Dr. Teruko Ishizaka (Terry) died on June 4, 2019 in Yamagata, Japan. It was about one month before the first anniversary (July 6) of the death of her beloved husband, Dr. Kimishige Ishizaka (Kimi; 1925–2018).1 Both of them, who were partners in research as well, were best known for their discovery of immunoglobulin E (IgE) in 1966 (Fig. 1).2

Terry was born in Japan on September 28, 1926. She received a doctorate in medicine from Tokyo Women’s Medical School in 1949 and a PhD from the University of Tokyo in 1955. Working alongside Kimi, whom she married in 1949, she spent eight years at Professor Keizo Nakamura’s laboratory at the Japanese National Institute of Health. From 1957 to 1959, Terry and Kimi spent 3 years at a laboratory at the California Institute of Technology. In 1962, Terry and Kimi were recruited to the Asthma Research Institute and Hospital in Denver, where they reported their discovery of the IgE antibody class in 1966.3

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 co-purified. 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. The discovery of IgE then was officially recognized by the 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 (Mr. P. S.) was identified. In response to the Ishizaka’s passion for elucidating enigmatic allergic diseases, Mr. P. S. provided more than 30 L of plasma by undergoing weekly plasmapheresis until his death. Kimi isolated IgE myeloma protein (named PS) from his plasma. Since many allergists and immunologists were interested in the IgE system, the Ishizakas 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.4 This generous policy is said to have been initially proposed by Terry. Thus, the PS protein, and antibodies to it, greatly facilitated progress in allergy research in the 1970s.

In 1970, when Kimi was appointed the O’Neill Professor of Medicine and Microbiology at Johns Hopkins University School of Medicine in Baltimore, Maryland, Terry was also appointed as an Associate Professor. In 1980, she was promoted to Professor of Medicine at Johns Hopkins. Kimi wrote in a Japanese essay that he was so proud of Terry because she was the first Japanese female professor in the U.S. After the discovery of IgE, she had been working on research into mast cells and basophils, and the Ishizaka’s discovered in 1970 that these were the only effector cell types of IgE-mediated allergic reactions. Mature mast cells are present only in the tissues but not in the peripheral blood. As a result, it had been difficult to investigate the biology of mast cells, especially of humans.

In the late 1970s, bone marrow hematopoietic cells were found to give rise to mouse mast cells.5 It then became possible to obtain many mouse mast cells by cultivating mouse bone marrow cells in the presence of a T cell-derived factor, IL-3, although the factor was later found not to be an important growth factor for human mast cells. In 1989, through a continuing process of trial and error over many years, Terry, as a principal investigator almost independent of Kimi’s support, demonstrated for the first time that human mast cells are capable of developing from hematopoietic stem cells by employing a co-culture system with mouse fibroblasts.6 This discovery was the direct result of her enthusiasm for advancing our knowledge about human mast cells.

The Ishizakas officially retired in 1996, primarily because of the gradual worsening of Terry’s Parkinsonism symptoms. Kimi decided to dedicate the rest of his life to her because he knew that, until then, she had dedicated all of her life to him and their shared careers. In 1998, her symptoms became much worse and she was hospitalized in Yamagata University Hospital after being diagnosed with degeneration of nigrostriatal neurons. Kimi visited Teruko from 9 a.m. to 5 p.m., almost every day until his death in 2018.7 Kimi thought that, by persistently talking to her, he might be able to save Terry’s mental life.

For their achievements related to the discovery of IgE, Terry and Kimi together were awarded the Passano Foundation Award in 1972, the Gairdner Foundation International Award in 1973, and the Borden Award in 1979. In 1990, Terry was awarded the Behring-Kitazato Award (for the best immunologist in Japan of that year) for the first success in in vitro culture of human mast cells.

Terry and Kimi are survived by their son Yutaka Ishizaka of Carlisle, Massachusetts, and his wife, Sally T. Ishizaka. We hope that Terry and Kimi are now very happy about their reunion in Gokuraku-Jodo (a land of bliss).
Conflict of interest

The authors have no conflict of interest to declare.

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Fig. 1. Teruko (Terry) and Kimishige (Kimi) Ishizaka in 1974.