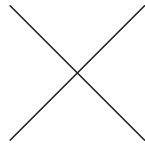


**SHINYA
YAMANAKA**

Director, Center for iPS Cell Research
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**KAZUTO
OKU**

President & Chief Executive Officer,
The Norinchukin Bank



**PASSIONATE
TALK ON
“LIFE”**

Shinya Yamanaka is focused on daily efforts to realize clinical applications of iPS cells as soon as possible and deliver the benefits to patients.

Despite busy days traveling not only nationwide frequently but also between Japan and the United States every month, Dr. Yamanaka maintains an exercise routine of running.

His favorite running course during his frequent Tokyo visits is the area surrounding the Imperial Palace.

At our request, he stopped by The Norinchukin Bank's Head Office, which faces the moat of the Imperial Palace, for a talk with Kazuto Oku, who recently became President & Chief Executive Officer of The Norinchukin Bank.

Status of Research

Oku: Professor Yamanaka, I heard that your father encouraged you to become a medical doctor.

Yamanaka: Yes. That is true. My father used to run a small factory in Osaka. He suggested I should be a doctor because he thought I was not suited to run a company. That he had an illness and a declining health condition might also have led him to wish his son would become a doctor. President Oku, did you major in science too?

Oku: Yes. I majored in agriculture with a specialization in marine biochemistry. I was born and raised in a mountainous area called Yabakei in Oita Prefecture. Until I was an elementary school student, a dispatched doctor treated people in my village. One day, the doctor had to return to his hometown, causing my village to become a doctor-less one. At that time, I constantly felt that my father wanted me to become a doctor, because my father was the president of an agricultural cooperative whose members discussed that the cooperative ought to establish a clinic. I ended up focusing on a different world, though.

Yamanaka: I see. In fact, Oita is my second hometown. My maternal grandfather and grandmother used to live in Kannawa Onsen, Beppu, Oita. I often visited them and spent time there during summer and winter vacations.

Oku: Beppu is a scenic and beautiful place with rich hot-spring (onsen) resources. Professor, you ran the Beppu-Oita Mainichi Marathon this year, didn't you?

Yamanaka: Yes, I did. I really enjoyed my stay at Beppu for my first visit there in many years.

Oku: I'm sure you are leading a busy life, but it is sur-

prising that you run almost every day.

Yamanaka: Yes. This morning, I ran around the Imperial Palace. But "every day" is an overstatement. I run about 260 days a year and a little less than 10 kilometers (6.2 miles) a day. I also run full marathons to raise donations for our lab a few times a year.

Oku: At what stage is your research on iPS cells?

Yamanaka: We are currently compiling an inventory of iPS cells. It would be overly time-consuming if we make iPS cells every time a patient comes to us with damage from various diseases or injuries. Because each person has a different type of immune system, if a prepared iPS cell is used without considering such differences, the patient's body could have an immunological response that refuses to accept such a cell. However, some people have a unique immunity type that does not cause much of a rejection response when the cells are transplanted to others.

Oku: My blood type is "O," which is versatile for blood transfusion. Is what you just said analogous to O type blood?

Yamanaka: That's right. Some people have cells with a certain immunity type that is transplantable to people with other types like the blood type "O." We have made iPS cells from three such persons with a special immunity type. Cells from those three persons can cover approximately 30% of the entire Japanese population. In the next two years, we will make iPS cells from another seven persons. Then, we can cover nearly 60 million Japanese people, approximately half of the entire Japanese population. However, the increase in the coverage ratio diminishes beyond that because the remaining Japanese population would have rare immunity types. To cover the entire Japanese population, we are developing a methodology to change im-

“ *Until our treatment method can cover all the Japanese population.* ”

Shinya Yamanaka

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We continue further efforts toward our 100th anniversary.

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————— Kazuto Oku

munity types by genome editing so that iPS cells can be used for many people. This research takes time and money.

Oku: Are there any other obstacles in your research?

Yamanaka: iPS cells transplanted in a human body stay there for many decades. Because such cells are artificial, the risk is whether these transplanted cells remain harmless for a long time. Our biggest concern is that such cells might start increasing out of control and, in the worst-case scenario, cause a cancer. We have spent a decade doing research to minimize such a risk. However, despite such efforts, such a risk never becomes completely zero. Therefore, whether to

receive a cell transplant should be determined by the patient weighing the benefits and risks.

It Takes Time to Achieve the Vision

Oku: Do you have an idea of when your research can reach the clinical stage, which is your goal, and how much you can shorten the time frame?

Yamanaka: It has been a little more than 10 years since the first iPS cell was created. Thanks to so many people's efforts, we have finally reached the entry point of clinical application. A new treatment method cannot be delivered to everyone right away. First, with the cooperation of a small number of people, experiments need to be conducted regarding safety and efficacy slowly and carefully. The clinical research stage has finally started in the field of ophthalmology. I predict that experimental treatment and clinical research using iPS cells will start for Parkinson's disease and heart failure this year or next, and that is just the beginning. Although our final goal is to get our iPS cell method approved and covered by public health insurance, that will likely take another decade or so. Moreover, we will face increasing difficulties and obstacles from now on. Just like mountain climbing, things become harder as we get closer to the summit. The clinical applications of our method have finally reached the entry point of climbing a mountain. Now there is more to come.

Oku: Of course, you are not climbing the mountain by yourself, are you?

Yamanaka: Yes, we need many people. Our fundamental research to date could be done by one researcher or a small team of researchers if we pushed ourselves hard. When it comes to its application for medical treatment, however, researchers alone cannot move that forward. We need various talent including people with non-science backgrounds—staff for intellectual



SHINYA
YAMANAKA

property and contracts, for preparing applications for governmental permits and approvals, for bioethics and for raising funds so that we don't run out of resources.

Oku: Professor, you have the dual roles of making your vision understood by your research team, or specialists, and then the general public, or non-specialists, such as bankers and government officials. What are your thoughts when you discuss your vision with specialist researchers?

Yamanaka: We are fortunate in that we have a clear vision: "We want to save life." I don't have to say much about the vision because each MD on our research team has the same goal and people with other roles want to contribute to saving "life" as well.

The problem is that it takes a long time to achieve the vision—20 to 30 years. Maintaining our motivation over such a long period is important. When we face difficulties, everyone's conviction tends to waver: "Can we really save life using the iPS cell technology? Are other methods better?" In our occupation, it is harder to maintain motivation than to generate the initial enthusiasm.

From Growing Out to Spreading Wings

Oku: There is a Japanese saying that "Medicine and food share a common origin." We both wish to sustain "life"—you through "medicine" and we through "food" by contributing to the food-related primary industry.

Yamanaka: When I arrived at this head office, I was impressed by the word "life" displayed here and there. The video images of various places throughout Japan that I saw in the lobby show the working of "life" via the agriculture, fishery and forestry industries, which are linked to "food." "Life" is the keyword for us too. I was glad to learn that we share the same keyword.

Oku: Let me explain why we established a corporate brand featuring "life."

Since its establishment in 1923, The Norinchukin Bank has grown out of its old skin many times. Our first mission during the era when farms did not have money was to get money from the Japanese government and supply funds for the agriculture. Over time,

regional financial disparities emerged and fund distribution became important. The next phase was to shift funds from agriculture to the manufacturing industry because the latter needed money.

Today's major mission of The Norinchukin Bank is to receive money from farmers, manage the money globally to generate profits and return them to farmers and the primary industry in Japan so they can utilize such profits for further growth. That's our history to date.

Our 100th anniversary is just around the corner. Facing this milestone, we should tackle a challenge at the level of "emergence" rather than "molt." We need to make efforts analogous to a caterpillar's tremendous struggle from getting out of its cocoon to spreading its wings to become a butterfly. When we thought about our fundamental basis, we rediscovered the importance of how to configure and derive our mission from "life," and then determined to set "life" as our corporate brand.





PROFILE

Shinya Yamanaka

Born in Osaka, Japan. Graduated from Kobe University Graduate School of Medicine/School of Medicine in 1987. Professor of Institute for Frontier Medical Sciences, Kyoto University, in 2004. Director of the Center for iPS Cell Research and Application (CiRA) in 2010. Received the Nobel Prize in Physiology or Medicine in 2012.

The industry that produces food is called the “primary industry.” The meaning of the term *primary* is, in my opinion, not “first” but rather “most important.” The primary industry produces the “food” that people eat and nurtures “life,” connecting generations and the future. Also, the existence of the agriculture, fishery and forestry industries helps maintain communities themselves. Within these connections, I think we need to continue grappling with three challenges—first, to bring the profit via overseas investments to Japan and generate more “national wealth” in Japan; second, to support each region’s cooperative organizations to be able to manage themselves soundly; and third, our focal point, to set up schemes in which The Norinchukin Bank can directly engage in generating cash flows to agricultural, forestry and fishery villages.

Our Thoughts as a Financial Institution

Yamanaka: Today, the population is concentrated in ur-

ban areas with many other regions experiencing depopulation, putting our rich country at risk of succumbing to an irreversible situation, which is scary. For example, beautiful fishing ports, rice paddies and crop fields cultivated for many years could become dilapidated in five years or so if abandoned. Once such a region is so ruined, restoring it to habitable conditions could take much longer. Those at-risk regions are spreading nationwide.

Oku: I also regard the decline in population and the concentration of population into urban areas as a major threat. We need to take measures to alleviate this trend. To that end, such regions need industry, or, if not industry, something to be able to live on.

Yamanaka: To grow the primary industry seems essential.

Oku: For that purpose, we need to circulate money in a good way.

Yamanaka: Though the government’s support is necessary to conduct long-term research and development, we can’t rely solely on government aid because Japan has the world’s highest level of debt. Though we cannot expect donations as high as those in the United States, where some individuals donate on the scale of hundreds of billions of yen, I think there are many people in Japan who have the mind-set to donate for good causes. We need to find ways to reach such people. Because that cannot be done from a lab, I want to go out and make such efforts. In the United States, fund-raisers are making tremendous efforts.

Oku: Regarding donations, we have some thoughts as a financial institution. A financial institution’s operations mostly involve loans, traditionally. Although a financial institution could require collateral for security when providing loans, it could not do the same when it entered the investment world, where you need to bet on the quality of the entrepreneurs and to measure future return on target investment. So far, Japan has been behind in such investments compared to the United States. I believe it is important to develop the investment field—to configure how to circulate money to help those in areas where we see dreams and a great future despite uncertainty rather than just financing secure entities. Moreover, the Japanese government has an annual budget of approximately 3 trillion yen to help the agriculture, fishery and forestry industries. As a private entity, we want to do something that

“ I would like to deliver a superior and inexpensive treatment method. ”

Shinya Yamanaka

the government budget cannot do by utilizing our power as a cooperative organization with a mind-set to help each other. The major resource for such activities comes from profits via overseas investments. We aim to distribute returns of ¥400 billion–¥500 billion annually to our members in various forms such as dividends and interests to help agricultural, forestry and fishery workers and related community residents.

Reasons to Seek Donations

Yamanaka: Until recently, Japanese society, including researchers, did not allow failure. In such a society, a financial institution makes loans only to secure entities and government and bureaucrats, not wanting to risk failure or be criticized, just keep quiet and do nothing during a few years in charge. This approach no longer works even in Japan. I think real success will depend on how much risk everyone can afford to take.

Oku: That is true.

Yamanaka: Therefore, we ask for investments rather than loans. And although investments are important, donations are even better. There are reasons why we put the most value on donations. Even if the development of a medical drug or a treatment method is successful in the end, when that success is based solely on loans and investments, profits will need to be returned as reimbursements and dividends, and that will be reflected in the overall development costs. Then, drug prices and diagnosis fees under public health insurance must be high enough to absorb the return on profit. A new treatment method and a new drug can cost tens of millions of yen or nearly a hundred million yen per patient. Given that reality, we couldn't say that the drug was a complete success. I believe it is our social mission to keep medical treatment costs affordable.

Oku: Your point is that it doesn't do any good if profits do not benefit patients and end up profits only for investors.

Yamanaka: We need to think again about what medicine is. The purpose of healthcare treatments is to save “life.” Although the resulting profitability is good, I think the order is currently upside down. We want to deliver affordable and effective treatments to patients.

Oku: That's wonderful.

Yamanaka: Japan's healthcare system provides universal coverage, with patients' payment responsibility at 30%, and a subsidy system for high-cost treatments so that most patients can access even high-priced drugs. In the United States, poor people cannot access high-priced medical treatment at all. Though Japan is a



PROFILE Kazuto Oku

Born in Oita, Japan. Graduated from the Faculty of Agriculture, University of Tokyo, in 1983. Joined The Norinchukin Bank. Managing Director in 2011. Senior Managing Director (Representative Director) in 2017. President & Chief Executive Officer in June 2018.

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*I learned many things
about organization management.*

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————— Kazuto Oku

good country in that sense, considering the future decline in population, we need to face a severe reality.

Oku: Everyone needs to face the reality and take the necessary risks. Otherwise, the situation will not change. I understand. An airplane that does not fly never falls, but the view from the sky can never be seen. To enjoy the beautiful scenery, we must take a risk and try to fly. To try to tackle various challenges is important for The Norinchukin Bank as well, I believe.

Aiming to Become a Rugby-Style Organization

Yamanaka: There are two kinds of risks—the risk of starting something and the risk of stopping what was started. It also takes courage not to stop what was started. It is easier than we expect to stop what was started to prevent further damage. If everything stops that way, however, many things end up half done.

Oku: Professor, have you stopped something in research or organization development?

Yamanaka: It happened many times in organization development. When I noticed that I made a significant error, I thought about what to do. It might have been possible to leave it as it was, but I chose to admit my mistake and decided to dissolve the organization (laughs). I think I have done crazy things in organization development.

Oku: Management plans of banks also sometimes end up just tweaking organizations. You have led organizations and teams for many years. What have you done to motivate your team members and subordinates so that they work hard?

Yamanaka: I believe I shouldn't do what I don't have to do because team members are there for that reason. Though delegation is the basis for that, the responsibility is on me as the top management. Our lab is a venture in corporate entity classification. That's why

everyone tends to look at facial expressions of the manager/founder and base their judgments on “because President said so.” Sometimes I didn't recall if I had said what they said I had done. I think we need to change such a culture.

Oku: How can we change such a culture?

Yamanaka: That is extremely difficult. Although I wish we had an option to stay where we are without doing anything, there is no option like that because patients are waiting for our research results. We need to keep making clear decisions. On the other hand, it is also important to withhold your decision when nobody other than me decides what to do, even if I am tempted to make every decision to continue operation. Why are my team members here? I want the specialists to make professional decisions of their own. In sports, a rugby-like organization is preferable to a baseball-like one, which requires that each player wait for a sign from a coach. In rugby, once a game starts, signs are exchanged among players while a coach cannot do anything. To become such an organization, each team member needs to be highly motivated.

The Brain Often Makes a Mistake

Oku: These days, corporations are facing a situation where engagement (talking to employees) by officers and managers is increasingly important to maximize each employee's commitment. In the human body too, a past understanding that the brain dispatches commands to each organ is changing to a recent understanding that the brain makes only the final decisions, which might be the case with an organization as well.

Yamanaka: The brain often makes mistakes. I am allergic to oysters. Although I know that well, when we went to a Japanese restaurant renowned in New York, I saw in front of me oysters cooked to perfection that looked extremely delicious. My wife was eating a lot

of them and enjoying them so much. Then, my brain made an erroneous judgment: “You will be fine eating oysters today” (laughs). Then, I ate them! But my intestines were not deceived. At the moment I digested the oysters, my whole body tried to reject them. My intestines protested to my brain, “What in the world have you done!?” I had a terrible time (laughs).

Likewise, the brain is often deceived but humans survive thanks to the subordinate (my intestines) covering the mistakes of the president (my brain) to save life. My intestines might want to tell my brain, “Have you finally learned your lesson?” (laughs)

Oku: There are many things to learn from that. I will keep that in mind.

The significance of your explanation that patients’ needs cannot be adequately addressed without donations, while such funding tools as loans, investments and donations exist, weighs heavy on my mind. We

want to refine our thoughts on how to make money work well with investments and other methods.

Yamanaka: Your corporate brand is *Inochi* or “life” in English. “Life” refers not only to life or death but also to a person’s whole life and daily life. The term “life” covers all such meanings. We, medical professionals, have the same thoughts about life and want not only to save patients’ lives but also to contribute to their whole life and daily life. To sustain “life,” “food” is indispensable. Your occupation is a driving force to save life and support the entire primary industry throughout Japan, therefore I think you bear a heavy responsibility. Please continue to carry out your mission.

Oku: Thank you for wonderful encouragement. I look forward to the results of your research reaching patients as soon as possible.

