BIOGRAPHICAL SKETCH

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NAME: Raizada, Mohan K.

eRA COMMONS USER NAME (credential, e.g., agency login): mraizada

POSITION TITLE: Distinguished Professor of Physiology & Functional Genomics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Lucknow, India	B.Sc.	1966	Biol., Chem., & Botany
University of Lucknow, India	M.Sc.	1968	Biochemistry
Central Drug Research Institute/University of Kanpur, India	Ph.D.	1972	Biomedical Sciences
Medical College of Wisconsin	Postdoctoral	1973-1974	Biochemistry
Lady Davis Institute, Montreal	Postdoctoral	1974-1976	--

A. Personal Statement

I have a proven record of leadership, technical, and intellectual expertise to lead and complete the proposed investigation. I have been extremely successful in elucidation of fundamental signaling concepts in neural control mechanisms in cardiopulmonary diseases and seizing them to study their therapeutic potential. Three clinical trials are now underway by our group as a direct result of these basic science studies.

I have broad multidisciplinary training and experience that spans from cellular and molecular biology, biochemistry, microbiology, and integrative and genomic physiology. I have exploited this multidisciplinary approach to focus on elucidating the role of the renin-angiotensin system (RAS) in pulmonary hypertension (PH) and systemic hypertension (HTN). Our investigations have made significant advancements and some of our concepts have resulted in “paradigm shifts” in delineating the mechanisms of the RAS in PH and HTN. As a result, I have been fortunate to have continuous, uninterrupted R01 funding from the NIH for the last thirty years, including being the recipient of the MERIT award.

I believe that my unique ability to collaborate with scientists of diverse ideas and expertise have been the single most important attribute to our success. In fact, the present proposal is a true example of such an effort. I have assembled a diverse team of outstanding scientists and clinicians who are experts in neurophysiology and cardiovascular physiology, infection and immunity, gut microbial biology and pathology, cancer biology, mechanical engineering, high-throughput bioinformatics, and clinical trials. Most of them have an outstanding history of working together on this and related projects. Evolution of the present project is an example of our “out-of-the-box” thinking that originated from the observations of our ongoing project on the role of angiotensin converting enzyme 2 (ACE2) neuroinflammation and PH. I believe if proven, it will be truly transformative in the way we think and treat PH.

I am fully aware of all road-blocks that need to be overcome on an almost daily basis in order to run an intellectually charged and conceptually exciting research program. We have all the administrative training and supervisory protocols in place that are time-tested for success. Thus, I do not envision any difficulty in successfully completing the project.

B. Positions and Employment

2007– Present - Distinguished Professor, Department of Physiology & Functional Genomics, UF
1987-2006 – Professor, Department of Physiology & Functional Genomics, University of Florida
1993-1998 – Associate Dean, Graduate Education, College of Medicine, UF
1981-1986 – Associate Professor, Department of Physiology, University of Florida
1979-1981 – Assistant Professor, Department of Physiology and Biophysics, University of Iowa
1977-1978 – Associate, Department of Physiology and Biophysics, University of Iowa

Other Experience and Professional Memberships:

2011-Present	Various CSR study sections Review Panels
2009-2010	NIH-VCMB study section, Regular Member
2006- 2008	AHA Peer Review Committee, Regular Member
2002-2006	NIH-HM study section, Regular Member
2005- 2013	British Physiological Society
2004- Present	American Heart Association
1996-2000	NIH-ECS study section, Regular Member
1983- Present	Member, American Physiological Society
1980- Present	The Endocrine Society

C. Contribution to Science

1. The concept that the **brain has an intrinsic renin-angiotensin system** with profound cardiovascular impact was gaining momentum in the 1980's. However, there was little direct evidence to support this view. My group provided important evidence to fill in this gap in knowledge with the use of neuronal and glial cells in primary culture, complemented with *in vivo* physiological studies. Following are a few key publications:

    a) Landas S, Phillips MI, Stamler JF, **Raizada MK**. Visualization of specific angiotensin II binding sites in the brain by fluorescent microscopy. *Science* 1980; 210:791-3. PMID: 6254147.
    b) **Raizada MK**, Phillips MI, Gerndt JS. Primary cultures from fetal rat brain incorporate [3H]-isoleucine and [3H]-valine into immunoprecipitable angiotensin II. *Neuroendocrinology* 1983; 36:64-7. PMID: 6828210.
    c) **Raizada MK**, Phillips MI, Crews FT, Sumners C. Distinct angiotensin II receptor in primary cultures of glial cells from rat brain. *Proc Natl Acad Sci U S A* 1987; 84:4655-9. PMID: 3474621; PMCID: PMC305149.
    d) Phillips MI, Shen L, Richards EM, **Raizada MK**. Immunohistochemical mapping of angiotensin AT1 receptors in the brain. *Regul Pept* 1993; 44:95-107. PMID: 8469778.

2. My group has been among the leaders in **neuronal and brain angiotensin receptor signaling**. We have demonstrated that increased expression of the AT_1R in the SHR was genetically linked since it was preserved in neurons from the neonatal SHR in culture. We also established a distinct mechanism of the coupling of the AT_1R in the SHR to the PI3 kinase pathway, implicating its hyperactivity in the brain of hypertensive animals. Following are some of our key publications:

    a) Lu D, Yang H, **Raizada MK**. Angiotensin II regulation of neuromodulation: downstream signaling mechanism from activation of mitogen-activated protein kinase. *J Cell Biol* 1996; 135:1609-17. PMID: 8978826; PMCID: PMC2133950.
    b) Lu D, Yang H, Lenox RH, **Raizada MK**. Regulation of angiotensin II-induced neuromodulation by MARCKS in brain neurons. *J Cell Biol* 1998; 142:217-27. PMID: 9660875; PMCID: PMC2133039.
    c) Yang H, **Raizada MK**. Role of phosphatidylinositol 3-kinase in angiotensin II regulation of norepinephrine neuromodulation in brain neurons of the spontaneously hypertensive rat. *J Neurosci* 1999; 19:2413-23. PMID: 10087056.
    d) Sun C, Zubcevic J, Polson JW, Potts JT, Diez-Freire C, Zhang Q, Paton JF, **Raizada MK**. Shift to an involvement of phosphatidylinositol 3-kinase in angiotensin II actions on nucleus tractus solitarii

neurons of the spontaneously hypertensive rat. *Circ Res* 2009; 105:1248-55. PMID: 19850939; PMCID: PMC2810537.

3. My group was among the **first to use viral vector-mediated gene transfer of the RAS genes for PH and HTN** therapeutics. We demonstrated that a single administration of AT_1R-AS in retroviral vector in newborn pre-hypertensive SHR prevented the development of hypertension for life. Furthermore, viral-mediated overexpression of ACE2 in the lungs prevents PH. Following are a few key publications in this area:

   a) Lu D, Yu K, **Raizada MK**. Retrovirus-mediated transfer of an angiotensin type I receptor (AT1-R) antisense sequence decreases AT1-Rs and angiotensin II action in astroglial and neuronal cells in primary cultures from the brain. *Proc Natl Acad Sci U S A* 1995; 92:1162-6. PMID: 7862653; PMCID: PMC42658.
   b) Iyer SN, Lu D, Katovich MJ, **Raizada MK**. Chronic control of high blood pressure in the spontaneously hypertensive rat by delivery of angiotensin type 1 receptor antisense. *Proc Natl Acad Sci U S A* 1996; 93:9960-5. PMID: 8790439; PMCID: PMC38537.
   c) Katovich MJ, Grobe JL, Huentelman M, **Raizada MK**. Angiotensin-converting enzyme 2 as a novel target for gene therapy for hypertension. *Exp Physiol* 2005; 90:299-305. PMID: 15640278.
   d) **Raizada MK**, Der Sarkissian S. Potential of gene therapy strategy for the treatment of hypertension. *Hypertension* 2006; 47:6-9. PMID: 16344374.

4. My group was among the first to establish the importance of ACE2 and the vasoprotective axis of the RAS in pulmonary hypertension and pulmonary fibrosis. We discovered the **first small molecule ACE2 inhibitor** and **two ACE2 activators** by virtual screening of its crystal structure. We demonstrated the potential of these ACE2 activators in pulmonary disease therapeutics. This concept of ACE2 activation has now been validated by many other investigators. We are also the **first to produce ACE2 protein in plants to test an oral delivery system** for ACE2 in cardiopulmonary diseases. Following are a few key publications:

   a) Hernández Prada JA, Ferreira AJ, Katovich MJ, Shenoy V, Qi Y, Santos RA, Castellano RK, Lampkins AJ, Gubala V, Ostrov DA, **Raizada MK**. Structure-based identification of small-molecule angiotensin-converting enzyme 2 activators as novel antihypertensive agents. *Hypertension* 2008; 51:1312-7. PMID: 18391097.
   b) Ferreira AJ, Shenoy V, Yamazato Y, Sriramula S, Francis J, Yuan L, Castellano RK, Ostrov DA, Oh SP, Katovich MJ, **Raizada MK**. Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179:1048-54. PMID: 19246717; PMCID: PMC2689912.
   c) Shenoy V, Gjymishka A, Jarajapu YP, Qi Y, Afzal A, Rigatto K, Ferreira AJ, Fraga-Silva RA, Kearns P, Douglas JY, Agarwal D, Mubarak KK, Bradford C, Kennedy WR, Jun JY, Rathinasabapathy A, Bruce E, Gupta D, Cardounel AJ, Mocco J, Patel JM, Francis J, Grant MB, Katovich MJ, **Raizada MK**. Diminazene attenuates pulmonary hypertension and improves angiogenic progenitor cell functions in experimental models. *Am J Respir Crit Care Med* 2013; 187:648-57. PMID: 23370913; PMCID: PMC3733435.
   d) Shenoy V, Kwon KC, Rathinasabapathy A, Lin S, Jin G, Song C, Shil P, Nair A, Qi Y, Li Q, Francis J, Katovich MJ, Daniell H, **Raizada MK**. Oral delivery of Angiotensin-converting enzyme 2 and Angiotensin-(1-7) bioencapsulated in plant cells attenuates pulmonary hypertension. *Hypertension* 2014; 64:1248-59. PMID: 25225206; PMCID: PMC4239698.

5. Our studies from the last 4 years have provided the conceptual and experimental support for a **dysfunctional brain-gut communication in PH**. They have demonstrated that sympathetic nerves have profound influence in maintaining gut homeostasis, and that PH pathophysiology is associated with increased SNA to the gut leading to ACE2-gut microbial dysbiosis. This concept is supported by our profound preliminary data. The present proposal is based on these key observations. Following are some of our key publications in this area:

a) Shenoy V, Kwon KC, Rathinasabapathy A, Lin S, Jin G, Song C, Shil P, Nair A, Qi Y, Li Q, Francis J, Katovich MJ, Daniell H, **Raizada MK**. Oral delivery of Angiotensin-converting enzyme 2 and Angiotensin-(1-7) bioencapsulated in plant cells attenuates pulmonary hypertension. *Hypertension* 2014; 64:1248-59. PMID: 25225206; PMCID: PMC4239698.
b) Hilzendeger AM, Shenoy V, **Raizada MK**, Katovich MJ. Neuroinflammation in pulmonary hypertension: concept, facts, and relevance. *Curr Hypertens Rep* 2014; 16:469. Review. PMID: 25090964; PMCID: PMC4167643.
c) Shenoy V, Qi Y, Katovich MJ, **Raizada MK**. ACE2, a promising therapeutic target for pulmonary hypertension. *Curr Opin Pharmacol* 2011; 11:150-5. Review. PMID: 21215698; PMCID: PMC3075309.
d) Bruce E, Shenoy V, Rathinasabapathy A, Espejo A, Horowitz A, Oswalt A, Francis J, Nair A, Unger T, **Raizada MK**, Steckelings UM, Sumners C, Katovich MJ. Selective activation of angiotensin AT2 receptors attenuates progression of pulmonary hypertension and inhibits cardiopulmonary fibrosis. *Br J Pharmacol* 2015; 172:2219-31. PMID: 25522140; PMCID: PMC4403089.

Finally, I believe that one of my greatest contributions to Science has been to provide outstanding mentorship and training opportunities the next generation of scientist. I have mentored – postdoctoral fellows, - Ph.D. students and numerous Clinical Fellows. Most of them have continued on to pursue biomedical research as their primary career with success.

Complete list of Published work in PubMed: http://www.ncbi.nlm.nih.gov/pubmed/?term=Raizada+MK

D. Research Support

ACTIVE

R01 HL33610-29 (Raizada & Sumners, Co-PIs) 08/13 – 08/18
NIH/NHLBI
"Dysfunctional neural-bone marrow communication in hypertension**"**
Our overall objective in this application is to investigate the hypothesis that the brain-bone marrow communication and activation of microglial cell in the autonomic brain regions plays important role in the development and establishment of neurogenic hypertension. We also propose to conduct clinical studies to determine if attenuation of microglia activation and inhibition of brain inflammation by minocycline would result in the beneficial outcomes in drug resistant hypertensive patients.

R01 HL56921-16 (Raizada & Katovich, Co-PIs) 09/11 – 07/16
NIH/NHLBI
"CVD protection mechanisms involving ACE2/Ang-(1-7) axis"
The overall objective of this study is to use gene transfer technology to regulate the expression of various components of the RAS for long-term control of hypertension.

HL102033-05 (Raizada & Katovich, Co-PIs) 05/10 – 04/15
NIH/NHLBI
"ACE2 in vascular endothelial function"
The overall objective of this application is to investigate the role of ACE2 in pulmonary hypertension therapeutics.
This grant is in "No Cost Extension"

UF Opportunity Funds (Raizada) 06/14 – 05/16
UF Division of Sponsored Research
"Oral Delivery of ACE2 for pulmonary hypertension therapeutics"
Overall objective of this proposal is to develop transplastomic plant derived oral delivery system for ACE2 is for the treatment of pulmonary hypertension.

PENDING

R01 HL132448-01
NIH/NHLBI
“Brain-Gut Microbiome-Immune Axis in Hypertension”

OVERLAP

There is no scientific or budgetary overlap.