Robert Koch Prize Acceptance Speech by Tasuku Honjo

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[Address]

I am deeply grateful, honored, and humbled to be the recipient of the 2012 Robert Koch Prize. I would like to thank the Robert Koch Foundation, and the referees who have chosen me for such an esteemed prize.

Professor Radbruch, I am extremely grateful for your gracious and erudite laudation. You have given a far more generous account of my career than I would dare give myself on this occasion. Nevertheless, I would like to offer a few personal observations on the course of my career. I will try to keep my remarks suitably brief.

I would like to start my remarks by referring – quite appropriately on this occasion, I think – to Robert Koch. As I'm sure you are all very well aware, Robert Koch is the father of microbiology. Together with Edward Jenner and Louis Pasteur, he demonstrated that vaccination is the most powerful medical strategy for the prevention of infectious diseases. Many other scientists have dreamed of the glorious discoveries of Robert Koch, and have gone on to identify many previously unknown pathogens.

Among these microbial hunters was Hideyo Noguchi, the famous Japanese bacteriologist who discovered the cause of syphilis, and who died in Ghana in pursuit of the yellow fever virus. As a child, I was profoundly affected by his story. Noguchi's fame, tragedy, and devotion – all were overwhelming to me as a 10-year-old boy. I adored him, and was strongly motivated by his example to become a medical scientist.

In spite of the enormous success of vaccination measures around the world, for many years it remained a mystery why immunization with bacterial antigens can prevent the onset of diseases upon subsequent encounters with the same pathogen. Researchers assumed that our body has the capacity to "remember" pathogens it has been previously exposed to, but nobody knew the exact mechanisms behind this "memory". The work of a number of investigators revealed that antigen-induced memory is manifested as two distinct phenomena: One is somatic hypermutation, which replaces amino acids at the antigen binding sites of antibodies to increase affinity to the antigen; the other is class switch recombination, which generates different classes of antibody to provide the most effective processing of captured antigens.

Somatic hypermutation was theoretically postulated by Niels Jerne and Macfarlane Burnet. Their hypothesis was experimentally demonstrated by Melvin Cohn and Martin Weigert at the protein level. Subsequently, Susumu Tonegawa and Robert Perry showed the existence of point mutations in immunoglobulin genes. The subsequent work of numerous scientists demonstrated that somatic hypermutation is responsible for the antigen-induced affinity increase that occurs in immunoglobulins.

Class switch recombination was originally described by Jonathan Uhr, who observed the change of immunoglobulin classes caused by strong antigen stimulation. Gustav Nossal showed that a single B cell expressing IgM changes its immunoglobulin class in in vitro culture. Max Cooper demonstrated that removal of IgM positive cells abolished other immunoglobulin classes in chicken. More directly, Hugh Fundenberg showed not only that IgM and IgG from a single myeloma patient shared an identical variable region, but also that these antibodies differed as expected in the C-terminal region of the heavy chain, thereby clearly demonstrating that only the C-terminal region was replaced by class switching.

Turning to my own part of the story, upon finishing my medical education at Kyoto University, I was convinced that molecular biology was a tremendously powerful approach to revealing the molecular mechanism of life. I first crossed paths with Robert Koch as a graduate student in Kyoto in 1968, when I discovered that the diphtheria toxin catalyzes ADP-ribosylation of protein synthesis factor EF-2 and inactivates it. This finding gave me the confidence to continue my career as a scientist, and also gave me the opportunity to learn about the research collaboration between Emil von Boehring and Shibasaburo Kitasato in Koch's laboratory. After finishing graduate school, I moved to the Carnegie Institute of Washington in Baltimore, where I learned a great deal from Don Brown, not only about the molecular biology of DNA, but also about the genetic mystery of how immune diversity is generated. To pursue this basic question in immunology, I moved to Philip Leder's laboratory in 1973. I was very fortunate that this was exactly at the time when recombinant DNA technology began to emerge. We demonstrated that the number of genes for the light chain constant region was very small. Since the number of variable region genes had to be very large, our results suggested a DNA rearrangement was taking place in the Ig gene.

In 1974 I came back to the University of Tokyo as an assistant professor, where I had the very rare and fortunate opportunity to choose my own research project. I was fascinated by the fact that, during class switching, the C-terminal constant region of the Ig heavy chain protein is replaced, but its N-terminal variable region remains unchanged. This phenomenon was totally puzzling from the point of view of themolecular biology dogma of the mid-1970's; namely, one gene for one polypeptide. When my research group examined the immunoglobulin constant-region gene in antibody-producing tumors called myeloma, we found that the deletion of specific constant region genes accorded with given immunoglobulin classes expressed in the myeloma. After screening a large number of myelomas, we developed the hypothesis that this deletion is not accidental, but rather that it is programmed to generate different immunoglobulin classes. In other words, antibody-producing cells delete a specific segment of DNA to accomplish a class switch. This was a real surprise, because nobody expected controlled DNA alteration in somatic cells.

After we published this model in 1978, the development of molecular cloning technology allowed us and others to determine DNA structure before and after class switching, and we clearly demonstrated that class switching is mediated by the DNA recombination that accompanies deletion of DNA segments. I was very happy that our model had proved to be correct.

After that, I wished to understand which molecule is responsible for class switch recombination. Fortunately, in 2000 we identified an enzyme, activation-induced cytidine deaminase, abbreviated as AID, that is required for class switch recombination.

Unexpectedly, we found that AID is also responsible for somatic hypermutation. This finding led us to conclude that AID is the master gene for both class switch recombination and somatic hypermutation, and therefore that AID is the master regulator of the antigen memory that is essential for vaccination. In collaboration with a French group led by Alain Fischer and Anne Durandy, we found that patients who have mutations in AID suffer from an immune deficiency called hyper IgM syndrome type II. They experience neither class switch recombination nor somatic hypermutation.

Max Cooper, who received Robert Koch Prize in 2010, discovered that the most ancient form of AID is found in the lamprey eel, which shares a common ancestor with all modern vertebrates. The origin of acquired immunity is likely to have occurred at the time that AID evolved, because the enzymes RAG1 and RAG2, which mediate VDJ recombination and generate the antigen receptor repertoire, are believed to have been introduced later by transposon insertion in jawed fish vertebrates. How could AID evolution alone alter DNA sequences to generate acquired immunity? We hypothesize that AID took advantage of a preexisting genome instability mechanism, which depends on aberrant DNA structure

induced by strong transcription. Such genome instability is found in all animals, from bacteria to mammals. AID simply enhances the efficiency of aberrant DNA structure formation, introducing a mutation frequency rate almost 10,000 times higher than that of general genome instability. Unfortunately, however, AID can also target other, non-immunoglobulin genes which can form similar aberrant DNA structures. This may be the reason why dysregulated AID expression is associated with tumorigenesis in various mouse and human cancers. The dilemma of AID, namely immune diversification with a risk of tumorigenesis, thus arises from its evolutionary origin. I am very pleased that our pursuit of the origin of class switch recombination brought us to the molecular explanation for the generation of the antigen memory that is essential to vaccination.

Just before I finish, if I may, I would like to introduce to you one other line of research from my laboratory, one that has resulted in the application of immunology to medicine. In 1992, we isolated a negative immune coreceptor called PD-1, and later showed that anti-PD-1 antibody treatment can cure various types of cancer in mice. This finding has been applied to human cancer patients using a humanized anti-PD-1 antibody. Recent clinical trials carried out in the U.S. and Japan indicate that anti-PD-1 antibody treatment has remarkable effects against melanoma, renal cancer, and non-small-cell lung cancer. A recent editorial in the New England Journal of Medicine described this treatment as the most powerful immune therapy against tumors to have emerged in the past 30 years.

I am very pleased that our two lines research, both of which developed out of curiosity about basic biology, have led both to an understanding of the mechanism of tumor generation, and also to the treatment of tumors. As scientists, we never know where our curiosity will take us. I would like to emphasize the importance of curiosity-derived science, and to encourage young scientists to take up the challenge of basic questions that fascinate them, especially questions that have remained unsolved for many years.

In finishing, I would like to briefly thank the many people who have supported me in my research over the years. I would like to express my sincere appreciation to my long-term collaborators, who now number some 300 students, postdoctoral fellows, and colleagues. I have learned a tremendous amount from working together with them. In addition, I appreciate the very warm and stimulating collaboration that I have had with many international scientists in Europe and North America. I would especially like to thank my many German colleagues, who have been very supportive and who have stimulated me to carry my studies further. We have made many exchanges of information, reagents, and ideas. The long tradition of warm friendship between German and Japanese academia is still very active and lively, and I heartily wish to continue this wonderful association.

And I would also thank my family, who I think have suffered from my stubborn and rather narrow-minded concentration on science, to the detriment of daily family life. I deeply appreciate their support.

Lastly, I would like to once again thank the Robert Koch Foundation for this honor, and I thank all of you for your kind attention.
Thank you very much.