Takashi Sugimura: In Memoriam (1926–2020)–A Personal Perspective

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Takashi Sugimura was a pioneer in cancer research and a figure recognized internationally for his seminal contributions to the understanding of mutagenicity and chemical carcinogenesis. Rather than focusing on the many accolades, honors, and influential positions that he held, the authors wish to present a more personal perspective on Dr. Sugimura's life. In particular, we focus on his early research activities from 1950 to the late 1970s, when the author Susumu Nishimura first came to know him, with additional descriptions of his major scientific accomplishments from 1980 to recent years, through the eyes of the authors.

Dr. Sugimura's research was very much driven by his independent nature and unwavering pursuit of research findings over many decades. While working as an intern in the late 1950s at the Radiation Department in the School of Medicine of the University of Tokyo (Bunkyo–ku, Tokyo, Japan), Dr. Sugimura came to the realization that the treatment of many patients with cancer by radiation was of little benefit and instead was contributing to adverse events. He redirected his focus to basic research to gain a greater understanding of human cancer etiology. Toward achieving this aim, Dr. Sugimura moved to the Cancer Institute of the Japanese Foundation for Cancer Research, a private cancer institute in Tokyo, Japan, which was the only cancer institute that existed in Japan at the time.

The director of the Cancer Institute was Dr. Waro Nakahara, a mentor and collaborator of Dr. Sugimura, whose research outlook and personal interaction proved to be of great influence. Indeed, Dr. Nakahara was an extraordinary person in his own right. He had studied at Cornell University (Ithaca, NY) under the supervision of Dr. W.A. Riley, who was the department director. While there, Dr. Nakahara met and married Dorothy, a U.S. national who served at the time as secretary to Dr. Riley. Dr. Nakahara moved to the Rockefeller Institute (New York, NY), following the recommendations by Dr. Riley, and worked under the supervision of Dr. Peyton Rous. His immersion in U.S. culture truly influenced Dr. Nakahara's research style and personality in an era when distinct differences existed between Japanese and Western cultures. After he returned to Japan, the impact of his excellent experience overseas was reflected in the staff of the Cancer Institute, who had freedom to follow individual research pursuits. Indeed, Dr. Nakahara himself worked in the laboratory alongside his research trainees. Dr. Sugimura also worked closely with Dr. Nakahara at this time and collaborated on investigating the carcinogenicity of 4-nitroquinoline *N*-oxide (4NQO; ref. 1).

Subsequently, Dr. Sugimura traveled to the United States as a postdoctoral fellow and worked from 1957 to 1960, first at the NCI (Bethesda, MD) under Dr. J.P. Greenstein and then at the Case Western Reserve University (Cleveland, OH). This experience contributed markedly to Dr. Sugimura's style of research. In 1960, he returned to the Cancer Institute in Tokyo, Japan, and became acquainted with Dr. Nishimura. Dr. Nishimura was immediately struck by Dr. Sugimura's passion and scientific ability, and through the years, the two friends and colleagues had innumerable research discussions that continued over a lifetime.

In 1962, the Japanese government established the National Cancer Center (NCC) in Tsukiji, Tokyo, Japan, and Dr. Nakahara was selected to be the director. After the research institutes became aligned under the Ministry of Welfare, a number of researchers considered that greater career opportunities existed in the new NCC, and they were enticed by the possibility of working with their former mentor, Dr. Nakahara. Dr. Sugimura was one of the people who moved and was appointed as the director of the Division of Biochemistry.

From 1958 to the late 1970s, Dr. Sugimura and his colleagues made numerous impactful discoveries, including the identification of novel carcinogenic heterocyclic amines produced by the cooking of meats. Anecdotally, it is said that Dr. Sugimura came to the realization of a link between cooked foods and carcinogenic risk factors while watching his wife cook in their modestly sized house and observing the large amount of smoke that cooking generated on a pivotal Sunday in 1976 (2). This moment encapsulated his highly inquisitive character, and mutagenic heterocyclic amines subsequently were established as multi-organ carcinogens in rodent bioassays. These accomplishments reinforced the human relevance of naturally occurring environmental mutagens and carcinogens and inspired numerous other scientists at the national and international level to enter the field of genotoxicology (3).

Equally of note was the discovery of poly(ADP)-ribosylation, which is now known to contribute to DNA damage signaling, inflammation, and cancer. This research avenue became a long-standing scientific interest of Dr. Sugimura and his many colleagues (4). Dr. Sugimura's inquisitive nature never allowed him to put this project to one side, as it arose from his own research efforts, despite it being many

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years before the true physiologic importance became known. As a distinctive extension of this work, Dr. Sugimura identified in 1999 a novel apoptogenic protein with ADP-ribosylation activity, pierisin, from the larvae and pupae of the cabbage butterfly, *Pieris rapae* (5). Pierisin was demonstrated for the first time to cause mono(ADP)-ribosylation on the N^2-position of guanine in DNA, not on proteins, in 2001 (6). This unique finding was derived from his pure scientific curiosity regarding the molecular mechanisms underlying insect metamorphosis (7). Butterfly collection was Dr. Sugimura's long-standing hobby, as was the case with Dr. Sugimura's mentor, Dr. Waro Nakahara.

As mentioned previously, while working at the Cancer Institute, Dr. Sugimura contributed to studies on the carcinogenesis of 4NQO in rats and demonstrated that skin cancer was induced by 4NQO (1). He continued his research on chemically induced carcinogenesis and observed that *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) produced gastric tumors in the rat (8). This was a significant discovery, because there existed no animal model that could appropriately replicate the high incidence of stomach cancer, which is common in Japan. Because 4NQO and MNNG were active in bacterial mutagenicity assays, Dr. Sugimura began searching for other mutagenic compounds, determining that many such agents were carcinogenic. This brought him to the realization that mutagenic activity might be a major contributing factor to cancer induction, including in humans. Dr. Sugimura was among the earliest to highlight that cancer is a disease initiated by mutations in DNA (9).

Dr. Sugimura was driven by a strict personality that demanded the highest levels of precision, integrity, and reproducibility at all times. He also had an outstanding talent for administrative work. For example, in 1984, he was involved in organizing the Comprehensive 10-Year Strategy for Cancer Control, which was initiated by the then Prime Minister, Mr. Yasuhiro Nakasone (10). As a consequence, the NCC greatly extended its research activities, establishing new postdoctoral and visiting scientist fellowships that facilitated increased international exchange. Dr. Sugimura was also very keen to strengthen other international relationships, especially with the American Association for Cancer Research (AACR). One year after the U.S. National Cancer Act was established in 1971, Dr. Sugimura and other key figures of the Japanese Cancer Association (JCA) launched a U.S.–Japan Cooperative Cancer Research Program with collaborative efforts by JCA and AACR members (11). In addition, he served as a cochairman, along with Dr. Enrico Mihich, of the first joint conference of the AACR and the JCA in Hawaii in 1989. These various activities have provided a platform for cancer researchers from Japan and the United States to discuss, develop, and nurture innovative science and to foster close personal friendships. In recognition of his stellar scientific accomplishments and contributions to cancer research, the AACR awarded him its highest honors by electing him as an Honorary Member in 1980 and a member of the inaugural class of Fellows of the AACR Academy in 2013.

Lastly, we would like to touch briefly upon Dr. Sugimura's humanity and heartwarming character. Dr. Sugimura is widely recognized for many of his valued scientific achievements, but equally he has touched the lives and careers of numerous individuals, including Dr. Nishimura. Dr. Nishimura received the prestigious dual national honors of the Imperial Prize and the Japan Academy Prize in 1988, kindly supported by a strong recommendation from Dr. Sugimura, who clearly devoted much time and personal commitment to the nomination process. Receiving this prize had a very significant impact on Dr. Nishimura's ability to continue his later research career. Another personal episode occurred shortly before Dr. Sugimura's death, when he phoned Dr. Nakagama, requesting several scientific publications and wishing to discuss recent progress in worldwide trends in cancer research as well as future directions for the entire community of Japanese cancer research. Dr. Sugimura was as enthusiastic as always on the telephone and eagerly looked forward to the visit of Dr. Nakagama. To the very end, Dr. Sugimura kept himself actively committed to biomedical science and was devoted deeply to cancer research throughout his entire life.

Naturally, it was a great sadness to receive the news of Dr. Sugimura's passing. However, Dr. Sugimura's spirit remains, and it propels us to continue our active research endeavors in the same manner for the rest of our lives.

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