Results generated through the Grants-in-Aid for Scientific Research Program No.1(Dec.2011)

Story about discovery of Adult T cell leukemia and HTLV (first part of the story)

1. From discovery of the disease to finding its virus

The discovery of Adult T cell leukemia and its pathogen virus was a success story of Japanese researchers through their efforts made in Japan. The discovery was not simply the finding of a single disease and virus; it significantly affected the discovery of the human immunodeficiency virus, or HIV, and even theories on where the Japanese people originally came from. The discovery of the leukemia and its virus was the result of the researchers' original efforts, which had been supported especially by cancer studies aided by the Grants-in-Aid for Scientific Research Program. In that sense, their findings were also a success story of the program.

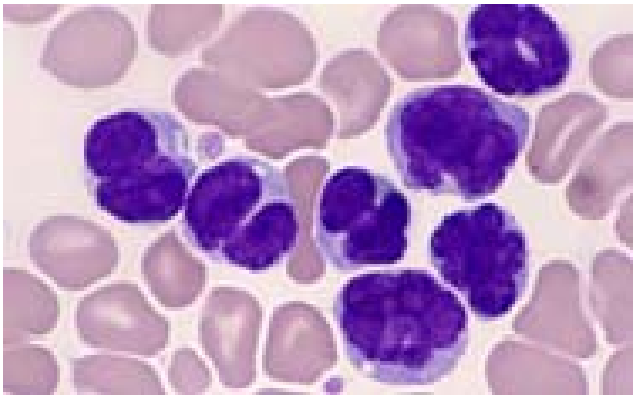
The story started at a medical doctor’s office at Kyoto University Hospital in Kyoto in 1973. Dr. Kiyoshi Takatsuki of the hospital's hematology department saw a slightly unusual leukemia patient. While lymphocytic leukemia usually derives from B lymphocytes, the patient's leukemia cells stemmed from T cells. Moreover, the nuclei of the leukemia cells were sharply constricted in the middle. The female patient in her 50s was from Kagoshima Prefecture on Kyushu, the southernmost of Japan’s four main islands. With the clues of T cells and Kagoshima Prefecture, Takatsuki found not only that this type of leukemia was more common among people on or from Kyushu than among people in other regions, but also that only adults catch the disease. In 1977, he named it Adult T cell leukemia, or ATL.

Professor Kiyoshi Takatsuki, discoverer of Adult T cell leukemia

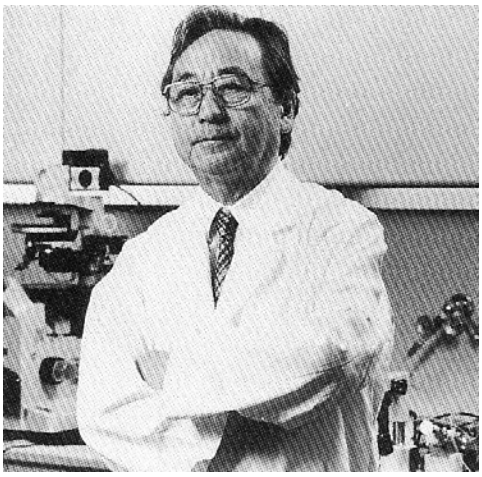
Yorio Hinuma heard about Adult T cell leukemia shortly after being transferred from Kumamoto University to the Institute for Virus Research at Kyoto University. On November 24th, 1980, a substitute holiday, he made cultured leukemia cells react to sera derived from six patients. He saw the cells glow green with fluorescent pigment. The sera reacted to the leukemia cells, indicating the existence of antibodies common among the patients that reacted to the cells. Hinuma instinctively realized that the antibodies must be antiviral agents. This was the moment when the human cancer virus that researchers around the world were desperately trying to find showed its shadow under a microscope for the first time. Hinuma decided to shift his research from the Epstein-Barr virus to concentrate on the new virus. The virus in question fully validated his decision.

Dr. Isao Miyoshi of the internal medicine department of Okayama University was very skilled at culturing cancer cells. The cells used by Hinuma in his antibody reaction study were from the MT-I cell line established by Miyoshi. He was trying to establish another cell line at that time. Miyoshi cultured a mixture of lymphocytes of a female Adult T cell leukemia patient and healthy cells from a boy's umbilical cord, expecting that the cancer cells would be promoted to multiply at a faster pace by the healthy cells. Two months after starting the culturing, he was surprised to observe cells that began to drastically increase. He found that they were not those of the female patient but the boy's healthy cells. This most likely showed that the virus of the patient's leukemia cells may have infected the healthy cells and changed them into leukemia ones. This finding unintentionally demonstrated the virus's infectious ability. These cells (MT-II cells) played a central role in subsequent research on the disease and its virus.

Dr. Haruo Sugano was then the chief of a special cancer research group at the education ministry and the head of the Cancer Institute of Japan. He talked about Adult T cell leukemia with Dr. Mitsuaki Yoshida, who had just become the head of the virus tumor department at the Cancer Institute. Yoshida earnestly asked Sugano to allow him to study the leukemia, saying that Yoshida had been studying a chicken cancer virus in order to study a human cancer virus in the future.



Adult T cell leukemia cells whose nuclei appear to have swollen



Professor Yorio Hinuma, the discoverer of the Adult T cell leukemia virus

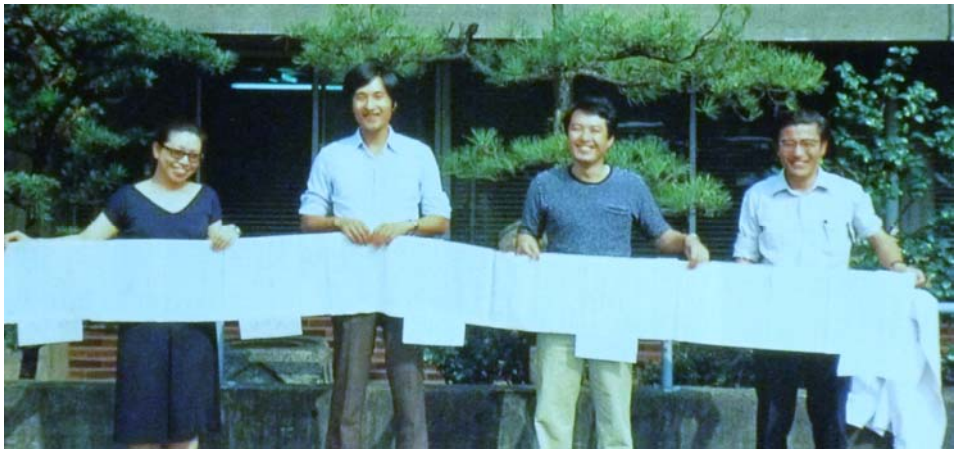
Yoshida was invited to a meeting of the special cancer research group led by Hinuma in July 1981 because virus researchers of the group were seeking to make use of the knowledge and experience of molecular biologists like Yoshida. His participation made the group a very

powerful team for studying the new disease and its pathogen virus. Yoshida took MT-II cells from the group back to his laboratory, and within a few days discovered the existence of reverse transcriptase. Having such an enzyme indicated that the virus was a retrovirus with RNA as its genome. The virus's reverse transcriptase synthesized DNA based on its RNA. Then, the DNA sneaked into the genome of cells to express its own genome, and the cells were changed into leukemia ones as a result. This demonstrated for the first time that a retrovirus existed in humans and that it was a cancer virus. Until then, retroviruses had been known to exist only in chickens, mice and other animals. Moreover, it was found that the virus's genome had been taken into the DNA of every Adult T cell leukemia cell. The leukemia was undoubtedly caused by this cancer virus. These research results were reported in the International Symposium of the Princess Takamatsu Cancer Research Fund, the Proceedings of the National Academy of Sciences of the United States and Nature magazine from the late 1981 to spring of 1982. The results of the research supported by the Grants-in-Aid for Scientific Research Program in Japan astonished researchers around the world as the first study to demonstrate that human cancer is caused by a virus that is a retrovirus. In 1983, the group led by Yoshida at the Cancer Institute clarified the virus's full genetic makeup.

In 1980, Dr. R. Gallo at the National Cancer Institute (NCI) in a suburb of Washington, D.C. isolated a retrovirus from a black person from the Caribbean Sea region who had been diagnosed with mycosis fungoides. Yoshida analyzed the genetic makeup of the retrovirus isolated by Gallo and found that it was the same virus as that discovered by Hinuma. The virus was later called HTLV, the acronym of the Adult T cell leukemia virus.

Acquired immunodeficiency syndrome, or AIDS, was discovered in 1981. The disease spread at an astonishing speed globally, killing many people. Its virus, the human immunodeficiency virus, or HIV, was isolated in 1983 and found to be a retrovirus like HTLV. HIV's genetic structure is similar that of HTLV as well. Accumulated data about HTLV made a considerable contribution to HIV research. If HTLV had not been discovered, progress in HIV research would have been slower.

(The second half of this story will be in the next issue.)



Members of a Cancer Institute team that successfully sequenced the genome of the Adult T cell leukemia virus (known as HTLV-1 later): From right, Mitsuaki Yoshida (now at the Cancer Institute), Motoharu Seiki (now at the Institute of Medical Science, the University of Tokyo), Seisuke Hattori (now at the School of Pharmaceutical Science, Kitasato University) and Youko Hirayama (now at the Cancer Institute)

Written by Toshio Kuroki -- Deputy Director, Research Center for Science Systems, the Japan Society for the Promotion of Science, emeritus professor, the University of Tokyo (Institute of Medical Science), emeritus professor, Gifu University (former president)

Kuroki participated in the government's comprehensive 10-year strategy for cancer control, special cancer research project and specific cancer research work from 1983 to 2003. He was president of the Japanese Cancer Association in 2000.