The Truth behind the STAP Cell Case

Reality of research institutions, international competition, morality of researchers — Why wasn't the fraud avoidable?

Panel discussion by SAKURA Osamu (Professor, Interfaculty Initiative in Information Studies, University of Tokyo), KATASE Kumiko (Science writer) and YASHIRO Yoshimi (Research Associate Professor, Center for iPS Cell Research and Application, Kyoto University)

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What Happened, and What Came to Light

Sakura Osamu: Obokata Haruko, Unit Leader at RIKEN, announced in late January this year (2014) that she had established a method of producing STAP cells (acronym for Stimulus-Triggered Acquisition of Pluripotency; cells that have the capacity to become any type of cell that forms the body when stimulated), and the media reported it as "the discovery of the century." But circumstances have changed significantly in a mere two months, and STAP cells are now the subject of numerous doubts.

I would first like to ask the two of you about your basic understanding of this case. First, do you think that two *Nature* papers, principally authored by Obokata, were falsified in a critical manner? And second, should we consider that STAP cells are not yet verified, or are they?

Professor Yashiro, you have studied stem cells at the Institute of Medical Science at the University of Tokyo, and as a current member of the Center for iPS Cell Research and Application (CiRA) at Kyoto University you actively voice your opinions on science's relationship with society. What do you think now?

Yashiro Yoshimi: I must say that the *Nature* papers did have serious problems. Now that the origins of STAP cells and the data that define their qualities have been certified as having been falsified, it has lost its credibility as papers. The phenomenon of stress factors resetting a cell may actually occur, of course. But we can't deny the possibilities of intrinsic fluorescence or the abnormal expression of genes, and now that the authors are back to gathering data again, it should be treated at the hypothesis level.

Sakura: Katase-san, you used to work in the field of life science research, and you are now working as a science writer. How do you view the case from your position?

Katase Kumiko: I also think that due to the fact that crucial data were falsified and a range of other inconsistent data was found, the papers now have barely any credibility. Many people who have attempted follow-up tests on STAP cells (including many veteran researchers in the field of pluripotent stem cells) have all failed to obtain the same results. While the possibility is still there, it doesn't appear that it can be produced easily within a short timeframe from various body cells, as was initially advertised. It seems that they misinterpreted the autofluorescence of a dying cell, and everything started from there. Although there is a possibility that STAP cells may exist, appearances are quite against. For example, it was revealed that the mouse lineages of two STAP cell strains that Obokata handed to Wakayama (Wakayama Teruhiko, professor at Yamanashi University) were different from original lineages respectively. Given the reality that the cells can't be produced without Obokata being involved in the process, we can't help but doubt their very existence.

Sakura: Then I see that I can safely assume that the three of us are largely on the same page on this issue.
So what exactly was the biggest problem in this case?

Yashiro: What disappoints me at this point is that nobody has clarified why such a thing occurred in the process of writing the papers and structuring the experiments. The papers list as its coauthors some of Japan's most prominent professors in Wakayama, Niwa (Niwa Hitoshi, Project Leader at RIKEN) and Sasai (late Sasai Yoshiki, former Vice President of RIKEN). Professors Wakayama and Niwa are both individuals that are responsible for their own work, and Niwa in particular has an extremely profound knowledge of ES cells and pluripotent stem cells. Why these people with such prominent accomplishments would fail to notice the inconsistent factors puzzles me. I would like to understand the process for the sake of my own learning.

Sakura: It probably includes the fact that the authors hadn't contacted each other sufficiently. I, too, feel that this case is less an issue of certain individuals or organizations than it is of structural issues within Japan's academic circle.

Katase: What lies at the core of this issue is undeniably disregarding reproducibility and a lack of reciprocal checks. They accepted the fact that only one person was able to reproduce the result, and released the papers without sufficient checks being undertaken by other people. Confirming reproducibility and checking each other's results are procedures that must be followed. Due possibly to expectations of a flashy research project and the demand to rush the papers, they seem to have failed to pay attention to the basics.

The same thing has occurred in various other cases of misconduct in the past, such as the Schön scandal. People acclaim a star researcher as "the hand of God" or "the golden arm," who has come up with a wonderful achievement that no one else can imitate. But they find out that it was falsified, and it becomes a social issue. In these types of cases, we see disregarding reproducibility and a lack of mutual checks, and a senior researcher appraising the young star as a truly competent researcher and offering to serve as a producer. The young researcher cannot win trust alone, but when a prominent senior researcher acknowledges his/her study, society considers it to be trustworthy.

Our latest case was the same: The papers were initially denied publication in *Nature* but were later approved, which, I heard, owed in large part to the fact that the papers added the STAP stem cells and joined the big names of Niwa and Sasai as their coauthors. But these two barely participated in the experiments. Their roles were those of advisors, and I have to wonder whether people in such positions should serve as coauthors.

Sakura: I'm hardly proficient in the life sciences field, yet I, too, felt that with such names listed as coauthors, the project was systematically led by RIKEN CDB (Center for Developmental Biology) — as if Sasai, Niwa and Wakayama had formed a scrum and had piggybacked Obokata on it.

Patents and Information Warfare

Katase: I heard that the details of Obokata's research were known to only a handful of people within RIKEN until the papers were released, and that there were hardly any opportunities for other people to check it. It was a secretly veiled, special project even within RIKEN, and the reason for this likely had to do with patents.

Information warfare has intensified recently. In the past, researchers honestly disclosed the progress of their work and discussed it openly in study meetings with colleagues in the same field. But now they tend to hide it out of fear that others might steal it or take the topic to their side. The quality of science as academics is changing for the sake of patents and rights.

Sakura: Science is essentially about making information public among experts, sharing it and criticizing each other on it to build up a reliable source of knowledge. That's probably the most important aspect of producing scientific knowledge. But when it comes to patents, it goes completely against this. But then again, researchers need to live on something, and patents may provide them with the drive for competition.

Yashiro: Academic meetings and research sessions these days often use the phrases "Gene X" or "Compound X." There are cases in which they explain everything but how they are arranged, or make disclosures while holding onto the key aspect. Secrecy is not completely wrong, and the iPS cell project, for example, was run only by professors Yamanaka Shinya and Takahashi Kazutoshi and was not even disclosed within the laboratory. An old but famous story is that professor of medical science Numa Shosaku of Kyoto University was an extremely secretive person. So I don't think secrecy is something that has occurred of late.

Katase: They should keep it secret from people outside but undertake sufficient checks within the group, including collaborators.

Yashiro: In the case of the iPS cell, CiRA made sure it had the patent and then set up a strategy of a give-and-take type of situation, saying, "We'll disclose this, now you disclose yours." That way, they had the vested rights and did things without closing the whole thing in — that was Professor Yamanaka's policy. Patents can benefit the public depending on how they're played out, yet we're in a time and age where we can be self-supportive, so we need to think of the balance.

Sakura: In the past, labs were operated under the seminar system, where researchers, almost like apprentices, continued on-the-job training from assistant to lecturer, then to assistant professor, and then to professor. There was a lot of experiential wisdom acquired in the process that was passed down. We have fewer seminar systems now, and there's more fluidity. That in itself is a good thing, but I wonder how much of the tacit knowledge is passed onto successors.

In recent years, in particular, the trend has been in promoting young talent. RIKEN itself has had some successful examples, such as promoting biological clock researcher Ueda Hiroki to a leadership position in his twenties. I think it's a wonderful trend, but they should also think about how they will support the talent after their promotions and teach them how to operate the lab, otherwise the system won't necessarily work.

Yashiro: If we're promoting young talent, we should assign them mentors. In the United States, the status of an RA (research administrator) is quite high in research society, as their range of interest and knowledge spans wide, from how they can obtain funding and what the application rules are to where research trends are at the moment. There are frequent RA conferences, at some of which RAs of universities and research institutions gather to consult in alliance.

RAs in Japan are still considered underdogs of research, but in the United States, RAs can earn higher wages than lab heads. We could enhance this RA system to have senior RAs pass down knowledge of lab operations to young RAs to produce specialists in the field.

Sakura: That's interesting. I don't know if this is the right metaphor to use, but it's like a military force needing sectors for supplies, logistics, telecommunications and welfare. We need people like RAs to do this, but Japan is not very good at creating such organizations and allowing them to function. We rely too much on the individual actions of people with high-level skills, as in Yamanaka-san running a marathon to collect research funding. Unless we form this system strategically, we can't possibly compete overseas.

Yashiro: Even in terms of the research genres of ES and iPS cells, we look at the international research trends as summarized by iCeMS (the Institute for Integrated Cell-Material Sciences, Kyoto University) and see that Japan has very few joint research projects. Systems can be brought in from abroad, but they won't function unless we add meat to them. In order for this to happen, I feel that we have no option but to enhance the organization while building on international joint research.

It's easy to criticize the organization RIKEN, but that alone is structurally the same as criticizing RIKEN for making Obokata a scapegoat.

Is Obokata a Victim of the System?

Katase: Enhancing the system that supports the people who undertake research would indeed be a solution. But one thing concerns me, and that's the fact that the incidence of misconduct in the United States is higher than any other advanced nation, and it is as high as that in Japan. I don't think we can easily state that the incidence will decline if we imitate America's policies. The United States has a national justice system on research that strengthens penalties for research misconduct, but it doesn't seem to be functioning enough, as compared with the results of other countries. We need to note that strengthening the penalties doesn't necessarily yield the anticipated results.

Sakura: I thought that, having experienced and overcome the waves of a major misconduct case in the 1980s, America had developed a decent system of its own — the U.S Public Health Service established the Office of Scientific Integrity and the Office of Scientific Integrity Review (later integrated as the Office of Research Integrity) in 1989 — but I suppose that wasn't quite the case?

Katase: Research misconduct in the United States has increased since the 2000s.

Sakura: Does that mean that the ideals and the system of research changed from around that point on?

Katase: I suppose that competition to obtain research funding intensified.

Yashiro: It almost turned into a state of, "Publish, or perish."

Katase: We have yet to see misconduct cases go into a declining trend in the United States. Misconduct cases in Europe also increased from around 2000, but figures have turned in a tendency to decrease in Germany since 2006 and in the United Kingdom since 2008. In the United States, an extremely large number of cases are indicted for misconduct, likely due to the severe competition, but, of them, only about 15% actually proceed to investigation. In European nations, on the other hand, 30%–50% of those alleged to have committed misconduct are investigated. It seems that scientist communities of European nations are widely sharing information on the criteria that determines what is or is not a misconduct.

Sakura: Then what should Japan do? It doesn't have an independent body like the Office of Research Integrity, and while academic conferences release statements, they are general philosophical comments that don't reach the actual fields of work.

Katase: We should study the characteristics of preventive measures against misconduct in each country to incorporate the advantages of each one, while considering measures that match Japanese characteristics. People who would cause problems like scientific paper fraud are few, but could its system check and prevent problems when such people do enter the communities?

Sakura: What is often said to be a characteristic of the Japanese researcher community is that it is under a strong hierarchical relationship and tends to be bound by it. If you think something has to be done a certain way, but your superior says you don't have to do it, it's hard for you to ignore that comment and do it. The same thing applies when you think it's rude to doubt what your coauthor is doing since he *must be* doing it fine on his own.

Katase: Value harmony.

Sakura: That seems to be one reason why a new rule to prevent fraud would not function so well.

Katase: Studies have proven that imposing stricter penalties is not effective. I only wish that everyone would go back to the basics of asking, "Show me your sample" or "Let me see some raw data" and casually exchanging opinions.

Sakura: I want to ask you, Yashiro-san; is it possible that a lab could regain this type of open exchange as a result of how it is run by its head or manager?

Yashiro: Sure, it's true that a lot can change depending on the character of the boss. When a lab grows to have more than 100 people, you start losing touch with what your neighbor is doing. But even in a big lab, you shouldn't have any problems if you can hold discussions with the "middle boss" level.

Katase: That's what Obokata was — a Unit Leader is the "middle boss." It's the supervisory position that directs its members not to do misconduct. But the very person promoted to that position was someone who was immature.

Yashiro: They treated an incomplete person as an adult. We need to make it clear that no matter how they view the potential of an individual and promote that person, a child is a child.

The minute they promote the person, they start treating him/her as an adult, believe that he/she has the same standards or values as them and is keeping proper lab notes, and let that person go on his/her own. Some people survive this, but some are weeded out. There are so many people in labs who fail when they become a middle boss.

Sakura: If they're promoting someone, they need to provide a mentor or some form of support, right?

Yashiro: That's right. For example, there's the criticism that Obokata was accepted to the Faculty of Science and Engineering at Waseda University through the AO Exam instead of the regular entrance exam. If they've accepted someone through a different method than previously, they should take advantage of it.

Sakura: You start wondering why they do AO Exams at all. When we look at Obokata's profile, we find that she's made her way through pretty lenient checkpoints, including the AO Exam. She became a Unit Leader without undergoing the proper checks, and went as far as to the point of publishing two papers in *Nature*. If you develop a system of promoting talents, you have to create a system of following up on those skills to go with it. In that sense, Obokata may be a victim of the system.

Katase: She probably missed the opportunity to learn how to take notes or to understand that she can't copy and paste images inappropriately.

Sakura: Yesterday, I was at an orientation for first-year masters students where I talked about research morality. I said exactly the same thing as last year, but the topics on the importance of reproducibility and how plagiarism is wrong found so much practical association — which I felt was a little unfortunate.

Yashiro: I often hear that people didn't have the opportunity to receive proper training or just didn't know, but the way you talk about morality every year, RIKEN is probably doing the same with its newly assigned people. But the problem is a lot more basic. If you went shopping and got to the cash register only to find that the price was completely different from what you had seen, and you flipped the tag over to see that a new tag had been attached without prior notice, you would think that they were trying to rip you off. In the same way, I see this issue more as an incorrect social norm than as a problem of the system or education, although I do think that we need to advocate the lack of a system to follow up on skills.

The Danger of Giving In to the Temptation of Your Dream

Sakura: Hendrik Schön, who we mentioned earlier, had an experience during his undergraduate years of seeing his fraudulent report pass. But I don't think Obokata had any ill intentions. She could have tricked everyone a lot better if she had really wanted to. So why didn't all those coauthors identify the fraud?

Yashiro: Honestly, I don't know. But there's one thing that philosopher Azuma Hiroki said to me that really sunk in. He said that they probably didn't give in to the temptation of greed; instead they gave in to the temptation of their dream. A person researching stem cells would have the awareness somewhere in his mind that it would be an outstanding achievement to find or produce pluripotent stem cells within a body. Once he knows that he could be close to doing so, he could possibly give in to the temptation of his dream. When I first heard the STAP news, I must admit that I immediately wrote about how amazing this discovery was.

Sakura: When I first saw it on the news, I couldn't believe that such a thing was possible either. So I asked a professor at Kyoto University, who told me, "It's unbelievable, and that's why it means so much," so I had to make myself think positively.

Katase: It is indeed an appealing subject, isn't it? The Schön case was "high-temperature superconductivity of our dreams." As it was with this case as well, the problem that arises when the misconduct comes to light is that the author is the only one who can reproduce it, which has become the typical scenario in such cases.

Researchers are self-critical, so when they can't reproduce something, they think about what they might have done wrong. They doubt themselves rather than other people. They ask "How can I get it right?" and are told, "*I* was able to do it easily," and they wonder again. Then they find out it was fraud and they think, "Oh, no wonder."

Sakura: When research becomes as categorized and advanced as it has become today, I hear that there are cases where it's difficult to reproduce the results because the technique is indeed difficult. Couldn't researchers have other people check it before they write the paper, or doesn't *Nature* offer some kind of feedback?

Katase: In my experience, I handed a sample to my collaborators to check. I obtained results that were different from what had been said before and rejoiced over the discovery, only to worry moments later, "What if I have made a mistake?" I immediately contacted my collaborators, but my worry was not alleviated until they then confirmed that it was not an error.

Yashiro: That's right. If I were in the discoverer's position, I would ask my group members to run a follow-up test in their spare time. If it would take quite an amount of time, I'd have them carry out the follow-up test while the paper was being peer reviewed.

Katase: In terms of the STAP case, Wakayama performed a replication study while he was at RIKEN, and did it repeatedly when he moved to Yamanashi University. I think that Wakayama did what he should do as a researcher. But the replication studies performed at Yamanashi University had all failed and weren't able to reproduce the results without the involvement of Obokata.

Sakura: About three or four years ago, the Anilir Serkan case occurred at the University of Tokyo. He advertised himself as Turkey's first-ever NASA astronaut, and wrote a research paper on a space elevator with which he had obtained a doctorate degree in engineering at the University of Tokyo. He wrote so many papers, but they were all fraudulent. Despite the sad truth that nobody bothered to check the papers carefully, what we found out then was that in terms of human relationships, it's hard to doubt someone every time he writes a paper. Serkan intentionally took advantage of that. I think that Obokata is also intuitively good at taking advantage of that. She rode the dreams of the older generation and lit the fire.

I don't think that leaving everything to a researcher's morality would solve the problem. A researcher can lack a little morality or may not have his or her eyes on society as long as he or she has the research skills. The system to support it is what I think is important.

We should not allow the STAP case to lead to stricter rules and objections against the AO Exams or against promoting young researchers to Unit Leaders.

Yashiro: I agree.

Mass Media and Science Publicity

Sakura: What was most striking was how excessively the first press conference announcing the development of the STAP cell was staged. A pink research lab; a Japanese apron. The mass media immediately lapped it up.

Katase: There have been so many cases in the past when researchers were made into heroes or heroines because of an innovative finding, only to see it backfire later. A physician in the United Kingdom by the name of Andrew Wakefield once released a paper stating that there was a relationship between vaccinations and autism. It was falsified, but because it was reported sensationally, many people stopped getting vaccinations. The media elevated Wakefield to "a hero who saves children." Even after the fraud was revealed and Wakefield's physician's license was revoked, many claimed that he had been framed by pharmaceutical companies and other physicians, and many people still firmly believe in him and continue to refuse to be vaccinated. The same chain of events took place when Hwang Woo-suk of South Korea made a fabricated announcement that he had produced a human embryonic stem cell through somatic cell nuclear transfer.

In the STAP case, the mass media quickly began celebrating Obokata as "The Star of Science Girls" and "Nobel Prize candidate" immediately following the first announcement. I tweeted, "Wait, not so fast," but I was not taken seriously.

Sakura: Then do you think that the mass media should not report on a science paper when it has just been released?

Katase: No, they shouldn't. They should take it carefully, including a comment stating that it has not yet been fully evaluated.

Sakura: Aren't you being wise after the event to say that the media was too quick because the case turned out to be fraud?

Katase: I do believe that it's important for the media to understand that scientific papers can be accepted only after multiple third parties have confirmed their reproducibility.

Yashiro: It's also an issue of science publicity. We can't deny that science gets greater bureaucratic attention when it appears in a newspaper than when it's released as a thesis paper. That ultimately comes back to funding. And before we knew it, the very act of releasing a science paper had become publicly approved as a scientific achievement.

The science experiments we carry out at school are all verification tests as we see it. They produce the same, concrete results no matter how often you repeat them. If they produce a different result, you point out what is wrong and they immediately produce the correct result. You can teach that much as early as junior high school. There's also the issue of how science administration evaluates science papers. If you evaluate only a paper's impact factor on journals (citation frequency), it is only an evaluation of the starting point, so we're trying a lot of things.

Katase: There is a method of tracing the number of citations and using that as an index.

Yashiro: We want all those who are not experts to understand that a science paper is only a starting point. If we're talking of "science communication," the research institutions should each play a certain role to constantly share with the media how to read and handle science papers. On the other hand, the STAP case brought not only researchers of different fields but also people of fields other than science to take part in the verification process. We can't really say that this "variety show" type of method is good, but I believe that it is almost like making a "cloud system" of reviewing science papers, and that we are entering an age where we need to seek an open form of reviewing in which non-experts can also participate.

Katase: I'm hoping that more of the general public will understand the science system better. For example, product ads that resort to pseudoscience often use the phrase, "Presented at an academic conference." But academic conferences allow the presentation of studies of low reliability, and many have not even undergone peer review. I wish that compulsory education would include teachings on the process whereby research gains approval as scientific knowledge.

Sakura: Hmm, I do agree that elementary, junior high and high schools should teach more about the need for controlled experiments and the things you mention, but I wonder to what extent scientists should impose demands on the general public? I feel that there's also a major problem in how scientists release information. If one side keeps saying, "The media and society have low literacy," and the other keeps saying, "Scientists are talking nonsense," nothing will ever change.

Earlier, Yashiro-san mentioned the bureaucratic appeal, and how the way research institutions and scientists are evaluated leads to how they are funded, which ultimately turns things in that direction.

Yashiro: Researchers and research institutions are not only facing the bureaucrats but also the politicians. And politicians are seeing the faces of the people who are influenced by newspapers.

Sakura: This had me thinking that Japan may still be a society that's vague from top to bottom in terms of who makes the actual decisions. We need to slowly change that, not only within the narrow meaning of science but to include issues such as energy policy as well.

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