Dankesrede

von

Prof. Dr. Shimon Sakaguchi

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter- Preises

2020

14. März 2020

Die Dankesrede wurde im kleinen Kreis gehalten, weil der Festakt in der Frankfurter Paulskirche wegen der aktuellen Entwicklungen in der Coronavirus-Pandemie abgesagt worden war.

Distinguished Guests, Ladies and Gentlemen,

I am truly humbled and grateful to be receiving this year's Paul Ehrlich and Ludwig Darmstaedter Prize. I would like to thank the Members of the Scientific Council of the Paul Ehrlich Foundation and Prof. Thomas Boehm, the Chairman of the Council, for bestowing on me this high prestige as a medical scientist.

I am honored for "the discoveries concerning the role of regulatory T cells". Regulatory T cells are a population of T-lymphocytes, or T cells, naturally present in our body, and, like policemen, they are responsible for maintaining immunological order throughout the body. As you may know, immune responses normally protect our body from invading viruses and bacteria. Sometimes, however, immune reactions cause damage to the body. For example, if the immune system is misdirected, attacking and destroying our own cells or tissues, it can cause autoimmune disease, such as type 1 diabetes and rheumatoid arthritis. Similarly, if cells of the immune system react excessively with an otherwise harmless environmental substance such as pollen, allergy can occur. Understanding how to control these unwanted immune responses and cure these immunological diseases has been challenging immunologists for many decades since the days of Paul Ehrlich. Around the turn of the 20th century, Emil von Behring and Shibasaburo Kitasato demonstrated that antiserum prepared by immunizing horses with tetanus or diphtheria toxin was able to cure patients suffering from tetanus or diphtheria. Paul Ehrlich noticed that, while immunization of animals with red blood cells or tissues from other animals produced specific antibodies against the immunized cells, immunization of animals with their own blood or tissues cells was unable to generate antibody production. This apparent inability of animals to make antibody against cells of their own led Ehrlich in 1901 to make a postulate he named as "Horror Autotoxicus", which literally means "avoidance of auto-toxication". This dictum stating that the occurrence of autoimmune disease should be impossible was broadly accepted because of Ehrlich's worldwide prestige. Importantly, he also stated in the same paper that there must be "certain contrivances" that prevent autoimmune reactions from self-destruction causing autoimmune disease.

Indeed, possible contrivances or mechanisms have been proposed in these 120 years since the proposition of Horror autotoxicus by Ehrlich. For example, 27 years ago in 1993, the Paul Ehrlich and Ludwig Darmstaedter Prize was awarded to three eminent immunologists, Philippa Marrack, John Kappler, and Harald von Boehmer, who demonstrated a simple and straightforward mechanism by which hazardous self-reactive T cells were deleted in the thymus where T cells are produced, resulting in immunological unresponsiveness to self. However, this process is imperfect and not all self-reactive lymphocytes are deleted. There is ample evidence that normal healthy individuals harbor small numbers of potentially hazardous self-reactive T cells in the blood, suggesting that there must be another mechanism, or contrivance, for controlling them. We have found that active suppression of harmful self-reactive lymphocytes by regulatory T cells is an important part of this process.

I shall briefly tell you the story of how regulatory T cells were discovered and how we and others have been studying them. In 1969, Yasuaki Nishizuka and Teruyo Sakakura, two Japanese pathologists, reported an interesting finding related to autoimmune disease and the thymus. They showed that removal of the thymus from newborn mice led to spontaneous development of various autoimmune diseases due to hyper-reaction of T cells against self-antigens. As a young immunologist, I became interested in this finding and joined Nishizuka's group to determine how the removal of the thymus causes autoimmune disease. What we found in 1982 was that the autoimmune disease could be completely prevented by injection of $CD4^+$ T cells from normal mice. This implied that $CD4^+$ T cells in normal animals contained a certain T-cell population capable of preventing autoimmune disease. Our efforts to further characterize this autoimmune-suppressive T-lymphocyte population by various markers culminated in our discovery in 1995 that $CD4^+$ T cells expressing a molecule called CD25, which is the interleukin-2 receptor, are the population specialized for immune suppression. Direct removal

of this population from normal mice was indeed sufficient to produce diverse autoimmune diseases and transfer of the population back prevented disease development. We thus named them as regulatory T cells, a population constituting only 10% of total $CD4^+$ T cells but highly critical in maintaining immune homeostasis. However, at that time, immunologists in general were skeptical about the existence of such T cells specialized for immune suppression. Deletion of rogue self-reactive T cells in the thymus, which I mentioned previously, appeared to be much simpler explanation of immunological unresponsiveness to self.

Then strong evidence for the existence and the importance of regulatory T cells came from human disease. There is a genetic disease in humans, called immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, abbreviated as IPEX syndrome. Patients with IPEX syndrome suffer from autoimmune diseases such as type 1 diabetes, inflammatory bowel disease, and severe allergy, due to mutations of a single gene. Around the year 2000, the gene mutated in IPEX syndrome was identified by geneticists and designated Foxp3, which encodes a transcription factor. We noticed that this genetic disease was so similar to the disorder we could induce in mice by removal of regulatory T cells. And, in 2003, Fred Ramsdell and Alexander Rudensky in the United States, and my group in Japan, Shohei Hori and I, found that regulatory T cells specifically express Foxp3, which controls the development and function of regulatory T cells. If the transcription factor Foxp3 malfunctions, regulatory T cells cannot develop or cannot work properly, and severe immunological disorders develop. This was clear evidence in humans that regulatory T cells are indispensable for the maintenance of immunological unresponsivenesss to self. Anomalies of regulatory T cells in number or function can be causative of not only autoimmune disease but also allergy against environmental substances and inflammatory bowel disease due to excessive immune responses against commensal bacteria in the intestine. It is well known now that the incidences of autoimmune diseases, allergy, and inflammatory bowel disease, are increasing in developed countries such as Europe, the United States, and Japan, in correlation with the decrease in infectious diseases. It is speculated that the immune system may not be much stimulated in our microbially clean hygienic society, and, as a result, regulatory T cells are not trained to be strong enough to effectively control hazardous immune responses.

With recent progress in our understanding of the roles of regulatory T cells in controlling physiological as well as pathological immune responses, we now know that there are many future possibilities for using regulatory T cells in the clinic. For example, if you reduce or weaken regulatory T cells you can strengthen cancer immunity. Indeed, drugs targeting regulatory T cell function are already being used in the clinic to help boost anti-cancer responses. A similar approach will help enhance vaccination against viruses or bacteria. In contrast, if you increase or strengthen regulatory T cells, you can potentially suppress immune responses, and treat not only autoimmune disease or allergy but also organ rejection following transplantation, establishing stable acceptance of grafted organs.

Receiving the Paul Ehrlich and Ludwig Darmstaedter Prize has a special meaning to me because our work on regulatory T cells is part of a direct lineage from Ehrlich's conceptualization of "horror autotoxicus", the body's innate aversion to immunological self-destruction. I hope that we have helped to explain his original suggestion of the existence of "certain contrivances" to maintain "horror autotoxicus". Thus, this award is a great encouragement for us to further study how immune responses can be controlled in normal and disease states, and devise ways to cure or prevent immunological disorders in humans.

In closing my remarks, I would like to express my deep gratitude to my mentors. Yasuaki Nishizuka and Teruyo Sakakura, who introduced to me autoimmunity induced by removal of the thymus from newborn mice, and Toshitada Takahashi for teaching me immunology especially how to characterize T cells by various molecular markers. I also thank many brilliant postdocs and students from various countries for working with me, and last and not least, my wife Noriko for sharing

wonderful time with me in the lab and at home these last forty years. Without the contributions and help from these people, I would not be here today to receive this great honor.

Thank you.