PEDRO A. JOSE

Searching for genes that cause the increase in blood pressure with large salt (NaCl) intake

by Van Villar

From a global perspective, essential hypertension has become a modern-day scourge of pandemic proportions. Essential hypertension—which manifests as an abnormal and sustained elevation of blood pressure—is a major risk factor for death and disability from heart disease, stroke and kidney failure. It represents an enormous economic burden, with the cost of health care and prevention running into billions of dollars annually. Of the estimated billion individuals afflicted worldwide, approximately half are unaware of their condition and, among those with diagnosed hypertension, less than half are properly controlled with drug therapy. Thus, the identification of environmental risk factors and elucidation of the molecular and genetic underpinnings of essential hypertension have been rigorously pursued for decades by many investigators, with Dr. Pedro A. Jose at the forefront, among others.

Dr. Jose is an internationally recognized and highly esteemed scientist who has distinguished himself for his contributions to the understanding of the molecular mechanisms of dopamine receptor signal transduction and for his pioneering work on several genetic models of hypertension. He is a preeminent authority on developmental and pediatric nephrology and on the physiologic ramifications of the peripheral dopaminergic system, a system that plays a crucial role in regulating salt and water homeostasis by engendering natriuresis at the proximal tubule and thick ascending limb of Henle.

Dr. Pedro A. Jose is Director, Center for Molecular Physiology Research, Children's National Medical Center and Professor of Pediatrics, George Washington University School of Medicine and Health Sciences, Adjunct Professor of Physiology and Biophysics at Georgetown University School of Medicine, Clinical Professor of Cell and Developmental Biology and Anatomy, University of South Carolina School of Medicine and Visiting Professor, Third Military Medical University of the People's Republic of China, Chongqing, P.R. China.

He received his M.D. (*magna cum laude*) in 1965 from the University of Santo Tomas in Manila and topped the Philippine Medical Licensure Examination on the same year. He performed his pediatric residency at SUNY Downstate Medical Center and then pediatric nephrology fellowship at the Children's Hospital of DC and Georgetown University Medical Center. After his training, Dr. Jose joined the faculty of Georgetown University School of Medicine as an Assistant Professor in 1970 and, due to his prolific research output, he was quickly

Pedro A. Jose and his laboratory celebrate his receiving the 2007 Ernest H. Starling Lecture Award from the Water and Electrolyte Homeostasis Section of the American Physiological Society.

promoted to Associate Professor of Pediatrics within 4 years. Concomitantly, he received extra training in cardiovascular research and earned his Ph.D. in Physiology in 1976 from Georgetown University, where he defended his dissertation with distinction. He was conferred full Professorship in Pediatrics in 1983 and in Physiology and Biophysics in 1986.

Dr. Jose's foray into the molecular mechanisms of essential hypertension began in the 1980s while working in the laboratory of Dr. Philip. L. Calcagno of the Department of Pediatrics and Dr. Gilbert M. Eisner of the Department of Physiology and Biophysics at Georgetown University School of Medicine, and Dr. Maral Mouradian at the National Institute of Neurological Disorders and Stroke. As a pediatric nephrologist, his initial research focused on the ontogenesis of the sympathetic control of renal function, the regulation of AT_1 and AT_2 receptors during ontogeny, and then the mechanisms of dopamine D1 receptor defect in hypertension. Since then, Dr. Jose's research interests have extended into the entire panel of renal dopamine receptors and their roles, interaction with, and regulation of other key players of water and electrolyte balance. Ever on the lookout for useful cutting-edge technology, he has applied novel molecular and biophysical techniques to complement standard methods to further his research goals [See figure on ubiquitination of EGF-tagged human angiotensin type 1 receptor (AT_1R.)]. With the advent of genetic and genomic analyses of the human genome, he spearheaded cohort, linkage and association studies to identify genetic risk factors and to determine the epistatic combination of gene variants that predispose the most to hypertension and salt sensitivity.

Throughout his career, he has forged extensive and fruitful collaboration and alliances with national and international scientists. His significant contributions toward the understanding of renal and extra-renal mechanisms of blood pressure regulation include the functional and structural analyses of the dopamine receptors in the various segments of the nephron, the development and characterization of knockout mouse models for all of the dopamine receptor subtypes, the molecular cloning of 5-HT_7 serotonin receptor subtype, receptor-receptor interaction, the elucidation of the role of the dopamine receptors on the reactive oxygen species (ROS)-mediated hypertension, and the establishment of select haplotypes that strongly associate with hypertension.

A major breakthrough in Dr. Jose's career was the identification of several single nucleotide polymorphisms (SNPs) in the gene encoding G protein-coupled receptor kinase 4 (GRK_4), *i.e.*, R65L, A142V, A486V which strongly associate with essential hypertension in several ethnic groups (Caucasians, Chinese, Ghanaians, and Japanese), with predictive values that are higher than those of other gene polymorphisms. The physiological significance of GRK_4 is underscored by it being the only gene postulated as causal of essential hypertension that fulfills all the criteria needed to link a gene to a complex disease. GRK_4 induces the development of hypertension by causing the abnormal post-translational modification of several dopamine receptors and increasing the transcription of the angiotensin type 1 receptor. Dopamine receptors lower blood pressure while angiotensin type 1 receptors increase blood pressure. At present, transgenic mice harboring human GRK_4 variants

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are the only rodent models that develop hypertension due to variants of a single gene. This work was awarded a US Patent (# 6,660,474), the 2003 Lewis K. Dahl Memorial Lecture (Council for High Blood Pressure Research, American Heart Association), and the 2007 Ernest H. Starling Distinguished Lecture (Water and Electrolyte Homeostasis Section of the American Physiological Society)—two of the numerous national and international honors and awards that Dr. Jose has received in recognition of his significant contribution to science and society alike. Moreover, the deciphering of the role of GRK_4 gene variants in the pathogenesis of human essential hypertension was recognized as the second "advance and discovery" for the fiscal year cited by the Director of National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) for its 2004 Budget Justification to the US Congress.

Dr. Jose has received more than US$ 35 million grant support, with two of his current grants having been funded for more than 25 years. He currently holds an NIH MERIT Award, two program project grants and two R01 grants. He has authored more than 300 primary papers

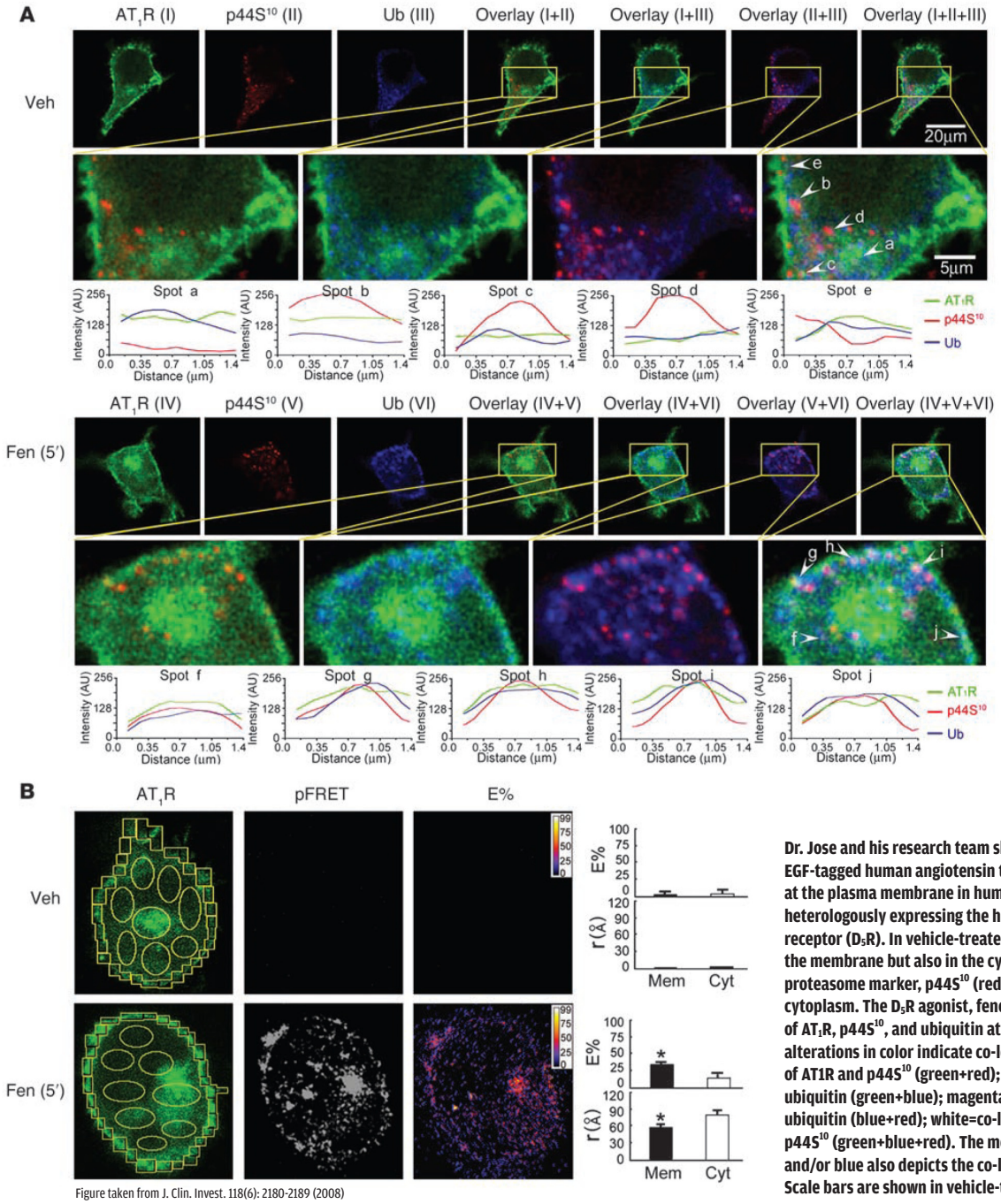

Figure taken from J. Clin. Invest. 118(6): 2180-2189 (2008)

Dr. Jose and his research team showed that ubiquitination of the EGF-tagged human angiotensin type 1 receptor (AT_1R) is initiated at the plasma membrane in human embryonic kidney-293 cells heterologously expressing the human AT_1R and human D_5 dopamine receptor (D_5R). In vehicle-treated cells, AT_1R (green) is mainly at the membrane but also in the cytoplasm. Ubiquitin (blue) and the proteasome marker, $p44S^{10}$ (red) are scattered throughout the cytoplasm. The D_5R agonist, fenoldopam, induces the co-localization of AT_1R, $p44S^{10}$, and ubiquitin at the plasma membrane. The alterations in color indicate co-localization: yellow=co-localization of AT1R and $p44S^{10}$ (green+red); cyan=co-localization of AT_1R and ubiquitin (green+blue); magenta=co-localization of $p44S^{10}$ and ubiquitin (blue+red); white=co-localization of AT_1R, ubiquitin, and $p44S^{10}$ (green+blue+red). The merging of the line drawings, red, green, and/or blue also depicts the co-localization of the different proteins. Scale bars are shown in vehicle-treated cells.

and reviews in top tier peer-reviewed journals, which have received 4,900 citations worldwide, as well as more that 50 chapters in books, all of which have been well cited by other researchers in the field. Dr. Jose is a highly admired speaker known for his expertise and views, as well as for his humorous jokes delivered in his own inimitable way. He has been very active in Georgetown University and has served in many committees both from the Medical School and the University. He was President of the American Society of Pediatric Nephrology, and has also held Offices in several important scientific societies, as well as many Expert Panels and Study Sections of the NIH. He has generously trained more than 50 pre- and post-doctoral students, most of whom have excelled in their careers and have maintained collaborative research with Dr. Jose.

The year 2009 marks another milestone in Dr. Jose's successful career when he was appointed Director of the newly established Center for Molecular Physiology Research at Children's National Medical Center in Washington, DC. The Center was recently established to further our current understanding of the genetic causes of human essential hypertension and salt-sensitivity and, eventually, to develop diagnostic modalities and therapeutic strategies that are tailor-made for the individual's pharmacogenetic profile. Indeed, Dr. Jose remains steadfast in his desire to help focus the future of healthcare, in general, and the management of hypertension, in particular, to be predictive, preventive, and personalized for the best outcome at the least cost.