

[Obituary] Ho Wang Lee (Oct. 26, 1928-Jul. 5, 2022)

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Ho Wang Lee 이호왕, a South Korean virologist, passed away on July 5. He is well-known as the scientist who first discovered *Hantaan virus* (HTNV), an agent of hemorrhagic fever with renal syndrome (HFRS), in 1976. In addition, he discovered *Seoul virus* (SEOV), a causative virus of hemorrhagic fever found in urban areas, and developed Hantadia, a diagnostic kit for HFRS, and Hantavax, a vaccine against HFRS. By thus both discovering the causes of an infectious disease and developing diagnosis and prevention methods, which is a rare feat for virus researchers, he was able to grow as an internationally noted scholar. In 2021, he was also nominated as a strong candidate for the Nobel Prize by Clarivate Analytics, which selects outstanding researchers with paper citations in the top 0.01% and announces its anticipated candidates for the award, thereby establishing himself once more as a medical scientist representative of South Korea. Taking note of his discovery of HFRS pathogens, which was his key research achievement, and growth as a global researcher, I have written a doctoral dissertation titled “From Periphery to Center: A Virologist Ho Wang Lee’s Research Activities 주변에서 중심으로: 바이러스학자 이호왕의 연구 활동.” In this essay, I would like to extend my condolences by retracing his life and major research accomplishments.

Ho Wang Lee was born in October 1928 in Sinhung County, South Hamgyong Province in what is North Korea today. Though he preferred sports to studying and was good at writing as well in his childhood, he decided to study medicine in accordance with the wishes of his mother, a daughter of a traditional Korean medicine (TKM) doctor, and entered the Hamhung Medical College in 1948. With the outbreak of the Korean War (1950-1953) while he was enrolled in the medical school, however, he came to leave Hamhung, his hometown, and to relocate to Seoul. Though this could have led to the premature termination of his medical studies, Ho Wang Lee was able to continue his education thanks to Seoul National University’s permission for North Korean students’ transfer in 1951, thus joining the institution as a first-year student in the regular course of its College of Medicine. With the armistice determined in 1953, the Seoul National University medical school, too, returned to the capital and resumed educational activities, and Ho Wang Lee was able to complete the undergraduate program in the college in 1954 amid chaos.

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Going on to graduate school after graduation, he chose microbiology. That is, he decided to study this field under the influence of Professor Ryong-sook Kee 기용숙, whom he had met in the microbiology laboratory of the Allied Universities during the Korean War. However, the research and educational environment in South Korea were very poor immediately after the war. This period saw the launching of the so-called Minnesota Project, a training program at the University of Minnesota aimed at rebuilding Seoul National University, which allowed him to go to the United States for studies. Studying in the master's and doctoral programs at the University of Minnesota starting in 1955, Ho Wang Lee was introduced to a new academic discipline. At the suggestions of his academic advisors Jerome T. Syverton and William F. Scherer, he chose the Japanese encephalitis (JE) virus as his research topic and received a master's degree in 1957 with "Studies on the Propagation of Japanese B Encephalitis Virus in Tissue Culture" and a doctoral degree in 1959 with "Studies on Immunity to Japanese Encephalitis Virus," respectively. Through these studies, Ho Wang Lee was able to learn about virology, a new field for him, and grew as a researcher, conducting research with the tissue culture technique, which was a state-of-the-art research method then, and searching for new cell lines for it.

Having earned a doctoral degree with a study on the JE virus, he sought to continue this research even after returning to South Korea. Because the research environment in the country was poor, however, he turned his attention to the United States and applied to the National Institutes of Health (NIH), successfully receiving funding necessary for research on JE. Though Ho Wang Lee initiated "Study on Overwintering Mechanisms of Japanese Encephalitis Virus in Korea 한국에서 일본 뇌염 바이러스의 월동 기전에 관한 연구" in 1964, he had to turn to other research topics because of the development of a vaccine against encephalitis in Japan. He obtained the idea of conducting research on HFRS from Col. Edward L. Buescher at the Walter Reed Army Institute of Research (WRAIR) while visiting the United States for research on JE. Though HFRS had been studied for long in diverse countries, researchers had continuously failed to discover the pathogen. In particular, American troops stationed near the 38th parallel north, the North-South border, during the Korean War had been severely affected, thus making HFRS an infectious disease to which the United States directed considerable attention. Based on an acknowledgment of his experience of having received American funding for research on JE and his educational background of having obtained a master's degree and a doctoral degree in the United States, he was able to begin research on HFRS with support from the US Army Medical Research and Development Command (USAMRDC) starting in 1970.

In his research on HFRS, Ho Wang Lee used serum from hemorrhagic fever patients as well as rodents and ectoparasites as the main objects of his experiments. He applied the tissue culture technique that he had learned in the United States to these

experiment materials. Ho Wang Lee's laboratory underwent hardships in the research process such as a member being mistaken for a spy while trying to catch wild rats, key materials of experiments, and falling gravely ill due to infection with HFRS. Though various types of tissue culture cells were secured and the organs of wild rats collected from areas with hemorrhagic fever were tested in diverse ways, desired results could not be obtained. Ho Wang Lee therefore decided to try the fluorescent antibody technique, which was a new research method, in addition to the tissue culture technique familiar to him. However, this method proved not to be satisfactory, either. Experiments continued to fail, and the termination of funding support was imminent as well. At this time, Ho Wang Lee happened to read a book by William L. Jellison, an American hemorrhagic fever researcher, which prompted him to turn his attention to the lungs, which he hitherto had not used in experiments. In fact, the lungs were inappropriate as experiment materials because they, as respiratory organs, contained many contaminants and also were excluded because they exhibited few or no lesions in comparison with other organs. As for the new experiment materials of the lungs, Ho Wang Lee conducted experiments where he applied the new research method of the fluorescent antibody technique, as a result of which he succeeded in discovering an agent of hemorrhagic fever in 1976. These contents were publicized through a press conference held on April 29, 1976 and introduced in the press abroad such as *Time* as well. Confirming the viral characteristics of this pathogen, he named it *Hantaan virus*. After discovering this virus, with the striped field mouse (*Apodemus agrarius*) as the host, Ho Wang Lee went on to discover a pathogen of hemorrhagic fever also through the house mouse (*Mus musculus*) inhabiting urban areas in 1980, which he named *Seoul virus*. When it became known that the host of SEOV, unlike HTNV, was the house mouse distributed nearly worldwide, he became a scholar attracting the attention of hemorrhagic fever researchers around the globe.

Not satisfied with the discovery of the new viruses, Ho Wang Lee began to study methods for diagnosing HFRS patients through joint research with a Japanese researcher. In 1986, he obtained viral antibodies of very high biological purity from the brain tissues of newborn mice and white mice. In 1987, the following year, Tet-suo Tomiyama 富山哲雄 of the University of Tokyo, Ho Wang Lee's co-researcher, developed a new technology called "high-density particle agglutination." With the combination of Ho Wang Lee's high-purity antigens and Tomiyama's high-density particle agglutination, it became possible to develop serum diagnosis technique capable of diagnosing HFRS. An HFRS diagnostic kit was developed on the basis of this research and was commercialized by Green Cross Corp. (present-day GC Biopharma Corp.) in 1989 as Hantadia.

The development of vaccines is the ultimate goal of virus researchers as well. While conducting research on JE and HFRS, Ho Wang Lee likewise devoted himself

to research under the intention of developing a vaccine. At the time that he was studying the JE virus, he had an experience of producing an inactivated vaccine with porcine kidney cells, and he made use of this method in HFRS vaccine research. Ho Wang Lee produced HTNV on a mass scale from the brain tissues of suckling mice and suckling rats and succeeded in creating an inactivated vaccine by using formalin. Created on the laboratory level, the vaccine was acknowledged for its efficacy through clinical tests, which began with personnel participating in the research, and, as a result, came to be commercialized in 1990 with the South Korean government's item approval. Thus emerged Hantavax, a vaccine against HFRS.

In addition to his own research, Ho Wang Lee devoted efforts also to the creation of academic spaces where South Korean virus researchers could gather. He founded the Korean Society of Virology in 1971 and the Korean Vaccine Society in 1998, respectively, thus establishing centers for domestic virus research. In addition, he taught students at the Seoul National University medical college from 1960 and, in 1973, transferred to Korea University medical college and continued his educational activities. In particular, the Institute for Viral Disease that he managed at Korea University was designated as the World Health Organization's (WHO) Collaborating Centre in 1982, thus going beyond South Korea and implementing international education and research as well. By successively holding positions such as the president of the South Korean National Academy of Sciences (2000) and of the Science Council of Asia (2003), respectively, Ho Wang Lee also demonstrated leadership in the academia both at home and abroad. In particular, in relation to virology, he was active as a member of the Japanese Society for Virology (1976), American Society for Virology (1981), Chinese Society of Virology under the Chinese Medical Association (1989), and American Society of Tropical Medicine and Hygiene (1993). Active as a member of the American Philosophical Society (1998), a foreign member of the US National Academy of Sciences (2002), a foreign honorary member of the American Academy of Arts and Sciences (2004), and an honorary member of the Japan Academy (2009), respectively, he formed international research networks and elevated the status of South Korean virology.

Ho Wang Lee's discovery of HTNV and subsequent research activities formed a context important for the overall history of science in (South) Korea: a latecomer in science, the country made a global research achievement and, based on this, formed an international hub of research on hemorrhagic fever viruses. In order to commemorate this achievement, he was inducted into the Korea Science and Technology Hall of Fame in 2003, and the Dr. Ho Wang Lee Memorial Hall was built within the Freedom Protection Peace Museum in the city of Dongducheon in 2012. In addition, he was selected as a person of distinguished service to science and technology in 2017 for his service of having contributed to the development of the nation's science and technology.

Following his discovery of HTNV, in recognition of this achievement, Ho Wang Lee was presented with prizes such as the Department of the Army Distinguished Civilian Service Award (1979; United States), National Academy of Sciences Award (1980; South Korea), Prince Mahidol Award (1994; Thailand), Nikkei Asia Prize (2001; Japan), and Changjo Medal, Order of Science and Technological Merit (2002; South Korea). Though his reception of the award regrettably did not materialize, he was honored as a South Korean scientist and greatly moved younger researchers and students by being nominated as a strong candidate for the Nobel Prize in 2021. Even when COVID-19 was rampant, he maintained passion as a virus researcher so that, despite his advanced age, he held an interview on the need to establish infectious disease response plans and to support basic medicine. Paying my respects once again to his unswerving dedication to research, I would like to extend my condolences.