidney, and hypertension, as well as his work on the G protein-coupled natriuretic peptide receptor research. Dr. Minolfa Prieto served as the Chair of the 2022 Angiotensin Gordon Research Conference held in Ventura, California in November 2022, a testament to her leadership role in prorenin receptor and hypertension research. Many of our faculty members and postdoctoral fellows attended and presented their recent renin-angiotensin research at the Gordon Conference.

We have also continued to host a robust Frontiers in Hypertension and Kidney Research Seminar Series, with many nationally well-recognized and accomplished scientists invited to give onsite/hybrid seminars. We express our gratitude to the speakers who joined us, including Dr. Joo-Seop Park (Cincinnati Children's Hospital Medical Center), Dr. Kailash N. Pandey (Tulane University School of Medicine), Dr. Cooper Woods (Tulane University School of Medicine), Dr. Alfred K. Cheung (The University of Utah School of Medicine), and Dr. Mark C. Chappell (Wake Forest University School of Medicine), for sharing their most recent frontier hypertension and kidney research. The Seminar Series continues to play a key role in promoting and improving the THRCE's research and training programs.

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Lastly, we are proud of our faculty members, postdoctoral fellows, and graduate students who have remained active in presenting their new research results at many local, national, and international meetings. We extend our sincere gratitude to all members of the THRCE for their dedication and perseverance to their research work, and we wish everyone a safe, healthy, and successful 2023.

Sincerely, Jia 'Joe' Zhuo, MD, PhD

New Chair at the Department of Physiology

Heddwen Brooks, PhD, joined Tulane University as the new Chair of the Department of Physiology in November 2022. She arrived in Tulane from the University of Arizona, College of Medicine, where she was Professor of Biomedical Engineering and Professor of Medicine/Nephrology and Medical Pharmacology. Her research focuses on sex differences in physiology, integrating cross-disciplinary expertise in hypertension, diabetes, menopause, renal physiology, how the molecular signaling pathways involved in postmenopausal accelerated aging and how sex differences in inflammation, T-cells and macrophages change hypertension onset and the development of metabolic syndrome. In a recent interview, she expressed her excitement at joining Tulane and stated, regarding her new role, "The vision for the Department of Physiology is to build on our strong history of neuroscience and cardiovascular disease research. We will recruit additional outstanding researchers so that we can tackle some of the important health issues here in New Orleans and Louisiana including diabetes, hypertension and women's health." We are looking forward to collaborate with her team for many years to come.

Honors to THRCE Investigators

L. Gabriel Navar, PhD:

- Has stepped down as the Chairman of the Department of Physiology after thirty-four years. Dr. Navar's honorable services to the department and to Tulane University was recognized and acknowledged in a Reception hosted by Dr. L. Lee Hamm, the Dean of Tulane School of Medicine, on January 23, 2023.
- Was acknowledged by APS in the July 2022 issue of the Physiologist Magazine for receiving the distinguished "Research Hall of Fame" award from Tulane University.

Kailash Pandey, PhD:

- The American Heart Association (AHA) Council on Hypertension honored Pandey for his research with the 2022 Lewis K. Dahl Memorial Lecture Award. The Lewis K. Dahl Memorial Lecture was established in 1988 in honor of Dr. Dahl's pioneering work on the relations between salt, the kidney and hypertension, and for establishing a major genetically based experimental model of hypertension. As the recipient of the award, Dr. Pandey presented a lecture during the 2022 AHA's Hypertension Scientific Sessions.

2022 Angiotensin Gordon Research Conference

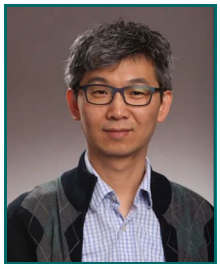
A number of THRCE affiliated investigators attended the 2022 Angiotensin Gordon Research Conference (GRC) held in Ventura in California. The meeting, chaired by Dr. Minolfa Prieto, focused on the latest advances in the renin-angiotensin-aldosterone system (RAAS) from discovery science to clinical impact. A highlight was the celebration of 22 years of the discovery of ACE2. The enigmas of ACE2 as a critical enzyme in the protective arm of the RAS and as mediator and potential therapeutic target in COVID-19 were discussed. Controversies on the progression of COVID-19 infection and long-term outcomes in populations treated with ACEi and/or ARBs were addressed. This conference featured novel topics, including the paracrine and intracrine RAAS and the interactions between systems at the subcellular and organelle levels, the role of the RAAS in non-cardiovascular systems, such as adipose tissue, bone marrow, liver, and immune cells and, sex differences in the regulation and changes of the RAAS during the life course.

2022 American Heart Association Heart Walk

The Tulane Hypertension and Renal Center of Excellence participated as one of 12 teams under the Tulane Health Banner in the 2022 American Heart Association (AHA) Heart Walk. In 2022, Tulane University was able to raise 9,926.54 for the 2022 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 2022 Heart Walk was held at Lasalle Park in Metairie, Louisiana on November 19, 2022.

Frontiers in Hypertension and Kidney Research Seminar

Researchers in the field of cardiovascular, hypertension, kidney, and associated diseases who are invited to present a THRCE Seminar are asked to provide a summary of their talk that we share with our newsletter audience. From July through December, 2022, the following speakers presented THRCE Sponsored Seminars.



Joo-Seop Park, PhD presented, "**Gene Regulatory Networks in Kidney Development**" on September 1, 2022, at the THRCE Frontiers in Hypertension and Kidney Research Seminar. Dr. Park is Associate Professor at the UC Department of Surgery, Divisions of Pediatric Urology & Developmental Biology, at the Cincinnati Children's Hospital in Ohio. The presentation was hosted jointly by THRCE & Kathy Newman Lecture of the Department of Pediatrics.

SUMMARY OF PRESENTATION:

Dr. Park's research interest is in how multipotent nephron progenitor cells make their cell fate decisions to differentiate into all of the various cell types found in the nephron. To address this, his lab aims to identify transcription factors that define cell identities for each nephron segment and elucidate how they interact with developmental signaling pathways in gene regulatory networks. Dr. Park presented recent findings on signaling pathways that regulate self-renewal and differentiation of nephron progenitors and transcription factors that define cell identities for proximal tubules and distal tubules.

Kailash N. Pandey, PhD, Professor and Vice Chair of Medical Research in the Department of Physiology at Tulane University School of Medicine, presented "**Genetic and Epigenetic Mechanisms Regulating Blood Pressure and Renovascular Function**" on September 29th, 2022.

SUMMARY OF PRESENTATION:

The mechanisms regulating BP are known to have a strong genetic component; however, the roles of specific genes involved in the pathogenesis of hypertension and kidney disorders are not well defined. Among the key regulators, are atrial and brain natriuretic peptides (ANP, BNP), signaling through GC-A/NPRA and second messenger cGMP. The genetic and epigenetic mechanisms regulating transcriptional activation and functional expression of candidate genes and receptor signaling cascades that control BP are not well understood. To delineate one of such mechanisms, we have determined the role of stimulatory transcription factors (TFs), including Ets-1 and SP-1, histone acetylases (HATs), and positive histone codes, which lowered BP and improved kidney function in disease states. On the contrary, the inhibitory TFs (CREB, HSF-4a, δEF-1), histone deacetylases (HDACs), and negative histone codes that suppressed Npr1 transcription and receptor signaling, heightened the renal and vascular dysfunction. Luciferase assay of Npr1 promoter and chromatin immunoprecipitation analyses indicated that RAR-α agonists recruited the stimulatory TFs (Ets-1/SP-1), p300-transcriptional co-activator, and positive histone marks, which dramatically enhanced Npr1 promoter activity and receptor signaling, thereby, lowering high BP and reducing renal dysfunction by subsequently suppressing the expression of proinflammatory and fibrotic genes. On the contrary, angiotensin II (ANG II) and transforming growth factor-β1 (TGF-β1) affected the Npr1 promoter embodying inhibitory TFs (CREB, HSF-4a, δEF-1) and negative histone marks that exhibited there pressive effect on Npr1 transcription, receptor signaling, and renal and vascular reactivity. Ongoing efforts are aimed at elucidating in vivo cell-specific mechanisms of genetic and epigenetic factors that might control high BP and renal and vascular dysfunction.

T. Cooper Woods, PhD, Associate Professor at the Department of Physiology and at Tulane Heart & Vascular Institute in Tulane University School of Medicine, presented a THRCE seminar on October 27th titled, "**miR-221 and -222 in Atherosclerosis.**"

SUMMARY OF PRESENTATION:

Atherosclerosis is a common co-morbidity of type 2 diabetes mellitus, driving an increase in heart attacks and strokes in this population. Atherosclerosis is a complex disease where multiple cell types interact in response to an injury to an artery. As the disease progresses a plaque forms in the artery wall that, if it ruptures, can cause heart attacks and ischemic strokes. Early in atherosclerosis, monocytes are recruited by an activated endothelium. Pro-inflammatory macrophages then promote vascular inflammation and vascular smooth muscle cell (VSMC) proliferation. We have found that in diabetes, two microRNAs, microRNAs-221 and -222 (miR-221/222) are elevated in vascular smooth muscle cells (VSMCs). This increase in miR-221/222 reduces the mRNA encoding proteins that prevent VSMC proliferation and allows for acceleration of plaque development. Exosomal transfer of microRNAs has emerged as a paracrine signaling mechanism regulating atherosclerotic plaque development. We obtained exosomes from VSMCs, following exposure to non-targeting or miR-221/-222 siRNA (-KD), isolated from diabetic (DVEs) and non-diabetic (NVEs) sources

and found that the miR-221/-222 content of DVEs was elevated. Incubation of endothelial cells with DVEs, but not NVEs, NVE-KDs, or DVE-KDs promoted increased intercellular adhesion molecule-1 expression and monocyte adhesion. Exposure to DVEs but not NVEs, NVE-KDs, or DVE-KDs also promoted pro-inflammatory polarization of human monocytes in miR-221/222 dependent manner. Finally, intravenous administration of DVEs, but not NVEs, resulted in a significant increase in atherosclerotic plaque development. Together these findings demonstrate that elevation of miR-221/222 in VSMCs promotes the cardiovascular complications of diabetes mellitus.

Alfred K. Cheung, MD, Professor of Medicine and Chief in the Division of Nephrology at the University of Utah Hospital, in Salt Lake City, Utah, presented, "**Controversies about KDIGO BP Guidelines on Techniques and Target**" on November 10th, 2022.

SUMMARY OF PRESENTATION:

Dr. Alfred Cheung is Chief of Division of Nephrology & Hypertension and Vice Chair for Research in Department of Internal Medicine at the University of Utah. His research has focused on clinical CKD, hypertension and hemodialysis. He co-chaired the BP guideline update for KDIGO that was published in 2021. He is also part of the SPRINT family.

Mark C. Chappell, PhD, FAHA, FASN, Professor, Department of Physiology and Pharmacology at Wake Forest School of Medicine in Winston-Salem in North Carolina, presented, "**The Renin-Angiotensin System in Fetal Programming of Hypertension,**" on December 8th 2022.

SUMMARY OF PRESENTATION:

Dr. Chappell's major focus are the pathways and function of the non-classical or alternative arm of the renin-angiotensin system (RAS) that comprise the Ang-(1-7)-ACE2-MAS receptor axis in various pathologies including hypertension, salt-sensitive renal injury, fetal programming events, and more recently, COVID-19. An overriding tenet of these studies is that loss of Ang-(1-7) tone is a key factor in the dysregulation of blood pressure and tissue injury as exemplified in fetal programming events.

In this presentation, Dr. Chappell discussed recent studies in an experimental model of fetal programming whereby pregnant ewes receive betamethasone treatment (BMX) at an identical dose and gestational time to women at risk for premature birth, and both female and male offspring exhibit a marked increase in blood pressure that associates with reduced circulating ACE2 and a lower Ang-(1-7):Ang II ratio. In brain, the dorsal medullary peptide ratio of Ang-(1-7):Ang II is reduced in BMX offspring that reflects a significant reduction in tissue ACE2, as well as lower MAS expression. Although CSF levels of ACE2 were unchanged in BMX sheep, the half-life of Ang-(1-7) is lower due to increased dipeptidyl aminopeptidase-3 (DAP3) activity that rapidly degrades Ang-(1-7). Renal ACE2 and MAS expression are reduced in the male BMX offspring and the males no longer respond to the natriuretic actions of Ang-(1-7). These studies emphasize that the early life environment is a key period for perinatal events associated with increased cardiovascular risk and that chronic alterations in the alternative axis of the RAS may play a crucial role.

Abstracts & Presentations

The following Abstracts & Presentations were presented by THRCE affiliated investigators

Hypertension 2022 Scientific Sessions: San Diego, CA, Sept 7 – 10, 2022

Leite APO, Li XC, Hassan R, Zhuo JL. Deletion of Na^+/H^+ exchanger 3 selectively in the proximal tubules doesn't prevent the development of doca-salt hypertension in PT-Nhe3$^{-/-}$ mice. Hypertension: Volume 79, issue suppl_11 September 2022 – Poster presentation, abstract P111.

Li XC, Hassan R, Leite APO, Zhuo JL. Double deletion of AT_1a receptors and Na^+/h^+ exchanger 3 In the proximal tubules attenuates angiotensin II-induced and 2k1c goldblatt hypertension in proximal tubule-specific PT-Agtr1a$^{-/-}$/Nhe3$^{-/-}$ mice. Hypertension: Volume 79, issue suppl_11 September 2022 – Oral presentation, abstract 098.

Ramasamy C, Subramanian U, Pandey KN. Genetic mechanisms of cardiac hypertrophy and fibrosis in global Npr1 gene-ablated male and female mice. Hypertension: Volume 79, issue suppl_11 September 2022 - Oral presentation, abstract 068.

Satou R, Ye D, Lu HS, Katsurada A, Dugas CM, Daugherty A, Motazedian S, Navar LG. Stimulation of intrarenal angiotensinogen expression and the development of hypertension and kidney injury in angiotensin II-infused hepatic angiotensinogen knockout mice. Hypertension: Volume 79, issue suppl_11 September 2022 – Oral presentation, abstract 044.

Yokota R, Leite APO, Faça VM, Casarini DE. Mechanisms of signaling pathways triggered by angiotensin-I converting enzyme in CHO ECA cells treated with Captopril. Hypertension: Volume 79, issue suppl_11 September 2022 – Poster presentation, abstract P117.

2022 International Society of Hypertension Scientific Meeting: Kyoto, Japan, Oct 12 - 16, 2022

Li XC, Wang CH, Hassan R, Leite APO, Sato A, Dugas C, Sato R, Zhuo JL. Deletion of AT_1a receptors in the proximal tubules augments natriuretic response to atrial natriuretic peptide via NPR/cGMP/NO signaling. Journal of Hypertension. 41(Suppl 1):e63, January 2023. | DOI: 10.1097/01.hjh.0000913336.93041.94.

Li XC, Hassan R, Leite APO, Sato A, Dugas C, Sato R, Zhuo JL. Angiotensin II AT_1a receptors in the proximal tubules play a critical role in the development of two-kidney, one-clip goldblatt hypertension. Journal of Hypertension, 41(Suppl 1):e284, 2023. DOI: 10.1097/01.hjh.0000915632.41851.c9.

Annual Kidney Week Meeting: Orlando, FL, Nov 3-6, 2022

Li XC, Zhuo JL. Deletion of AT_1a receptors selectively in the proximal tubules of the kidney augments glomerular filtration in male and female PT-Agtr1a$^{-/-}$ mice. Abstract: SA-PO768.

2022 Angiotensin Gordon Res. Conference: Ventura, CA, Nov 13-18, 2022,

Navar LG, Satou R, Hansen-Estruch C, Bikhet MH, Javed M, Katsurada A, Shao W, Ayares D, Cooper DKC, Judd E. Is there an incompatibility of RAAS in baboons with pig kidneys?

Leite APO, Li XC, Hassan R, Zhuo JL. Important roles of Sirt3 on kidney functions of wild-type & Sirt3 knockout mice during angiotensin II-induced hypertension.

Li XC, Hassan R, Leite APO, Dugas C, Sato A, Sato R, Zhuo JL. Double deletion of AT_1a receptors and Na^+/H^+ exchanger 3 in the proximal tubules attenuates angiotensin II-induced and 2K1C goldblatt hypertension in proximal tubule-specific PT-Agtr1a$^{-/-}$/Nhe3$^{-/-}$ mice.

Invited Presentation

L. Gabriel Navar, PhD, was invited to participate in a PerfWeb Special Program on "The Kidney" October 22, 2022 as part of a PerfWeb Series by Joe Basha, CCP. He, along with Dr. Supaporn Kulthinee, discussed normal renal physiology and how the kidney reacts to the altered physiology associated with cardiopulmonary bypass and heart surgery. He was also invited to participate as a panelist in the 2022 Angiotensin Gordon Research Conference (GRC), held in Ventura, California on November 15, 2022.

Jia Zhuo, MD, PhD, was invited to Chair and as a discussant at the 2022 Angiotensin GRC, held in Ventura, California on November 15, 2022.

Also at the 2022 GRC meeting , **Ryosuke Satou, PhD**, presented, "Kidney Organoids: Progress and Remaining Challenges on November 17, 2022

Publications

Publications published between July through December, 2022 that acknowledges either funding awards affiliated to the center, the THRCE center itself, or one of the center's CORE facilities.

Gonzalez AA, Olsen EL, Killeen SZ, Blair RV, Seshan SV, Jaimes EA, Roy CJ, Prieto MC. Elevated soluble urokinase plasminogen activator receptor is associated with renal dysfunction in a Chlorocebus atheiops COVID-19 model. *J Med Primatol. 2023 Apr;52(2):131-134. doi: 10.1111/jmp.12626. Epub 2022 Nov 15.* PMID: 36377612, PMCID: PMC10023264.

Hansen-Estruch C, Bikhet MH, Javed M, Katsurada A, Satou R, Shao W, Ayares D, Venkataramanan R, Cooper DKC, Judd E, Navar LG. Renin-angiotensin-aldosterone system function in the pig-to-baboon kidney xenotransplantation model. *Am J Transplant. 2023 Mar;23(3):353-365. doi: 10.1016/j.ajt.2022.11.022.* Epub 2023 Jan 5. PMID: 36695679

Lara LS, Gonzalez AA, Hennrikus MT, Prieto MC. Hormone-dependent regulation of renin and effects on prorenin receptor signaling in the collecting duct. *Curr Hypertens Rev. 2022;18(2):91-100. doi: 10.2174/1573402118666220216105357*. PMID: 35170417

Li XC, Hassan R, Leite APO, Katsurada A, Dugas C, Sato R, Zhuo JL. Genetic deletion of AT_1a receptor or Na+/H+ exchanger 3 selectively in the proximal tubules of the kidney attenuates two-kidney, one-clip goldblatt hypertension in mice. *Int J Mol Sci. 2022 Dec 13;23(24):15798. doi: 10.3390/ijms232415798.* PMID: 36555438, PMCID: PMC9779213.

Lin H, Geurts F, Hassler L, Batlle D, Mirabito Colafella KM, Denton KM, Zhuo JL, Li XC, Ramkumar N, Koizumi M, Matsusaka T, Nishiyama A, Hoogduijn MJ, Hoorn EJ, Danser AHJ. Kidney angiotensin in cardiovascular disease: Formation and drug targeting. *Pharmacol Rev. 2022 Jul;74(3):462-505. doi: 10.1124/pharmrev.120.000236.* PMID: 35710133, PMCID: PMC9553117.

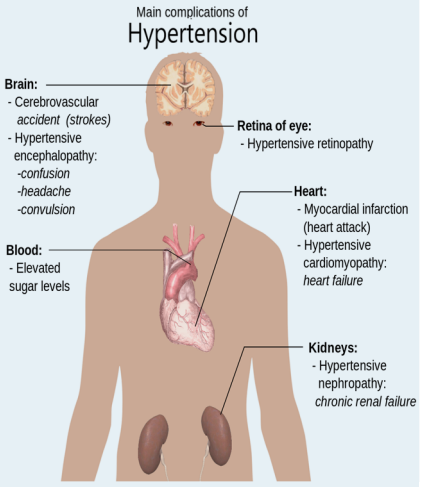
Patel NR, K C R, Blanks A, Li Y, Prieto MC, Meadows SM. Endothelial cell polarity and extracellular matrix composition require functional Atp6ap2 during developmental and pathological angiogenesis. *JCI Insight. 2022 Oct 10;7 (19):e154379. doi: 10.1172/jci.insight.154379.* PMID: 35998033, PMCID: PMC9675464.

Satou R, Franco M, Dugas CM, Katsurada A, Navar LG. Immunosuppression by mycophenolate mofetil mitigates intrarenal angiotensinogen augmentation in angiotensin II-dependent hypertension. *Int J Mol Sci. 2022 Jul 12;23 (14):7680. doi: 10.3390/ijms23147680.* PMID: 35887028 PMCID: PMC9319385.

Visniauskas B, Reverte V, Abshire CM, Ogola BO, Rosales CB, Galeas-Pena M, Sure VN, Sakamuri SSVP, Harris NR, Kilanowski-Doroh I, McNally AB, Horton AC, Zimmerman M, Katakam PVG, Lindsey SH, Prieto MC. High plasma soluble prorenin receptor (sPRR) is associated with vascular damage in male but not female mice fed a high fat diet. *Am J Physiol Heart Circ Physiol. 2023 Mar 17. doi: 10.1152/ajpheart.00638.2022.* PMID: 36930656.

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 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

2023 Southern Regional Meeting
~ Hotel Intercontinental, New Orleans: February 2-4, 2023

Tulane Research, Innovation and Creativity Summit
~ Tulane University: on March 1-2, 2023

World Kidney Day 2023
~ March 9, 2023

American Physiology Summit:
~ Long Beach, CA: April 20–23, 2023

European League Society of Hypertension (ESH) 2023
~ Milan (Italy): June 23-26, 2023

Physiological Society Annual Conference
~ Harrogate, UK: July 10 - 12, 2023

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