Obituary for Professor Tomio Tada

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Professor Tada, who founded the journal *International Immunology* in 1989 and served as Editor-in-Chief until 2000, died on April 21, 2010, the result of respiratory failure due to prostate cancer metastases to the lung. He was 76 years old.

Professor Tada had been president of the Japanese Society for Immunology (1985–1988) and served as an executive board member of the International Union of Immunological Societies (IUIS), vice president (1991–1994) and then president of the IUIS (1994–1997).

Professor Tada graduated from Chiba University School of Medicine in 1959, took his PhD degree at Chiba University in 1964 and was appointed Professor of Immunology at Chiba University in 1974. Then he moved to the University of Tokyo in 1977 as Professor of Immunology and became an ‘emeritus’ professor in 1994. From 1995 until his retirement in 1999, he was director of the Research Institute of Life Sciences at the Science University of Tokyo.

Professor Tada started his carrier as an immunologist during his stay as a research fellow (1964–1966 and also in 1968) in the laboratory of Drs Teruko and Kimishige Ishizaka, who discovered IgE at the Children’s Asthma Research Institute in Denver, Colorado, USA.

In 1971, Professor Tada did pioneering work by demonstrating the existence of ‘suppressor T cells’, which negatively regulate antibody responses in an antigen-specific fashion. This concept was contrary to the general view during that period that T cells only help antibody responses. At almost the same time, Dr Richard Gershon of Yale University (New Haven, Connecticut, USA) also demonstrated that
T-cell-mediated suppression is involved in immunological tolerance. Later, Professor Tada, in parallel with Dr Gershon, established the concept of immunological homeostasis is regulated by suppressor T cells, leading to a new paradigm—‘peripheral tolerance’.

This novel mechanism was quite distinct from that explained by ‘central tolerance’, which is mainly mediated by the clonal deletion of T cells in the thymus. The idea of suppressor T cells predated by many years the concept of ‘regulatory T cells’, which has recently become a topic of great interest among many immunologists. Although extensive efforts have been made to identify the mechanism responsible for the function of suppressor T cells, it still remains an enigma. In any event, Professor Tada made an enormous contribution in establishing the concept of immune suppression, which is now fundamental in immunology.

There are two lines of studies that have been influenced by Dr Tada’s original work—the concept of immune suppression. One line of study involves regulatory T cells, which negatively regulate autoimmune disease development. These regulatory phenomena that are mediated by T cells were originally described by Drs Yasuaki Nishizuka and Teruyo Sakakura, and this was followed by the discovery of Forkhead box p3 (Foxp3) regulatory T cells Dr Shimon Sakaguchi in 2003. Although it is believed that Foxp3 is a ‘master’ gene for this regulatory function, Foxp3 expression is negatively controlled by retinoic acid receptor-related orphan receptor γt (RORγt), which is a master transcription factor regulating the generation of pathogenic T, cells. The expression of Foxp3 determines regulatory function, whereas RORγt expression suppresses Foxp3 expression and turns regulatory T cells into pathogenic T cells. Regulatory T cells and pathogenic T cells are thus interchangeable upon expression of a particular transcription factor, whose expression is controlled by environmental factors.

The second line of the study that has been influenced by Professor Tada’s original work is the NKT cell, characterized by its expression of the ‘invariant’ Vα14 antigen receptor. Interestingly, 12 out of 13 suppressor T-cell hybridomas, that were originally derived from suppressor T cells studied by Professor Tada, selectively used the invariant Vα14 receptor. Thus, the invariant Vα14 receptor is in a sense a unique marker for some suppressor T cells. NKT cells are known to be bi-functional cells whose functions are also determined by their environment. They can mediate negative regulatory function, suppressing autoimmune disease development and maintaining transplantation tolerance by virtue of their IL-10 production, as well as protective functions in anti-tumor or anti-pathogen responses by producing IFN-γ. Collectively, it is likely that the regulation of immune responses, particularly as related to peripheral tolerance, is largely influenced by environmental factors, indicating the future importance of identifying the effector mechanisms in the regulation of immune responses.

After a stroke in 2001, Professor Tada was half paralyzed and unable to swallow or speak, but he continued to write by typing with the fingers on his left hand. Professor Tada created five original new Noh dramas (a traditional form of the Japanese theater) mainly dealing with his spiritual and philosophical exploration. They are ‘The Hermit Isseki’, his favorite, which concerns Albert Einstein’s theory of relativity; ‘The Well of Ignorance’, on the topic of brain death and heart transplantation; ‘Resenting Lament’, about cultural prejudice toward the people who were forcibly taken from Korea to Japan during World War II; ‘The Mourning of Atomic Bombing’, about the victims of the atomic bombing in Hiroshima; and ‘The Virgin Mary in Nagasaki’, for repose of the souls of victims of the atomic bombing in Nagasaki—this Noh drama in particular features an emotionally powerful hymn.

He also wrote a number of essays, such as ‘A Reticent Giant’ that describes his ‘second life’ after a stroke and was awarded the Hideo Kobayashi Prize (2008); ‘Semantics of the Immune System’, awarded the Jiro Osaragi Prize (1993); and ‘Sake for One’ (2000), awarded the Japan Essayist Club Award.

Professor Tada was an honorary member of the Medical and Science Academy of Romania (1997) and an honorary doctor of the Poland Copernicus Medical University (1998). He was awarded the Hideo Noguchi Prize (1976), the Emil Adolf von Behring Prize (1980), the Cultural Merit Award (1984) and the Order of the Sacred Treasure, Gold and Silver Star from the Emperor—one of the Japan’s highest honors (2009).

Professor Tada is survived by his wife, Norie, his children Chris, Ko and Aya, and five grandchildren. His life and work continue to inspire all those who knew him.