

Legends of Allergy & Immunology: Kimishige Ishizaka

Dr. Kimishige Ishizaka (Figure 1) passed peacefully away at dawn of July 6, 2018, in Yamagata, Japan. Dr. Kimishige Ishizaka and Dr. Teruko Ishizaka (the Ishizakas, partners in marriage and in research) were best known for their discovery of immunoglobulin E (IgE) in 1966.^{1,2}

Dr. Kimishige Ishizaka was born on December 3, 1925, in Tokyo. When he was a medical student of the University of Tokyo, he spent his summer vacation in 1946 training in bacteriology with Prof. Keizo Nakamura. He and Teruko met during the training course and later they got married in 1949. Immediately after receiving his MD, PhD from the University of Tokyo in 1954, Dr. Ishizaka was appointed the Chief of the Immunoserology Division of the Department of Serology at the Japanese National Institute of Health. During his tenure in that position (until 1962), he spent 2 years as a Postdoctoral Research Fellow at Caltech in Pasadena, California, in the United States (1957-1959) under the supervision of Prof. Dan H. Campbell. In 1963, the Ishizakas joined the Children's Asthma Research Institute and Hospital in Denver, Colorado, in the United States. Until then, Dr. Ishizaka was interested in the nature of so-called reagin, which was a yet-unidentified factor postulated as being responsible for Prausnitz-Küstner reactions in the sera of allergic patients.¹



FIGURE 1 Kimishige Ishizaka, December 3, 1925-July 6, 2018. Photograph courtesy of the Japanese Society of Allergology [Colour figure can be viewed at wileyonlinelibrary.com]

By the end of 1964, several researchers including the Ishizakas reported that “reagin” might belong to IgA class, which physico-chemical nature was relatively similar to that of IgE. However, Dr. Ishizaka was not confident to these reports even to their own. He had hypothesized that the Fc portion of immunoglobulin might determine its ability to induce anaphylaxis based on their previous experiments. Then, the Ishizakas found that, although the anti-ragweed IgA antibody seemed to show “reagin” activity, IgA antibody against human blood group A substance sharing the same Fc portion with the above antibody did not sensitize human skin for the Prausnitz-Küstner reaction.² After careful consideration, Dr. Ishizaka concluded that “reagin” must have been present in the IgA fraction as an impurity and that the amount of “reagin” contained in patients’ sera must have been too low to detect using the technology available at that time. They changed their approach from detecting “reagin” to producing anti-human reagin antibodies in experimental animals. Finally, using anti-human reagin rabbit antibodies, “reagin” became visible as a new class of immunoglobulin at an electrophoretic position that was distinct from the immunoglobulin iso-types known at the time (Figure 2).^{2,3} In this way, the Ishizakas discovered IgE in 1966. However, some investigators were still skeptical and did not rule out the possibility that reagin and the Ishizakas’ new antibody class were separate molecules that copurified.⁴ Resolution of this dispute came when Dr. Gunnar Johansson, Dr. Hans Bennich, and colleagues at Uppsala University in Uppsala, Sweden, discovered a novel myeloma protein that had reagin activity and found that their novel myeloma protein was bound by the Ishizakas’ antiserum.⁵ The discovery of IgE was officially recognized by WHO in 1968. Needless to say, the discovery of IgE was the groundbreaking event in our understanding of allergy.

In 1968, a second patient with IgE myeloma was identified. In response to the Ishizakas’ passion for elucidating enigmatic allergic diseases, he provided more than 30 L of plasma by undergoing weekly plasmapheresis until his death. The Ishizakas (mainly Kimishige) isolated IgE myeloma protein (named PS) from his plasma. Since many allergists and immunologists were interested in the IgE system, the Ishizakas (mainly Teruko) sent purified PS protein and/or anti-PS antibodies to many (close to 100) investigators upon request, including to those who had initially been skeptical of their findings. Thus, PS protein and antibodies to it greatly facilitated the progress of allergy research in the 1970s.¹

In 1970, Dr. Kimishige Ishizaka was appointed O'Neill Professor of Medicine and Microbiology at Johns Hopkins University School of Medicine in Baltimore, Maryland. From 1981 to 1989, he served as

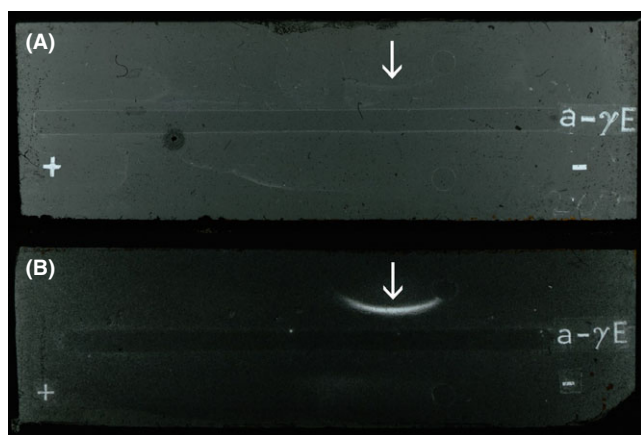


FIGURE 2 Radioimmuno-electrophoresis of the reagin-rich fraction of the serum of a ragweed-sensitive patient with hay fever. After electrophoresis, the trough was filled with antireagin antiserum, followed by ^{125}I -labeled ragweed antigen. The precipitin band faintly visible (A, arrow) became clearly visible by autoradiograph (B). The electrophoretic position of this band was distinct from those of the other immunoglobulin classes precipitated by anti-human serum (see ref. #3) [Colour figure can be viewed at wileyonlinelibrary.com]

Director of the Department of Immunology at the university. He became Scientific Director and then President, in 1990, of the La Jolla Institute for Allergy and Immunology in La Jolla, California. He officially retired in 1996, primarily because of gradual worsening of Teruko's Parkinsonism symptoms. Dr. Ishizaka decided to dedicate the rest of his life to Teruko because he knew that she had dedicated all her life to him and their shared career until then. Indeed, Dr. Ishizaka wrote in the essay written in Japanese that Teruko served as his wife, his housekeeper, his manager, his diplomat, and his scientific partner, at considerable sacrifice of her own scientific career. They returned to Teruko's hometown, Yamagata, in the northern part of Japan, where they built a new house. However, in 1998, her symptoms became much worse and she was hospitalized in Yamagata University Hospital after being diagnosed with degeneration of nigrostriatal neurons. He visited Teruko from 9 AM to 5 PM, almost every day. In her hospital room, he wrote many articles and talked to and advised people in various fields for 20 years. At the time of his death, he was serving as Honorary Director of the Institute of Immunology at Yamagata University and as President Emeritus of La Jolla Institute for Allergy and Immunology.

Dr. Ishizaka was proud of having mentored many young investigators who later became outstanding scientists. They include the late Dr. Tomio Tada, who found a T-cell subpopulation having immunosuppressive activity and had a second successful career as an author of traditional Noh stage plays⁶; Dr. Tadamitsu Kishimoto, who discovered IL-6; and Dr. Kiyoshi Takatsu, who discovered IL-5. As noted by Dr. Ishizaka, although the total number of postdoctoral fellows who had trained in their laboratories in the United States was

only 50, 25 of them became professors in medical schools and/or heads of departments at prominent institutions in the United States, Japan, and Europe.¹ His mentorship and support of his trainees often continued even after they returned to their native countries.

The Ishizakas received numerous awards for their achievements. In 1972, they received the Passano Foundation Award. In 1973, he received the German Paul Ehrlich and Ludwig Darmstaedter Prize, and the first Scientific Achievement Award of the International Association of Allergology, and they together received the Gairdner Foundation International Award. In 1974, he received the Imperial Prize of the Japan Academy and the Japanese Order of Culture. In 1979, they received the Borden Award. In 2000, he was awarded the 16th Japan Prize, which is awarded annually to scientists and engineers from around the world who have made significant contributions to the advancement of science and technology. Dr. Ishizaka said in his book written in Japanese that in the 1980s, a nominator for the Nobel Prize who wanted to nominate Dr. Ishizaka proposed to exclude Dr. Teruko Ishizaka from the candidates. Although he understood that she would be pleased to accept the proposal, Dr. Kimishige Ishizaka politely refused the nominator's proposal. Among the whole prizes and plaques he received, Dr. Ishizaka's favorite was the plaque awarded to them in 1970 from Children's Asthma Research Institute and Hospital, on which the following phrase was inscribed: "As Physicians and Researchers, You Are Second to None; As Human Beings You Are the Finest." We fully agree with this thought.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Ishizaka K. The way we walked with immunology. *Annu Rev Immunol*. 2018;36:1-18.
2. Ishizaka K, Ishizaka T. Identification of IgE. *J Allergy Clin Immunol*. 2016;137:1646-1650.
3. Ishizaka K, Ishizaka T, Hornbrook MM. Physicochemical properties of reagenic antibody: V. Correlation of reagenic activity with gamma E-globulin antibody. *J Immunol*. 1966;97:840-853.
4. Finkelman FD. Identification of IgE as the allergy-associated Ig isotype. *J Immunol*. 2017;198:3-4.
5. Stanworth DR, Humphrey JH, Bennich H, Johansson SG. Specific inhibition of the Prausnitz-Küstner reaction by an atypical human myeloma protein. *Lancet*. 1967;2:330-332.
6. Gellene D. Tomio Tada, Influential Immunologist and Author of Japanese Plays, Dies at 76. *New York Times* 2010 May 2; <https://www.nytimes.com/2010/05/03/health/research/03tada.html>.