

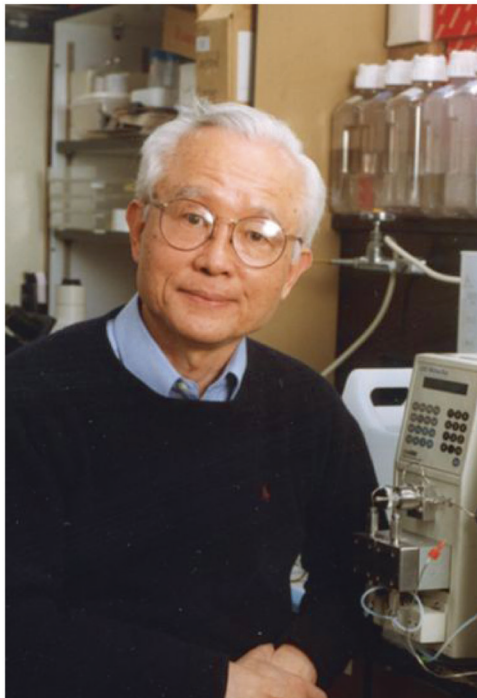


## Obituary: Dr. Tadashi Inagami, a legend in the field of renin angiotensin II research

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On March 13, 2023, we lost a legend in our field. Tadashi Inagami, PhD passed at age 92. On behalf of over 400 trainees including the authors of this tribute, we would like to express our deepest condolences to his wife Masako and the Inagami families. As scientists who trained with Dr.

Inagami, we are honored to present this article to celebrate Dr. Inagami's career and life story.

Dr. Tadashi Inagami was born in the port city of Kobe, Japan, on February 20, 1931 and spent his young life in Kyoto, a cultural and historical center in Japan. While attending high school during the post war period, Inagami started reading translations of American scientific journals which peaked his interest in the life sciences. In 1953, he received his bachelor's degree in nutritional chemistry from Kyoto University, one of Japan's top public universities. He began graduate school there, but quickly realized that educational opportunities in post war Japan were limited. He took advantage of the Fulbright Program for educational exchange, was accepted to Yale University in 1958, and completed his doctoral degree in Biophysical Chemistry. He then obtained his 2nd Ph.D. degree from Kyoto University but with limited postdoctoral positions in Japan, he decided to return to Yale. There he worked on protein crystallography and obtained the molecular structure of several enzymes.

With these “novel techniques” in hand, he was recruited as an assistant professor by the Biochemistry Department at Vanderbilt University School of Medicine. The Department desperately needed a protein structure specialist to collaborate with Dr. Stanley Cohen, whose discovery of epidermal growth factor (EGF) was a perfect candidate for crystallography. Notably, the collaboration with Dr. Cohen for EGF purified from mouse salivary gland not only contributed to Cohen's Nobel Prize winning research but also provided Dr. Inagami the opportunity to purify renin from the same source [1]. This seminal discovery of renin led to Dr. Inagami's legendary lifetime accomplishment of the identification and elucidation of the renin angiotensin system in blood pressure regulation.

Throughout his career, Dr. Inagami published over 500 scientific articles. His major contributions to the field include purification and identification of the primary

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structure of mouse renin [1, 2], identification and cloning of genomic DNA for rat atrial natriuretic peptide (ANP) [3], identification and cloning of the angiotensin II type 1 (AT1) receptor [4], identification and cloning of the angiotensin II type 2 (AT2) receptor [5], and characterization of angiotensin II type 2 receptor gene knockout mice [6]. These findings significantly impacted the field leading to the creation of the current first-line human anti-hypertensive treatments, the AT1 receptor blockers. Additionally, his work led to the discovery of the so-called protective arm of the renin angiotensin system.

In 1979, Dr. Inagami became director of the Specialized Center of Research (SCOR) in Hypertension and served in that role for 17 years, overseeing a large, interdisciplinary research center funded by the National Institutes of Health. During his career, he received a long list of prestigious accolades, including the Bristol-Myers-Squibb Award for Distinguished Achievement in Cardiovascular Research, the Research Achievement Award from the American Heart Association (AHA), and the Japan Academy Prize. He was particularly proud of the Ciba Award from the High Blood Pressure Research Council of the American Heart Association, which he received in 1985. The highly selective award recognizes the most original research in the hypertension field.

In 1994, I (Satoru Eguchi) became a postdoctoral fellow with Dr. Inagami. I discovered that he not only scientifically mentored his trainees but helped us adjust to life in Tennessee. He went above and beyond in facilitating my family's transition to Vanderbilt by helping to secure housing for us and welcoming us to the United States. We quickly figured out he would pass by my apartment on his way home from work and he was able to frequently stop by to enthusiastically discuss our research. During my postdoctoral period Dr. Cohen was still actively studying EGF receptor signaling mechanisms in cancer cells and he acted as my unofficial second mentor, leading to my second major paper from Dr. Inagami's laboratory [7]. It seems some kind of miracle that we were able to merge the renin angiotensin system and the EGF system ~40 years after Dr. Inagami and Dr. Cohen started their scientific journeys at Vanderbilt University in the 1960s. This paper changed my career trajectory. In 1999 Dr. Inagami recruited me as a research assistant professor and I was proud to contribute to his last NIH merit award. I feel honored that Dr. Inagami introduced me to this field and that I have been able to work on the angiotensin system for past ~30 years. It feels like I received a priceless gift from him.

In the spring of 1997, I (Takaaki Senbonmatsu) joined Vanderbilt University as a postdoctoral fellow in Dr. Inagami's laboratory. While I was originally trained as a cardiologist, I also had engaged in basic research at Osaka

University. In 1996, I had an opportunity to meet with Dr. Inagami, who was visiting Osaka for a party to celebrate his receiving the Japan Academy Award. Dr. Inagami asked me "what are you particularly interested in the renin angiotensin system?" Unfortunately, I was not prepared for such question, but made a reckless request to join his laboratory. I felt myself so lucky receiving a phone call from him asking me "When can you come to the States?" Soon after I joined, I was given a project to explore the signaling and functional significance of the AT2 receptor. In Dr. Inagami's laboratory, the AT2 receptor was believed to be the "Darkside" of the RAS, and everyone who worked on this project struggled despite tremendous efforts. I studied the AT2 knockout mice to test the hypothesis that deletion of AT2 receptor likely exaggerates cardiac pathology upon cardiac overload. The ultrasound cardiography of mice was collaboratively performed at University of Colorado. However, the results were the exact opposite of what we expected. When I reported, he seemed surprised and looking for the reason. I vividly remember Dr. Inagami arranged for mouse cardiac ultrasound to be performed at Vanderbilt University in order to immediately verify the results. The same results were obtained, and Dr. Inagami then requested me to explore the signaling mechanism by which AT2 receptor mediates cardiac myocyte hypertrophy [8]. I was very happy that we were able to shed a light on the "Darkside"! I have learned from Dr. Inagami how a respected researcher like him conducts research on challenging subjects. The motivation and passion of Dr. Inagami for his research now lies within me. Both Dr. Inagami and his wife were also very supportive and helped us assimilate into American lifestyle and culture.

Gerald Frank, Ph.D., one of Dr. Inagami's final trainees remembers his mentor, especially the last few years before his retirement, as maintaining his spark for scientific discovery and always reading the latest publications of interest to discuss with his research team. Dr. Luis Gabriel Navar, one of the pioneers in the intrarenal angiotensin II system and good friend of Dr. Inagami described that Tadashi was an icon in the field, a true scientist of incredible integrity and a wonderful and noble gentleman. We all will miss Dr. Tadashi Inagami and his extraordinary dedication to the renin angiotensin II research.

Picture is from Tadashi Inagami Retirement Symposium 2013 at Vanderbilt University.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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