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EDITORIAL

Too early passing away of the great man in renin-angiotensin research

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On May 14, 2025, one of the brightest stars of basic hypertension research disappeared. We would like to express our sincere condolences to Dr. Masatsugu Horiuchi for his 71 years of life devoted to research on the renin-angiotensin system (RAS).

Dr. Masatsugu Horiuchi's photo

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Dr. Masatsugu Horiuchi was born in Osaka on October 30, 1953. After graduating from Shinshu University School of Medicine in 1979 and engaging in research and medical treatment at Kinki University Hospital, he was employed as an assistant in the Department of Biochemistry, Institute for Cancer Research, Osaka University Medical School from 1981, a postdoctoral fellow in pharmacology at the University of Connecticut School of Medicine from 1986, an assistant in the First Department of Internal Medicine (Cardiology), Kinki University School of Medicine, and then a lecturer. In 1989, he joined the Department of Cardiovascular Medicine, Harvard University and Dr. Dzau's laboratory, where he began his distinguished research career in RAS. 1990, he moved to Stanford University when Dr. Dzau was transferred, and in 1991, he returned to Kinki University, but his research motivation led him to return to Stanford University in 1993. Thereafter, he served as an assistant professor at Stanford University and Harvard University until 1999, where he pursued cutting-edge research mainly related to angiotensin II type 2 receptor (AT_2R). In addition, he played a central role in pulling RAS research as a leader among many fellow international students in Dr. Dzau's laboratory. Nearly 30 Japanese postdoctoral fellows joined Dr. Dzau's lab by being attracted by his strong enthusiasm and high expertise in the research. In February 1999, he became a professor of the Department of Medical Biochemistry, Ehime University School of Medicine, and in April 2006, he became a professor of Molecular Cardiovascular Biology and Pharmacology, Graduate School of Medicine, Ehime University, due to a name change, until his retirement in March 2019. Since then, he has vigorously promoted education and research in medical chemistry, cell biology, and pharmacology, achieving many outstanding research accomplishments. He also guided 34 students, including 12 international students, to obtain their degrees, nurturing numerous younger scholars. He also led RAS research in Japan by organizing study groups and

establishing a platform for round-table discussions with Japanese researchers from Dr. Dzau's laboratory, many of whom became professors in various Japanese universities (e.g. Hiroshi Itoh, Masaaki Ito, Hiromi Rakugi, Masashi Mukoyama, Hiroki Kurihara, Masahiro Akishita, Ryuichi Morishita, Motokuni Aoki, Kouichi Tamura, Tomohiro Katsuya). In Ehime University, researchers (e.g. Hironori Nakagami, Masaki Mogi), who were always strictly and rigorously guided with his appropriate instruction on the results of experiments, have succeeded in Dr. Horiuchi's will and continue to promote hypertension research.

He served as President of the Japanese Society of Hypertension (JSH) for two years from 2012, and held the JSH 38th Annual Scientific Meeting on October 2015 in Matsuyama, Ehime, Japan. He has presented his research findings annually at the American Heart Association's Scientific Sessions, the High Blood Pressure Council, and the International Stroke Conference. He has promoted exchanges and collaborations with international researchers at the Gordon Research Conferences and other international conferences. He has also served as Treasurer of the Executive Committee of the International Society of Hypertension (ISH), and was a fellow of the American Heart Association. Owing to his sincere devotion to ISH activities, JSH could host ISH general meeting 2022.

He also served as Editor in Chief of Hypertension Research for three years from 2009, contributing greatly to the development of the journal. It is a great pity that he passed away just after he retired from Ehime University, where he had been making efforts in hypertension treatment in Osaka as a clinician, making use of his own hypertension research.

Dr. Masatsugu Horiuchi conducted a large number of RAS studies. He identified transcription regulators that bind to specific gene sequences that regulate renin gene expression and successfully regulated renin expression at the organ level using the cis element double-stranded oligodeoxynucleotides (ODN) ("decoy") approach targeting these specific transcription regulators by using the HVJ ribosome [1, 2]. In addition, he contributed to basic research on the establishment of gene therapy by suppressing inflammation using this decoy approach [3]. Dr. Horiuchi has also been actively engaged in research on the organ-protective arms of the RAS, which antagonizes the classical RAS that induces elevated blood pressure and organ damage, and has produced many research achievements. In particular, he pioneered the cloning of mouse, rat, and human AT_2R [4–7], which became the foundation for subsequent research on the protective arms of the RAS. Regarding the function of cloned AT_2R, he discovered for the first time in the world that AT_2R suppresses vascular damage by gene transfer to blood vessels [8], and since then, using AT_2R gene-modified mice, AT_2R stimulation antagonizes AT_1R stimulation, resulting in the protection of brain, heart, and blood vessel, and the prevention of metabolic syndrome [9–12]. In addition, focusing on its cerebroprotective effects, a multifaceted study proved that activation of AT_2R also has a preventive effect against dementia [13]. Such attention to the organ-protective effects of AT_2R led to the development of Compound 21, an orally available direct AT_2R agonist, in collaboration with Dr. Björn Dahlöf, Dr. Ulrike M Steckelings, Dr. Tomas Unger, and others. In addition, AT_2R interacting protein (ATIP), which regulates AT_2R function, was cloned [14] and its function was reported worldwide. He also focused on the angiotensin 1-7/Mas receptor axis, which is also an organ-protective axis of the RAS, and reported the interaction between AT_2R and Mas receptors and their brain protective effects [15]. The relationship between RAS and dementia has now been clinically implicated, and dementia research focusing on RAS is still being actively conducted around the world.

Dr. Masatsugu Horiuchi departed with these excellent contributions. What he left behind for us is immeasurably large and great. Looking back on his life of research, we regret his untimely departure with deep respect and thanks for his great achievement and leadership. We pray for his soul to rest in peace.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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