Hiroshi Shiku, MD, PhD: In Memoriam (1943–2022)

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The community of cancer immunology and immunotherapy mourns the loss of Professor Hiroshi Shiku, a cancer immunotherapy pioneer who developed tumor antigen–specific immunotherapies, such as cancer vaccines and adoptive T-cell therapies. He was born January 15, 1943, and passed away September 4, 2022, during a research event abroad. Dr. Shiku made major contributions to the analysis and molecular characterization of tumor antigens, dissecting T-cell responses in cancer, and to the development of cancer immunotherapy. He designed a novel protein-based cancer vaccine with a unique antigen delivery system, cholesterol-bearing hydrophobized polysaccharides (CHP). He also contributed to the development of adoptive-cell therapies with T-cell receptor (TCR) gene-transduced T cells aiming at a more effective and comprehensive approach to cancer immunotherapy. He was an enthusiastic and visionary scientist, a passionate mentor for his fellows, students, and collaborators including us, and deeply engaged in scientific discussions and debates within the scientific community.

Dr. Shiku graduated from Nagoya University School of Medicine in 1967 (Nagoya, Japan), with a thesis of medicine and was registered on the Japanese Medical Doctor Board. After completing his initial medical training as a resident, he went abroad as a research fellow in tumor immunology at Sloan Kettering Institute (SKI) for Cancer Research (New York, NY), of Memorial Sloan Kettering Cancer Center with Dr. Lloyd J. Old and Dr. Herbert F. Oettgen. After his research fellowship, he worked as a Research Associate and was promoted to an SKI Associate Member position in 1972, a position that he held through 1979.

Dr. Shiku was a pioneer of translational cancer immunology research. He contributed to the definition, expression pattern and function of the murine T-cell differentiation antigen system Lyt, which later was identified on human T cells as the $CD4^+$ and $CD8^+$ T-cell differentiation antigen. He translated his successes in animal studies to human cancers. By a technique called 'autologous typing', he identified multiple unique and shared human cancer antigens, first in patients with melanoma, and later also in other cancer types.

After his return to his home country Japan in 1981, he obtained his Doctorate with a thesis on the identification of human melanoma cell surface antigens from Nagoya University School of Medicine. In 1986, Dr. Shiku was appointed to the Department of Oncology, Nagasaki University School of Medicine (Nagasaki, Japan) as Professor and Chairperson. There, he built a program in humoral and cellular cancer immunology. He and his group identified mutated ERK-2 in the CMS5 cell line as a tumor-specific mutation antigen, recognized by $CD8^+$ T cells. Dr. Shiku uncovered the molecular basis of polymorphic tumor rejection antigens of chemically induced sarcomas of inbred mice. He also found various immunogenic epitopes of human tumor antigens for cancer vaccine constructs.

In 1994, he was appointed from Nagasaki University School of Medicine to the Second Department of Internal Medicine, Mie University School of Medicine (Mie, Japan) as Professor and Chairperson. There, he started a clinical trial program evaluating cancer vaccines targeting cancer antigens such as HER2/neu and NY-ESO-1. To strengthen the vaccine efficacy, he revisited the immune modulation by subsets of $CD4^+$ T cells, which he originally categorized with different expression patterns of T-cell differentiation antigens, using the SEREX (SERological identification of antigens by EXpression cloning) method. His studies revealed that $CD4^+$ regulatory T cells were favorably stimulated in tumors with the same antigens recognized by $CD4^+$ helper T cells and at the same time inhibited the activation of effector cells, stressing the importance of immune balance in tumors. To effectively stimulate $CD8^+$ T cells and $CD4^+$ helper T cells, he developed a lipid-based antigen delivery system of CHP. One of the compounds, CHP-NY-ESO-1 cancer vaccine is now under investigation in a clinical trial.

Over the years, he maintained long-standing collaborations with colleagues and friends in New York. After retiring from the clinical department at Mie University in 2006, he started a new clinical research department (Department of Cancer Vaccine and Immuno-Gene Therapy) at Mie University Graduate School of Medicine with support from Cancer Research Institute (New York, NY) to further explore the therapeutic potential of engineered cancer antigen–specific T cells. With the progress of his clinical research, his study was further promoted in the Center for Comprehensive Cancer Immunotherapy in Mie University, which he led as the director. There, he was mainly involved in the development of personalized cancer immunotherapies including adoptive cell therapy with TCR gene-transduced T cells. To avoid mis-paring with internal and transduced TCR chains, he established a novel method based on siRNA technology. Dr. Shiku authored or coauthored over 300 research papers and reviews in the areas of immunology and oncology. He served as an editorial board member for several immunology and oncology journals including *Cancer Immunology Research*.

Dr. Shiku was one of the early pioneers of modern cancer immunology. His strong commitment, vision, and enthusiasm led to multiple important novel findings in cancer immunology and cancer biology. His strength in cancer immunology research was the ability to translate laboratory findings into effective clinical applications. Some have now become standard methods in the design of cancer vaccines and for cancer immunotherapy in general, including adoptive T-cell therapies for patients with cancer.

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Our thoughts are with Dr. Shiku's family. He will be missed by his laboratory teams, his former fellows, colleagues, and friends. He was an outstanding mentor not only to his fellows and students but also to an uncountable number of colleagues who benefited from his profound knowledge, wisdom, and vision. Discussing with him, we remember his words: "Why don't you do the experiment?" With his depth of knowledge, he would challenge us all and guide his students, fellows, and colleagues towards new ways of thinking about and solving problems. He always was fair and professional, a strong and passionate teacher. He was a gracious and thoughtful devoted husband and father. He will be missed deeply and always remembered.

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