

Kimishige Ishizaka 1925–2018

Numerous symphonies and concertos were composed by Wolfgang Amadeus Mozart and Ludwig van Beethoven.

New World Symphony was composed by Antonin Dvořák. The *Mona Lisa* was painted by Leonardo da Vinci and *Guernica* by Pablo Picasso. We each have our own favorite music and artworks, always associated with the names of their creators. However, only a few scientific discoveries are attached to the names of their discoverers in the memories of younger generations of students. Ask students, postdocs and even your faculty-level colleagues who discovered a major cytokine or oncogene, and most will not have the answer. It seems that most individuals do not pay attention to these discoverers as much as they do the discoveries. One could argue that scientific research is in essence the anonymous pursuit of objective knowledge. However, the lives of eminent scientists and their influence in their fields are often interesting and noteworthy. Kimishige Ishizaka's scientific achievements and life fall well into this category.

Kimishige Ishizaka, known endearingly as Kimi by his colleagues, was born in Tokyo into the family of a highly ranked military officer. He entered the University of Tokyo during the Second World War and graduated after its conclusion. As a medical student, he spent a fateful summer in the laboratory of Keizo Nakamura, which determined his future as a scientist. He also met his future wife, Teruko Matsuura (known as Terry), in the same laboratory. They subsequently carried out postdoctoral studies with Dan Campbell at the California Institute of Technology and later at Johns Hopkins. After some time back in Japan, in 1962, they decided to return to the United States to continue their work on antibodies at the Children's Asthma Research Institute and Hospital in Denver. While there, in 1966, Kimi and Terry discovered a new antibody protein—later known as IgE—that caused allergic reactions when delivered together with allergen. They were later recruited back to Johns Hopkins and carried out research there for 19 years. In 1989, they came to San Diego to help found the La Jolla Institute for Allergy and Immunology (LJI). Kimi was the first scientific director of the LJI, and later he became the president.



He retired from the LJI in 1996, to reside in Yamagata City, Terry's hometown north of Tokyo. After returning to Japan, he helped to organize the newly founded Research Center of Allergy and Immunology (RCAI), a RIKEN component, in Yokohama and to guide Kirin Brewery's pharmaceutical research as well as Yamagata University's research portfolio.

In the field of allergy, IgE is one of the most important factors in research as well as clinical practice. However, the search for the factor termed 'reagin' that causes allergy was not straightforward (*Annu. Rev. Immunol.* **36**, 1–18, 2018). Observations made by Otto Prausnitz and Heinz Küstner in the 1920s showed that a subcutaneous injection of serum from an allergic donor followed by injection of specific antigen results in erythema and wheal responses. Using this so-called PK reaction, reagin was long believed to be IgA. However, Kimi's team demonstrated that reagin was not IgA, but a minor contaminating component of IgA preparations. This rare fraction with PK activity was found to have novel physicochemical properties different from those of any of the then-known antibody isotypes—IgM, IgD, IgG and IgA. Eventually, the identity of reagin was established as the novel antibody isotype IgE. Kimi also showed that IgE receptors reside on mast cells and basophils, the culprit cells in allergic reactions. The discovery of IgE opened a new era of allergy research and eventually led to novel anti-IgE therapies for asthma and other diseases. His achievements brought him many accolades: he was inducted into the National Academy of Sciences of the United States and became the president of

the American Association of Immunologists. He was bestowed with the highest honor for a Japanese person, the Order of Culture. He also received the Japan Prize, after which the LJI established the Kimishige and Teruko Ishizaka lectureship in 2002.

I was fortunate to be recruited to the LJI at the founding of the new institute. New to the allergy field, I tried to absorb as much experience from Kimi as I could. Conversations with Kimi and Terry over lunch every day for six years were a very educational experience for me, as I learned the more human details of the research on IgE, IgE receptors and mast cells. In addition to his own research achievements, Kimi made two great contributions to the immunology community. First, he trained postdocs who would later become consequential players in their respective fields. Immunologists trained by Kimi, such as the late Tomio Tada, Tadimitsu Kishimoto, Kiyoshi Takatsu and Junji Yodoi, became well known and dominated the immunology community in Japan from the 1980s to the 2000s. These immunologists were inspired by Kimi, but they took research directions different from their mentor's to achieve their eminence. Interestingly, without directly studying IgE or allergy, they all studied important aspects of immunity and inflammation. A second major achievement by Kimi was helping launch successful research institutes, the LJI in San Diego and RCAI (recently revamped as the RIKEN Center for Integrative Medical Sciences) in Yokohama. Kimi was very good at recruiting promising scientists. Starting from six research groups in 1990, the LJI has now grown to 23 laboratories. Also, both Kimi and Terry promoted a family-like and warm, collegiate environment at the LJI, which has become an unwritten tradition at the institute. Kimi lived a long, full and extremely productive life. Still, he is sorely missed by many. □

Toshiaki Kawakami

La Jolla Institute for Allergy and Immunology,
La Jolla, CA, USA.
e-mail: toshi@lji.org

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