BIOGRAPHICAL SKETCH

NAME: Sathish Kumar

eRA COMMONS USER NAME: kusathis

POSITION TITLE: Associate Professor (tenured)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Tamil Nadu Veterinary & Animal Sciences University (TANUVAS), India	DVM	1996	Veterinary Medicine
TANUVAS	MVSc	1999	Pharmacology & Toxicology
Indian Veterinary Research Institute, India	PhD	2003	Pharmacology & Toxicology
Southern University and A&M College (SUBR), Baton Rouge, Louisiana	Fellowship	2007	Cardiovascular Toxicology
University of Texas Medical Branch (UTMB), Galveston, Texas	Fellowship	2009	Cardiovascular Physiology and Perinatal Biology

A. PERSONAL STATEMENT

In this proposed grant, we will determine the impact of per- and polyfluoroalkyl substances (PFAS) on pregnancy-related maternal physiology. Specifically, to understand how perfluorooctanesulfonic acid (PFOS, a legacy PFAS) impacts maternal cardiovascular function and placental vascularization and nutrient transport capacity.

I have expertise in vascular and placental studies with many signaling pathways, including renin-angiotensin system (RAS), nitric oxide (NO), endothelium-derived hyperpolarizing factor, potassium channels, MAP kinases, protein kinase C, intracellular calcium and nutrient transporters, in endothelial and placental function. I have published more than 40 peer-reviewed articles on vascular and placental function and related signaling mechanisms. I have several years of experience in studies in rat models of vascular adaptations during pregnancy and their regulation by endocrine factors. Early in my career, I characterized the impact of Aluminium toxicity on brain dopamine levels and motor and cognitive function in rats. Then, I examined NO- and α_2 adrenoceptor-mediated vascular signaling mechanisms in pulmonary arteries. During postdoctoral research, I carried out studies to investigate the impact of environmental ozone in cardiovascular and neurological dysfunctions. I performed cellular signaling and gene expression studies in cardiac and vascular cells. I uncovered the role of a new class of oxysterols viz. cholesterol secoaldehyde, which is formed in the lungs due to the interaction of ozone with the membrane cholesterol, in mediating the ill-effects of environmental ozone on internal organs like the heart and brain. Later, at UTMB in the Ob/Gyn department, I expanded my cardiovascular studies to include pregnancy vascular adaptations and fetal programming of adult cardiovascular diseases. I examined the mechanisms by which maternal cigarette smoke exposure, binge alcohol drinking, unbalanced diet, and androgen excess affect maternal physiology and placental function. Recently, I laid the groundwork to develop a pregnant rat model of PFOS exposure through drinking water and provided strong evidence that elevated PFOS during pregnancy increased the risk of hypertension in adult male and female offspring. Recently, with the help of my lab personnel and collaborator, we obtained several exciting data sets on the role of PFOS on maternal vascular adaptations. Several data sets in the preliminary studies are very exciting: elevated PFOS levels in pregnant rats (at levels relevant to human exposure) increases blood pressure, with endothelial dysfunction in uterine arteries. PFOS also decreases the placental size, VEGF expression, and nutrient transport.

As a PI on NIH-funded grants (R03 HD069750, R01 HL119869, and R01 HL134779), I have successfully administered projects (e.g., staffing, research, and budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and the construction of a realistic research plan, timeline, and budget.

I have a broad background with specific training and expertise in key research areas for this application. In addition, Dr. Sarah Yang (other significant contributor), a toxicologist and groundwater specialist (in the Bureau of Environmental and Occupational Health, Wisconsin Division of Public Health), and Drs. Kathleen Antony (Co-I) and Dinesh Shah (consultant), physician-scientists, and expert clinical perinatologists have agreed to support me in the proposed work. In summary, my expertise and experience in both vascular and placental biology, along with the support of my collaborators, will aid in the successful completion of the aims proposed in this project.

Note: My publications prior to 2016 appear under the name Sathishkumar K.

1. Dangudubiyyam SV, Mishra JS, Zhao H, **Kumar S.** Perfluorooctane sulfonic acid (PFOS) exposure during Pregnancy Increases Blood Pressure and Impairs Vascular Relaxation Mechanisms in the Adult Offspring. *Reprod Toxicol.* 2020 Sep 24; doi: 10.1016/j.reprotox.2020.09.008. Online ahead of print. PMID: 32980420. PMCID: (in process)
2. **Sathishkumar K**, Elkins R, Chinnathambi V, Gao H, Hankins GD, Yallampalli C. Prenatal testosterone-induced fetal growth restriction is associated with down-regulation of rat placental amino acid transport. *Reprod Biol Endocrinol.* 2011 Aug 3;9:110. PMID: 21812961. PMCID: 3162507
3. Gopalakrishnan K, Mishra JS, Chinnathambi V, Vincent KL, Patrikeev I, Motamedi M, Saade GR, Hankins GD, **Sathishkumar K**. Elevated Testosterone Reduces Uterine Blood Flow, Spiral Artery Elongation, and Placental Oxygenation in Pregnant Rats. *Hypertension*. 2016;67(3):639-9. PMID: 26781277; PMCID: PMC4752400
4. Chinnathambi V, Balakrishnan M, Ramadoss J, Yallampalli C, **Sathishkumar K**. Testosterone alters maternal vascular adaptations: role of the endothelial NO system. *Hypertension*. 2013;61(3):647-54. PMID: 23339170. PMCID: PMC3596870

B. Positions And Honors

Positions and Employment

1998 - 2000	Deputy Manager, Alved Pharma and Foods Pvt. Ltd., Chennai
2003 - 2004	Research Scientist, Ranbaxy Research Laboratories, Gurgaon
2004 - 2007	Cardiovascular Toxicology Fellowship, Southern University and A&M College, Baton Rouge, LA
2007 - 2009	Postdoctoral Fellow, Department of Obstetrics & Gynecology, UTMB, Galveston, TX
2009 - 2010	Instructor, Department of Obstetrics & Gynecology, UTMB, Galveston, TX
2010 - 2016	Assistant Professor (tenure-track), Department of Obstetrics & Gynecology, UTMB, Galveston
2014 – 2016	Assistant Professor, Biochemistry and Molecular Biology Graduate Program, UTMB, Galveston
2014 –2016	Assistant Professor, NIEHS Center for Environmental Toxicology, UTMB, Galveston, TX
2016– 2017	Associate professor (Tenured), Department of Obstetrics & Gynecology, UTMB, Galveston, TX.
2017–	Associate professor (Tenured), Department of Comparative Biosciences, University of Wisconsin, Madison, WI
2017–	Associate professor (Adjunct), Department of Obstetrics & Gynecology, University of Wisconsin, Madison, WI

Other Experience and Professional Memberships

2005 - 2007	Member, Society of Free Radical Biology and Medicine
2005 - 2009	Member, North American Vascular Biology Organization
2007 - 2010	Member, Science Advisory Board
2008 -	Member, Society for Study of Reproduction
2011 - 2019	Member, Developmental Origins of Health and Disease
2011 -	Member, American Heart Association
2013 - 2019	Member, Perinatal Research Society
2014 -	Member, Society for Reproduction Investigation

Honors

1999	Best Postgraduate Student, Madras Veterinary College, Chennai
1999	Gold medal for being a topper in master's program and excellence in Pharmacology, Madras Veterinary College, Chennai
1999	Best Student in the Subject of Pharmacology, Madras Veterinary College, Chennai
2002	Senior Research Fellowship, Indian Council of Agricultural Research, New Delhi, Indian Council of Agricultural Research, New Delhi
2008	Excellence in Basic Science Research, 6th annual meeting of Center for Interdisciplinary Research in Women's Health (CIRWH), UTMB, Galveston, TX
2009	Travel award, 42nd Annual Meeting of the Society for Study of Reproduction, Pittsburgh, PA
2010	Young Investigator Award, Perinatal Research Society, Avon, CO
2011	Presidents Pfizer Award for meritorious research presentation, Society for Gynecological

	Investigation, San Diego, CA
2012	Invited to give oral presentation at the "Late Breaking Science" session, 18th World Congress of International Society for Study of Hypertension in Pregnancy, Geneva, Switzerland
2014	Editorial Board Member, Austin Journal of Obstetrics and Gynecology
2014	Board of Reviewing Editors, Biology of Reproduction
2014	Researcher of the Month April/May, UTMB Research Services
2014	Lalor Foundation Award for Outstanding Research, Society for Study of Reproduction, Grand Rapids, MI
2015, 2017 and 2020	Presidents Pfizer Award for meritorious research, Society for Reproductive Investigation, San Francisco, CA (2015), Orlando, FL (2017), and Paris, France (2019).
2020	Zoetis Distinguished Teacher Award for teaching effectiveness and leadership in veterinary education

C. CONTRIBUTION TO SCIENCE

1. Environmental ozone, cholesterol ozonation products and their biological effects: Dr. Kumar's early publications directly addressed the molecular mechanisms by which ozone inflicts damage to the heart and brain. Ozone does not penetrate far beyond the air-tissue boundary (≤2 μm) in the lung to cause damage to distant organs like the heart and brain. Dr. Kumar demonstrated that secosterols, the reaction product formed in the lung due to ozone's interaction with cholesterol, are a mediator of the cytotoxic effect of environmental ozone in heart cells and neuronal cells. Dr. Kumar also established that secosterols promote aggregation of β-amyloid proteins, the pathognomonic feature in Alzheimer's disease. These observations were consistent with the identification of cholesterol secoaldehyde in brain samples of Alzheimer's patients. Using genomic approaches including microarray and real-time PCR technologies, Dr. Kumar demonstrated activation of the plasma membrane-bound NADPH oxidase system in neuronal cells exposed to secosterols and that antioxidants efficiently reverses these ill-effects. Following these findings, Dr. Kumar was invited to contribute 2 book chapters to Free Radicals and Antioxidant Protocols for the Methods in Molecular Biology series (Humana Press, Totowa, NJ). The U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, cited Dr. Kumar's findings in their review of the "national ambient air quality standards for ozone." His finding is also cited in a well-known resource book, "Research Progress in Alzheimer's disease and Dementia," which is frequently referenced by clinical practitioners.
   a. **Sathishkumar K**, Haque M, Perumal TE, et al. A major ozonation product of cholesterol, 3beta-hydroxy-5-oxo-5,6-secocholestan-6-al, induces apoptosis in H9c2 cardiomyoblasts. FEBS Lett. 2005;579(28):6444-50. PMID: 16288747.
   b. **Sathishkumar K**, Murthy SN, Uppu RM. Cytotoxic effects of oxysterols produced during ozonolysis of cholesterol in murine GT1-7 hypothalamic neurons. Free Radic Res. 2007;41(1):82-8. PMID: 17164181.
   c. **Sathishkumar K**, Xi X, Martin R, et al. Cholesterol secoaldehyde, an ozonation product of cholesterol, induces amyloid aggregation and apoptosis in murine GT1-7 hypothalamic neurons. J Alzheimers Dis. 2007;11(3):261-74. PMID: 17851176.
   d. **Sathishkumar K**, Gao X, Raghavamenon AC, et al. Cholesterol secoaldehyde induces apoptosis in H9c2 cardiomyoblasts through reactive oxygen species involving mitochondrial and death receptor pathways. Free Radic Biol Med. 2009;47(5):548-58. PMID: 19477266.
2. Maternal Vascular adaptations and the impact of androgens: Dr. Sathish Kumar began working on the mechanisms that impair cardiovascular adaptations to pregnancy in 2007. Dr. Kumar initially received support for this work with an NIH R03 developmental grant. In contrast to most studies that examined the beneficial effects of estradiol and progesterone, Dr. Kumar discovered that androgens adversely affect maternal vascular and placental function. Dr. Kumar developed a unique rat model that mimics human testosterone levels and pattern as observed in preeclamptic pregnancies and showed that elevated testosterone levels during pregnancy includes key features seen in women with preeclampsia, such as hypertension, proteinuria, endothelial dysfunction, exaggerated vascular contractile response to angiotensin II, placental insufficiency with decreased nutrient transport capacity, and fetal growth restriction. This study was published in Hypertension in 2013. Later, a commentary appeared in Hypertension, stating that this study is novel and provides critical mechanistic insight and potential therapeutic targets for gestational hypertension, and emphasized the need for clinical translation of this

important work. Dr. Kumar was invited to present this finding in the “Late Breaking Science” session of the 18th World Congress of International Society for Study of Hypertension in Pregnancy in Geneva, Switzerland. Further work stemming from these findings led us to examine the placentas of preeclamptic women to find that the placenta contributes to increased androgen production and expresses higher androgen receptor levels. Recently, he demonstrated that clinically relevant concentrations of testosterone produced a reduction in uterine arterial blood flow and disruption of uteroplacental arterial vasculature, resulting in placental hypoxia and fetal growth restriction in pregnant rats. Elevated maternal testosterone-induced disruption of placental vascular development was associated with underlying alteration in the expression of genes involved in blood vessel development and angiogenesis. Intriguingly, elevated testosterone-induced striking differences in altering different sets of genes in the male and female placentas. The implication is that understanding testosterone’s influences on the maternal cardiovascular system could lead to new therapeutic approaches to ameliorate hypertensive effects during pregnancy.

a. **Sathishkumar K**, Balakrishnan M, Chinnathambi V, Chauhan M, Hankins GD, Yallampalli C. Fetal sex-related dysregulation in testosterone production and their receptor expression in the human placenta with preeclampsia. J Perinatol. 2012;32(5):328-35. PMID: 21904298; PMCID: PMC3712643.
b. **Kumar S**, Gordon GH, Abbott DH, Mishra JS. Androgens in maternal vascular and placental function: implications for preeclampsia pathogenesis. *Reproduction*. 2018; 156(5):R155-R167. PMID: 30325182. PMCID: PMC6198264
a. Chinnathambi V, Blesson CS, Vincent KL, Saade GR, Hankins GD, Yallampalli C, **Sathishkumar K**. Elevated testosterone levels during rat pregnancy cause hypersensitivity to angiotensin II and attenuation of endothelium-dependent vasodilation in uterine arteries. Hypertension. 2014;64(2):405-14. PMID: 24842922; PMCID: PMC4096063.
b. Gopalakrishnan K, Mishra JS, Chinnathambi V, Vincent KL, Patrikeev I, Motamedi M, Saade GR, Hankins GD, **Sathishkumar K**. Elevated Testosterone Reduces Uterine Blood Flow, Spiral Artery Elongation, and Placental Oxygenation in Pregnant Rats. Hypertension. 2016;67(3):639-9. PMID: 26781277; PMCID: PMC4752400

3. Fetal programming of adult vascular dysfunction: In his early work, Dr. Kumar discovered that prenatal insults, such as protein restriction and elevated testosterone levels, lead to adult life hyperandrogenism and hypertension that is more pronounced in males than females. This sex-related difference in cardiovascular risk has been attributed to the protective effects of estrogens. Dr. Kumar’s studies provide a different approach, addressing the effects of postnatal androgens. His work led to the important observation that elevated testosterone levels during adult life dynamically regulate blood pressure and that this effect is mediated via heightened angiotensin II type 1 receptor (AGTR1)- and protein kinase C (PKC)-mediated signaling. Dr. Kumar identified a novel androgen-mediated mechanism that controls the expression of PKCδ in mesenteric artery smooth muscle cells through positive regulation of PKCδ transcript and protein levels. He identified the functional androgen response and enhancer element that binds the androgen receptor in response to androgen stimulation in the PKCδ gene promoter and intron 1, respectively. These studies provide a paradigm shift in exploring the role of androgens in hypertension, not only in males but also in females. Dr. Kumar served as the primary investigator or co-investigator in all of these studies.
   a. Chinnathambi V, Balakrishnan M, Yallampalli C, **Sathishkumar K**. Prenatal testosterone exposure leads to hypertension that is gonadal hormone-dependent in adult rat male and female offspring. Biol Reprod. 2012;86(5):137, 1-7. PMID: 22302690; PMCID: PMC3364920.
   b. **Sathishkumar K**, Balakrishnan M, Chinnathambi V, et al. Temporal alterations in vascular angiotensin receptors and vasomotor responses in offspring of protein-restricted rat dams. Am J Obstet Gynecol. 2012;206(6):507.e1-10. PMID: 22537420; PMCID: PMC3361632.
   c. **Sathishkumar K**, Balakrishnan MP, Yallampalli C. Enhanced mesenteric arterial responsiveness to angiotensin II is androgen receptor-dependent in prenatally protein-restricted adult female rat offspring. Biol Reprod. 2015;92(2):55. PMID: 25550341; PMCID: PMC4342791.
   d. Blesson CS, Chinnathambi V, Hankins GD, Yallampalli C, **Sathishkumar K**. Prenatal testosterone exposure induces hypertension in adult females via androgen receptor-dependent protein kinase Cδ-mediated mechanism. Hypertension. 2015;65(3):683-90. PMID: 25489059; PMCID: PMC4326589.

4. Sex-specific vascular mechanisms of hypertension: Sex differences are often neglected when considering diagnosis or treatment. Dr. Sathish Kumar’s studies provide seminal observations that there are distinct

sex-specific hypertension signaling mechanisms in the endothelium. Dr. Kumar identified that the endothelial EDHF-mediated vasodilator pathway is selectively impaired in hypertensive males, whereas only the nitric oxide (NO)-mediated relaxation system is affected in hypertensive females. This information might be clinically relevant because sex differences in clinical responsiveness to antihypertensive therapies have been reported. Recently, Dr. Kumar demonstrated that the impaired EDHF relaxation in hypertensive males could be restored with the angiotensin-converting enzyme inhibitor enalapril. These studies lay the groundwork for the identification of novel, sex-specific therapeutic strategies, and new drug discovery paradigms for the treatment of hypertension.

a. **Sathishkumar K**, Elkins R, Yallampalli U, Yallampalli C. Protein restriction during pregnancy induces hypertension and impairs endothelium-dependent vascular function in adult female offspring. J Vasc Res. 2009;46(3):229-39. PMID: 18957856; PMCID: PMC2860528.
b. Chinnathambi V, Yallampalli C, **Sathishkumar K.** Prenatal testosterone induces sex-specific dysfunction in endothelium-dependent relaxation pathways in adult male and female rats. Biol Reprod. 2013;89(4):97. PMID: 23966325; PMCID: PMC4076398.
c. Chinnathambi V, More AS, Hankins GD, Yallampalli C, **Sathishkumar K.** Gestational exposure to elevated testosterone levels induces hypertension via heightened vascular angiotensin II type 1 receptor signaling in rats. Biol Reprod. 2014;91(1):6. PMID: 24855104; PMCID: PMC4434963.
d. More AS, Mishra JS, Hankins GD, Yallampalli C, **Sathishkumar K.** Enalapril Normalizes Endothelium-Derived Hyperpolarizing Factor-Mediated Relaxation in Mesenteric Artery of Adult Hypertensive Rats Prenatally Exposed to Testosterone. Biol Reprod. 2015;92(6):155. PMID: 25972013; PMCID: PMC4652613.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/sathish.kumar.1/bibliography/41995480/public/?sort=date&direction=descending

D. RESEARCH SUPPORT

Ongoing Research Support

NHLBI- R01 HL134779-01A1 (PI: Kumar) 08/15/2017 - 08/14/2021
Vascular AT2R expression and function during pregnancy
The goal of this proposal is to examine the molecular mechanism of vascular angiotensin type 2 receptor (AT2R) upregulation and its importance in normal pregnancy-associated vascular function. Studies will also examine if the activation of this receptor system can reverse preeclamptic vascular dysfunction and hypertension. The proposed study could lead to the identification of targets to treat or prevent preeclampsia.

Completed Research Support

NHLBI- R01 HL119869 (PI: Kumar) 08/09/2013 - 05/31/2019
Sex-specific fetal programming of adult vascular dysfunction and hypertension
The proposed studies, focusing on a mechanistic molecular link between adverse intrauterine environments and development of a hypertensive phenotype, will provide direct evidence that elevated androgen levels during pregnancy increase the risk of hypertension and cardiovascular disease in the offspring. This new evidence will provide several possible sex-specific approaches to improving vascular function and reducing high blood pressure.

NICHD- R03 HD069750 (PI: Kumar) 07/25/2011 – 06/30/2014
Maternal Androgen Excess: Vascular and Placental Function and Fetal Consequences
The main goal of this project is to examine the effect of elevated maternal testosterone levels on maternal cardiovascular adaptations to pregnancy and placental angiogenesis and nutrient transport capacity.

NHLBI- R01 HL102866 (PI: Yallampalli; Co-I: Kumar) 12/01/2010–11/30/2014
Developmental Programming: Influence of Sex Steroids and Mechanisms
This project will assess the mechanisms underlying the developmental programming of adult health and disease and the influence of sex steroid hormones.

NHLBI- R01 HL058144 (PI: Yallampalli; Co-I: Kumar) 07/01/2013–06/30/2017
Sex Steroid Hormones and Calcitonin Gene-Related Peptide
Our goal is to define the role of calcitonin gene-related peptide family peptides in the regulation of female vascular functions and to examine their involvement of these peptides in uteroplacental function.