

The Fruits of Curiosity and Courage in Research

An interview with Prof. Tasuku Honjo of the Department of Immunology and Genomic Medicine, Graduate School of Medicine.



Prof. Tasuku Honjo

Nivolumab (product name: Opdivo), an antibody to block a protein called programmed cell death 1 (PD-1), was developed based on the research of Prof. Tasuku Honjo and his colleagues. Nivolumab became commercially available in Japan last September and in the US last December following approval by the relevant authorities. This new breakthrough drug, developed by Ono Pharmaceutical and Bistol-Myers Squibb (BMS), is highly anticipated to change cancer therapy dramatically, and is attracting attention worldwide. The discovery of PD-1 was nominated Breakthrough of the Year 2013 by Science, America's leading scientific journal. Prof. Honjo also shared the inaugural Tang Prize in Biopharmaceutical Science with Dr. James Allison of the University of Texas MD Anderson Cancer Center in 2014. The acclaim for Nivolumab lends credence to the notion that "the best products can only be derived from the best science." In this interview, we asked Prof. Honjo about his research philosophy and the journey that led to this outstanding achievement.

Twenty years of basic research bears fruit

— **When the PD-1 protein was discovered in 1992,¹⁾ were you already seeking to develop a drug for cancer treatment?**

Honjo: No, I wasn't. PD-1 was originally discovered by Dr. Yasumasa Ishida (currently an associate professor at the Nara Institute of Science and Technology), who was a graduate student at that time. He was searching for a

molecule that could induce T-cell death, which had been a major challenge for the immune system.²⁾ I just regarded the discovery as a part of molecular immunology research, and didn't consider any relationship it may have with cancers.

However, since this discovery, high expression levels of programmed death-ligand 1 (PD-L1), a ligand of PD-1, have been demonstrated in many different cancer cells. In 2002, research led by

1) T. Okazaki et al., *Nat. Immunol.*, **14**, 1212-1218 (2013)

2) Y. Ishida et al, *ENBO J*, **11**, 3887-3895(1992)

3) Y. Iwai et al, *Proc Natl Acad Sci USA*, **99**, 12293-12297 (2002)

Dr. Yoshiko Iwai (currently a professor at the University of Occupational and Environmental Health, Japan) who was a graduate student at that time, found that the blockade of PD-1 signaling would restore a suppressed immune system and increase lymphocyte attack on cancer cells to suppress their proliferation.³⁾

— In 2002, two years after the beginning of the research, a patent application on the treatment of tumors and infections with PD-1 inhibitor was filed. And then, Ono Pharmaceutical and BMS jointly began developing drugs for cancer treatment. In 2006, the first clinical trial of an anti-PD-1 antibody began in the US. An application for approval to market the anti-PD-1 antibody as a drug for melanoma treatment was submitted in December 2013, and was approved in July 2014. Then, the new drug was brought on the market in September 2014. The authorities approved it with unprecedented speed in Japan—approximately six months after the application was submitted—which shows the great expectations being held in the country for the new drug. Do you think the research on PD-1 has achieved its ultimate goal, to a certain extent, by enabling the introduction of this new drug onto the market?

Honjo: No, I don't think so. We scientists believe that, as yet, only one aspect of PD-1 has been revealed. In fact, treatment with the anti-PD-1 antibody is only effective for approximately one third of all melanoma patients. Therefore, a great question still remains: why is it that the remaining two thirds cannot be treated? In the fundamental sciences, there are a lot of issues to be addressed by scientific institutes, such as whether there is a marker to identify who can be treated and who cannot be treated, or whether all the patients can be treated with a combination of different drugs. Currently, clinical trials using the anti-PD-1 antibody for treatment of different types of cancers are under way. As the antibody is anticipated to be effective for most types of cancers, ongoing these fundamental research efforts will make a significant contribution to society in the future.

In the medical sciences, I believe that fundamental research plays a vital role in enabling the field to make a great impact or contribution to society. Initially, when we first asked pharmaceutical companies in Japan and abroad to participate in the development of anti-PD-1 antibody drugs, they refused because they thought the risks were too high. However, now Nivolumab is on the market, and it is reshaping

THIS ARTICLE'S
KEY WORDS

Function of the molecule PD-1, and the anti-PD-1 antibody

Programmed cell death protein 1 (PD-1) is an immune-regulatory receptor, and is expressed on cell membranes when T-cells (or T lymphocytes) are activated by external stimuli such as the entry of pathogens. When T-cells are excessively activated, the expression of PD-1 causes T-cells to be down regulated. Programmed death-ligand 1 (PD-L1) is expressed in dendritic cells and binds to PD-1 to reduce the T-cell activation.

The human immune system has a function which finds and excludes cancer cells even after they are developed in the body. To escape this, cancer cells will express PD-L1 to suppress T-cell activation. The anti-PD-1 antibody is a drug which puts a “lid” on the PD-1 in T-cells, before the PD-L1 expressed on cancer cells binds to the PD-1 on T-cells. Without its activation being suppressed, the T-cells covered with the “lid” are able to actively attack the cancer cells.

Impacts of anti-PD-1 antibodies on the medical world and society at large

- Effective on a wide range of cancers, unlike conventional treatments with medications that are only effective on specific cancers.
- The effect of drug lasts for a remarkably long time, unlike conventional cancer therapy products.
- A very high cure rate compared to conventional cancer therapies.
- Side effects are mild.

For the above reasons, anti-PD-1 antibodies are anticipated to drastically change the structure of current cancer therapies, including surgical operation, radiation therapy, and chemotherapy. The discovery of anti-PD-1 antibodies has prompted a reevaluation of immunotherapeutic approaches to cancer treatment that were previously regarded negatively.

our approach to drugs for cancer treatment, and having a huge impact on medical treatment and the medical sciences. I have a theory that the

genuine innovation that leads to such a paradigm shift can only be derived from fundamental research.

Prof. Honjo's Research Philosophy and Style

— *When did you decide to pursue a career in academic research?*

Honjo: I had considered becoming a scientist in the field of basic medicine a potential career option since I was in high school, but it was when I was a second-year undergraduate student in Kyoto University's Faculty of Medicine that my encounter with molecular biology through the book *The Revolution in Biology*⁴ by Dr. Atsuhiko Shibatani⁵ greatly influenced my choice of career path. The book stated "the day will soon come when, just like a surgical procedure, DNA abnormalities can be corrected with a pair of tweezers." That statement, which implied that molecular biology might be closely linked with medical science, made me feel interested in engaging in such research. I went to visit Dr. Shibatani right away, and based on his recommendation, I entered the medical chemistry laboratory headed by Dr. Osamu Hayaishi⁶.

— *At that time, the Hayaishi Laboratory was famous for its "lunchtime seminars."*

Honjo: Yes, it was. In those seminars, the

participants brought interesting academic articles from the latest journals for discussion. Many people participated in the seminars every day—even on Saturdays. Although biochemistry articles were the main topic of discussion, researchers from diverse fields, including pharmacy, science, and agriculture, and researchers from other countries, participated in heated discussions about whether the idea or approach of the article was creative, whether it was strictly verified, or whether it was being approached from an international perspective. In that environment, I naturally adopted Dr. Hayaishi's philosophy on research, which emphasizes creativity, strictness of verification, and an international perspective. I was also influenced by the great American scientists Dr. Donald Brown and Dr. Philip Leder. Dr. Brown is a distinguished scientist who has covered a wide scope of research, and who has proposed a variety of impressive academic hypotheses. From Dr. Leder, I acquired the basic stance that scientists must disseminate their achievements clearly and accurately. I also learned how to make presentations, how to write theses, and how to convince people in a logical way from Dr. Leder.

— *For you, what is the real joy of research?*

Honjo: It's like finding water from a spring that has been disregarded, and then expanding the stream of water to develop it into a creek, and then a large river. Or it's like going deep into a pathless forest and building a rustic bridge there for the first time. It's about creating something completely new, rather than modifying or enhancing something that already exists—that

The Six Cs of creative research

According to Prof. Honjo, to achieve creative research researchers must have the following qualities: They must value their Curiosity and Challenge difficult issues with Courage. Concentrate solely on your research, and Continue to try without quitting. Then you will get Confidence. Prof. Honjo says that, above all, Curiosity is the single most important quality for creative research.

4) Atsuhiko Shibatani, *The Revolution in Biology* (Tokyo: Misuzu Shobo, 1960)

5) Atsuhiko Shibatani, MD, PhD (1920–2011): Dr. Atsuhiko Shibatani graduated from the College of Science of Kyoto Imperial University (Animal Science). He served as a professor at Yamaguchi Prefectural Medical University, professor at

Hiroshima University's Research Institute for Radiation Biology and Medicine, a principle investigator at the Commonwealth Scientific and Industrial Research Organization in Australia, professor at Kansai Medical University, a visiting researcher at the Free University of Berlin in Germany, and professor and president of Kyoto Seika University, where he was later

would be more like turning the rustic bridge to a ferroconcrete bridge.

Another type of joy can be compared to picking up a stone that everyone else has disregarded, considering it to be just an ordinary stone, but in polishing it for ten or twenty years, you find that it is a diamond. I have picked up many such stones. Whether it really is just a stone, or whether it turns out to be a diamond can be said to be a matter of luck, but I think that the researcher's keen sense of insight is also important.

— **How can we develop the sense needed to find such diamonds?**

Honjo: That's a difficult question, but I think it relies heavily on personal experience and intuition. We can develop our intuition by constantly thinking about which one of our stones has the highest probability of becoming a diamond. For example, life science research has produced various unexpected results, and every time an unexpected result is produced, we explore as many possibilities for it as we can identify. Then, we will verify them one by one, ranking them from the greatest potential to the lowest. We repeat this process to eliminate the impossible and come to definite conclusions.

One of the appeals of medical life science is that from a hypothesis being developed, a clear path appears in the midst of complex phenomenon which previously seemed to be chaos. There is no better feeling of fulfillment than that which comes from proving such a hypothesis by repeating the challenge of testing its validity. This is the research style that I have adopted since I was a student. I think that the reason I was daring enough to take the discovery of PD-1 and apply it to the development of products for cancer treatment is because I am not a cancer researcher. If I were, I may not have touched immunotherapy. Like the proverb says: "fools rush in where angels fear to tread."

appointed professor emeritus.

6) Osamu Hayaishi, MD, PhD (1920–): Dr. Osamu Hayaishi graduated from the College of Medicine of Osaka Imperial University. He served as an assistant professor at Washington University's School of Medicine (Microbiology Laboratory), dean of the Division of Toxicology of the National Institutes



Prof. Honjo at the ceremony of the Tang Prize, 2014

— **Finally, could you share with us your vision for your research activities and initiatives in the future?**

Honjo: I am currently engaged in research on two themes, including the PD-1 research that we have already discussed. The other is research into the molecular mechanisms of antibody diversity control by activation induced cytidine deaminase (AID), which we discovered in 2000. We proposed the hypothesis that AID is an RNA editing enzyme. Although many people have been refuting this hypothesis, I am reaching the point where I can prove that it is correct. In four or five years, I hope to complete the verification of the hypothesis.

— **We are looking forward to seeing your continued success. Thank you very much.**

of Health in the US, professor of the Department of Medical Chemistry of Kyoto University's Faculty of Medicine, president of Osaka Medical College, and director of the Osaka Bioscience Institute. He is chairman of the Board of Trustees of the Osaka Bioscience Institute and a professor emeritus of Kyoto University.