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The Case of Inferred Doability: An Analysis of the Socio-institutional Background of the STAP Cell Scandal

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Abstract On 28 January 2014, Haruko Obokata and her colleagues held a press conference regarding their new method of producing stem cells. The cells, named STAP (stimulus-triggered acquisition of pluripotency) cells, were of considerable interest not only for stem cell scientists but also for the wider society in Japan because both its government and citizens enjoyed the international reputation earned for the country by Shinya Yamanaka's earlier success in developing a novel technique of cell reprogramming. However, it was soon pointed out that the data in the research article seemed fabricated and was hence suggested that their claims lacked scientific credibility. What was initially considered another triumph of Japanese stem cell research thus resulted in a major national scandal. Instead of seeing this case merely as one of scientific misconduct, I examine it as a window into the local culture of stem cell research and argue that the socio-institutional background of Obokata's work incited the researchers involved to infer doability of STAP cell research. The problem with this inference surfaced after those who did not share the culture challenged the robustness of her work, suggesting some cultures of science may be more vulnerable to scientific misconduct than others.

Keywords STAP cells · regenerative medicine · Japan · doability · local and global biologicals

Although scientific misconduct may be a universal problem (*Nature* 2014), not every case of misconduct results in a major national scandal to the extent of the case of STAP (stimulus-triggered acquisition of pluripotency) cells in Japan in 2014. In this article,

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I examine this case in relation to local specificities of ways of both seeing and doing stem cell research, which Sarah Franklin (2005) characterizes as a "local biological." Attending to socio-institutional culture that informs and is simultaneously informed by the local biological in Japan helps us understand how the case developed and why it was then managed in the way it was in that country. This by no means is to suggest that the other equally important aspect of stem cell research discussed by Franklin (2005), that is, the "global biological," was irrelevant to this case, however. When the original research article on STAP cells and its companion letter were published in *Nature* in January 2014, they immediately captured attention across the country as much as abroad. Notably, it was the international community of stem cell scientists that first raised concerns about the publications and flagged possible fraudulence by the authors (Lancaster 2016). Yet, analysis of how the international community reacted to the publications and made its collective effort to demonstrate that the STAP cell experiment was not reproducible deserves a separate study of its own; in this article, I instead focus on the discussion of STAP cells in Japan and look at how key individuals in the country reacted to such an effort.

The case of STAP cells in Japan is sometimes referred as Obokata's case, highlighting the lead author of the two *Nature* publications on STAP cells, Haruko Obokata, similarly to the earlier case of scientific misconduct in South Korean stem cell research, called Hwang's case, or in some cases "Hwang-gate" (see Chekar and Kitzinger 2007; L. Kim 2008; T.-H. Kim 2008). As her host organization, RIKEN (Rikagaku Kenkyūsho 理化学研究所), concluded officially that she was guilty of scientific misconduct, there is nothing wrong with referring to the case in this way. However, I avoid using the expression in this article for two reasons. First, the question I address in this study is not who was responsible for the misconduct but why it developed into a major national scandal, which necessarily entails shifting attention from the intentions of individual actors to their working environment; the expression highlighting the individual author could be inconsistent with this emphasis. Second, Mary Douglas (1992, 2002 [1966]) argues that allocation of blame, just like witch hunting in primitive society, serves to maintain and/or restore social order. From this perspective, RIKEN's conclusion should not be accepted at face value, and neither should Obokata's (2016) recent publication, which indicates that Teruhiko Wakayama, one of the corresponding authors of the *Nature* publications and also her former line manager at RIKEN Center for Developmental Biology (CDB), might have been more responsible than RIKEN concluded he was. Again, referring to the case as Obokata's could misrepresent this article's position to engage with, rather than to uphold, any social order implied in such blames.

In examining this STAP cell case, like others (e.g., Suda 2014) I was intrigued particularly by the level of confidence that some senior scientists at the CDB exhibited in the STAP cell experiment. When its reproducibility started being questioned in February 2014, two senior scientists at the CDB, Yoshiki Sasai and Hitoshi Niwa, helped Obokata publish its detailed protocol (Obokata, Sasai, and Niwa 2014). RIKEN's decision in April 2014 to undertake a year-long study to test the protocol even after it found Obokata guilty of misconduct equally indicated that some had not abandoned the hope that the experiment was genuine. Following the impartiality and symmetry principles of the Strong Programme in the sociology of scientific knowledge,

which emphasize the need to investigate true and false beliefs equally and that the same explanation ought to be applied to them both (Bloor 1991 [1976]), I examine the observed confidence in the STAP cell experiment in the same way as one might analyze confidence in scientific knowledge and argue that the socio-institutional environment of the scientists offered them compelling reasons to be convinced of the existence of STAP cells.

Among a variety of ways to study confidence in scientific knowledge sociologically, I found the analytical concept of doability particularly useful for the purposes of this article. In her study of cancer research, Joan Fujimura (1987) argues that a problem can be considered doable only where different levels of work organization are aligned. Because constraints and restraints on scientific research exist at different levels—namely, the levels of experiment, laboratory, and society—not only do resources to conduct the research need to be secured and managed at each level but also such management of resources has to be coordinated across the different levels. Although the tasks of resource management can be costly and often troublesome, once the alignment of the three levels is achieved and the research becomes considered doable, they may get standardized and packaged for others to pursue the same line of work, potentially resulting in the development of a bandwagon (see Fujimura 1988). As this article demonstrates, the senior scientists in the STAP cell case were more concerned about the resource-management tasks at the institutional and societal levels than with the nature of the original experiment—as they had little direct involvement in it—and grew confident in the doability of STAP cell research and hence in the existence of STAP cells. This observation led me to conclude that they inferred doability of the research because of its strong alignment between the institutional and societal levels, and with the expectation that its results would invite as much, if not more, favorable reaction, in both professional and public domains, as Shinya Yamanaka's work in cell reprogramming did less than a decade ago. However, because the institutional and societal levels are more closely tied to the aspect of stem cell research as a local biological than is the level of experiment, the problem of this inference became exposed after STAP cell research entered the global stage, where the aspect of stem cell research as the global biological is predominant. Here, I suggest that this STAP cell case became a major national scandal due in part to the gap between the local and global biologicals that has emerged since the late 2000s (see Mikami and Stephens 2016).

Before moving on to the analysis, I first summarize the STAP cell case based on the accounts provided by four different sources. The main sources of information are a series of news reports published by *Nature*, the publisher of the STAP cell publications, and a series of official announcements made by RIKEN, the host organization of the main authors.[1] The information was also corroborated by two published pieces of personal narrative or memoir: one by Obokata (2016) and the other by Momoko Suda (2014), a science journalist who was involved in the STAP cell case from its beginning. The case is then analyzed by situating it, both temporally and geographically, in the context of Japanese stem cell research. In doing so, the analysis draws on existing social science literature as well as the sociological fieldwork I conducted over four years between 2008 and 2011 with the aims of articulating the trajectory of

[1] The reports are archived and made accessible on the publisher's website (see *Nature* 2017).

regenerative medicine projected in Japan and understanding how the research community in that country became (re)organized to make this trajectory "real" (see Mikami 2015a, 2015b; Mikami and Stephens 2016). While this fieldwork predates Obokata's undertaking of her experiment at the CDB leading to the *Nature* publications, it was done during the critical period when Yamanaka's success on human induced pluripotent stem (iPS) cells made considerable impact on the national environment of stem cell research in that country. The observations made from the fieldwork therefore help us understand in what sociopolitical context STAP cell research emerged and its importance in relation to the political economy of Japanese regenerative medicine research. As shown in this article, the impact of human iPS cells on Japanese society was evident in the STAP cell case, but in a twisted manner.

1 What Was the STAP Cell Case?

The national scandal in Japan involving STAP cells developed around an original research article and its companion letter published in *Nature*, one of the most prominent journals in science, on 30 January 2014. Obokata et al. (2014a, 2014b) reported development of a new method to reprogram differentiated somatic cells of a mouse and induce them to be pluripotent, that is, capable of becoming any type of cell in the body. Two days before publication, the first author of the publications, Obokata, and her colleagues at the CDB announced at a press conference that they had successfully created what they named stimulus-triggered acquisition of pluripotency (STAP) cells and had established stable cell lines from them, which they called STAP stem cells. On 30 January 2014, the news was featured in both television news programs and national newspapers in Japan.

Two other methods to reprogram somatic cells existed already; nuclear transfer (i.e., cloning) and introduction of transcription factors (i.e., genetic manipulation). The pioneers of these methods, John B. Gurdon and Shinya Yamanaka, respectively, jointly received the Nobel Prize in Physiology and Medicine in 2012. Yet, as described in the research article (Obokata et al. 2014b), the new method differed in that STAP was understood to be a phenomenon that occurs naturally in organisms, while cloning and genetic manipulation are not. This biological phenomenon is known to happen in plants, and the authors claimed that they discovered it happens equally in animals. They also managed to trigger this phenomenon in vitro by exposing cells to an external chemical stimulus, what they called sublethal low-pH treatment—or at least, so they claimed. Furthermore, they argued that STAP cells had broader developmental potency than other pluripotent stem cells, including embryonic stem (ES) cells and iPS cells. Therefore, the discovery, if true, could have had scientific significance similar to that of the Nobel Prize–winning achievements of their fellow stem cell scientists (see Smith 2014).

Given the potential significance of this discovery, stem cell scientists in and outside Japan soon started attempting to replicate the experiment and produce STAP cells and STAP stem cells, but none were able to do so. Furthermore, it was found that some of the images were used falsely in the research article. Responding to the growing criticism, RIKEN established its investigation committee in mid-February

(Cryanoski 2014a). Then the situation became even more confusing when Teruhiko Wakayama, one of the corresponding authors, called for retraction of the publications not long after Obokata, Sasai, and Niwa (2014) published the detailed protocol of the STAP cell experiment, and before RIKEN's investigation committee released its report (Cryanoski 2014c). The report, which came out on 31 March 2014, concluded that Obokata was guilty of scientific misconduct—among six charges that it investigated, two were concluded to be intentional and fraudulent and the rest to be innocent errors (RIKEN Investigation Committee 2014; Cryanoski 2014f; Lancaster 2016).

RIKEN, the host organization for most of the authors, recommended that the research article (and hence its companion letter, too) should be retracted but at that stage did not make any clear statement regarding whether STAP cells actually existed. Instead, it announced that an internal team led by Shinichi Aizawa and Hitoshi Niwa was going to test if the method would actually work (RIKEN 2014a). A few months later, RIKEN (2014b) overturned its initial decision of not letting Obokata partake in this study and announced that she would join the team and conduct the test between July and November under strict surveillance so as to preclude any doubt of potential misconduct. On 2 July 2014, only two days after this announcement, both the research article and the letter in *Nature* were retracted (Cryanoski 2014d, 2014e). Then, about a month later, the tragic event happened: Yoshiki Sasai, an internationally renowned stem cell scientist and a coauthor of the retracted *Nature* publications, committed suicide (Cryanoski 2014g; also see Alvarez-Buylla 2014 for Sasai's obituary). RIKEN's investigation committee did not find him guilty of misconduct but held him, together with Wakayama, responsible for the STAP cell case as Obokata's mentor and coauthor.

On 27 August 2014, RIKEN (2014c) released an interim report of Aizawa and Niwa's team on the test, stating that they had not been able to produce STAP cells (and hence no STAP stem cells either) using the original protocol. As the problem began to appear more serious than its investigation committee concluded a few months earlier, RIKEN this time established an external investigation committee to undertake a thorough investigation of the research that led to the retracted publications. On 19 December 2014, Aizawa and Niwa's team ended its test earlier than originally planned without being able to reproduce the results of the original experiment, despite Obokata's participation for the final few months (RIKEN 2014d). Then, about a week later, the external investigation committee published its report and, based on its genetic analysis of what were claimed to be STAP stem cells and some other cell lines that Obokata's group still possessed in its laboratory, concluded that the STAP stem cells were contaminated and that ES cells were accountable for pluripotency reported in the *Nature* publications (RIKEN External Investigation Committee 2014; Abbot 2014; see Konno et al. 2015 for the genetic analysis). In full agreement with the conclusion that other research groups abroad drew from their collective efforts to reproduce the results (De Los Angeles et al. 2015), at the end of 2014 RIKEN finally refuted the claims that Obokata and her colleagues made in the retracted publications. RIKEN later announced that Obokata deserved dismissal on disciplinary grounds, although the decision was never implemented, as she resigned from her post even before the external investigation committee published its report (Cryanoski 2015b).

2 High but Skewed Expectation Growing in Japanese Society

To understand why the STAP cell publications drew so much attention in Japan, the expectation that had been growing around stem cell research in that country since late 2007 needs to be taken into account. Until the mid-2000s, regenerative medicine research in Japan had consisted mainly of two distinctive clusters of local researchers: a cluster of stem cell scientists and another of bioengineers, and their primary focuses were different (Mikami 2015a, 2015b). The former focused on mechanisms of cell growth and differentiation, while the latter focused on utilization of cellar functions for medicine. This situation changed rapidly when Shinya Yamanaka demonstrated in late 2007 that his technique to reprogram somatic cells, originally developed using mouse cells (Takahashi and Yamanaka 2006), is applicable to human cells and produced human pluripotent stem cells without using any human embryos (Takahashi et al. 2007). Seeing Yamanaka's accomplishment as a sign of the country's leadership in this field, the Japanese government decided to commit to his vision of developing regenerative medicine with iPS cells by providing substantial support for further advancement of his technique and soon turned it into a national research project, despite the resentment expressed by some local researchers (Mikami 2015b; Sleeboom-Faulkner 2011). From then on, better characterization of human iPS cells and fast development of their clinical applications became the primary goals of stem cell research in Japan, leading to major reformation of the local biological in the country.

Yamanaka's work brought to Japanese stem cell research not only new human pluripotent stem cells but also a renewed and rather intimate relationship between science and society. At that time, Yamanaka was still in his mid-forties—a relatively young figure in Japanese academia, in which age matters a great deal—and the country celebrated the emergence of this young world-class scientist. Yamanaka responded to such a celebratory mood by making frequent appearances in mass media and at public events, explaining the implications of his research and presenting his vision of how Japan might advance the field. The communication was further enhanced by the independent work of science journalists and science communicators, who tried to explain the significance of his work to both those with and without the knowledge of basic biology (e.g., Tanaka 2008; Yashiro 2009). As much as these multiple channels of communication helped emphasize the significance of Yamanaka's success (see Shineha et al. 2010), they also showed his "ordinary" personality, for example, characterizing him as a father of two daughters or as an amateur sportsperson who used to play rugby when he was a student. He gained massive popularity in the country and soon became recognized as a national hero. Yamanaka's group further consolidated this emotionally charged relationship with the public in 2009 by establishing the iPS Cell Research Fund, through which any member of the public can make a direct contribution to his research endeavor. In this context, the news of the 2012 Nobel Prize served as the icing on the cake. While the citizens in Japan had previously showed little interest in human ES cell research (Sleeboom-Faulkner 2008, 2010), their interest in iPS cell research grew rapidly over the period of half a decade or so (Shineha 2015).

The expectations for stem cell research, too, grew rapidly in this particular national context, and for this reason, such expectations have been not only high but also skewed, with the heroic figure of Shinya Yamanaka, rather than his cell-reprogramming technique, being central to it. If anything can shift the focus of Japanese stem cell research

away from iPS cells, it cannot merely be of scientific significance but has to be represented by a new hero or heroine who can act as a public figure carrying the flag for it, just as Yamanaka has done since 2007. And even though only very briefly at the beginning, Obokata appeared to fit very nicely with this role in the STAP cell case.

Obokata was little known in the community of stem cell scientists, just as Yamanaka was before his first article on iPS cells was published in August 2006. The sudden emergence of a world-class scientist was the common narrative in the two incidences. They were considered world-class not only for their research but also for their institutional credentials—when his article on human iPS cells was published, Yamanaka was affiliated with the Gladstone Institute of Cardiovascular Disease in San Francisco, where he previously worked as a postdoctoral research fellow and later became a senior investigator; similarly, Obokata was with Brigham and Women's Hospital in Boston, though most of her experiments were conducted at the CDB. Apart from such a commonality, several of Obokata's characteristics made her particularly popular among the public in Japan. Yamanaka was considered a "young" scientist back then, but Obokata was even younger and, more importantly, is a female in the historically male-dominated world of Japanese academia. Soon after she spoke in the press conference for the *Nature* publications in January 2014, she became described in mass media as "a new heroin of science in Japan" or as *rike-jo no hoshi* リケジョの星 (the star for girls inspired to become scientists) (see also Lancaster 2016). In some cases she was treated like a television celebrity—gossip magazines featured her lifestyle and fashion rather than her research. At one point, she had to ask mass media to "self-control" the quality and volume of their coverage so as to minimize the disturbance they caused to her work, while in some instances she also encouraged them to report her personal stories, for example, by wearing a Japanese-style cooking apron, rather than a lab coat, when journalists were invited to her laboratory after the press conference, and telling the story of her grandmother who gave her that apron (Suda 2014). Thus, the representation of the STAP cell experiment as "her" work helped the announcement of its success attract public attention in Japan.

This narrative of the emergence of a new heroine went hand in hand with the discourse that the new pluripotent cells (i.e., STAP cells) were "better" than iPS cells. This discourse was not a mere consequence of media (mis)representation. While STAP cells were compared mainly with ES cells in the original research article (Obokata et al. 2014b), their superiority to iPS cells was emphasized in the press conference (Suda 2014). First, it was highlighted that the reprogramming of somatic cells could be done more effectively and faster with the new method than with the "old" reprogramming technique. Second, it was explained that a transcription factor and a retrovirus vector used to produce iPS cells were associated with tumorigenicity, potentially indicating risk of causing cancer, while the STAP method was "natural." Finally, from the observation that STAP cells could develop even into placental cells, which neither ES cells nor iPS cells can do, STAP cells were argued to be "more" pluripotent than the existing stem cells. The ability to become placental cells might indicate their totipotency, but the emphasis was placed not so much on the ability per se as on the completeness of reprogramming with the new method, suggesting that it leaves little epigenetic memory—the biological signatures of original cell types that iPS cells can exhibit even after reprogramming. Although the value of iPS cells has been questioned in

terms of their unnaturalness (Hauskeller and Weber 2011), the superiority of STAP cells over iPS cells thus highlighted their usefulness as a tool for therapy (see Mikami and Stephens 2016).

Therefore, the initial excitement of mass media and the public about the news that Obokata and her colleagues successfully produced STAP cells and established new stem cell lines from them very much reflected the expectations for stem cell research that had developed in Japan since late 2007 and hence reflected the local biological in that country. It is difficult to evaluate how much of it was planned strategically by the researchers, but the ways in which STAP cells were presented at the press conference and in which Obokata was represented in mass media corresponded closely to what the public in Japan wanted to see at that time, that is, further confirmation that Japan was the leading country in regenerative medicine research. Moreover, the STAP cell experiment was done using mouse cells only, but it was expected to be applicable and soon to be applied to human cells too, just as Yamanaka's technique was. Not only did the public attention that the publications received backfire when their potential problems were pointed out, but also, even before that, it troubled many scientists working on iPS cells, including Yamanaka himself, who publicly criticized the way in which iPS cells and STAP cells were compared (Yamanaka 2014). One might wonder why the scientists at the CDB were not more careful about the messages they were sending, but, as explained in the next section, the STAP cell case manifested the desire of some local researchers to shift the focus of stem cell research away from iPS cells.

3 The Institutional Rivalry within the All Japan Platform

The growing expectations for stem cell research since late 2007 has resulted in mixed feelings among local stem cell scientists (Mikami 2015b; Sleeboom-Faulkner 2011). On the one hand, they benefited from the government support that it brought to the field; on the other hand, they had to adjust their research agendas to the political interests of the government. The latter also meant to some researchers, such as those at the CDB, undermining their authority in the field.

The CDB was established in 2000 as part of a large-scale government initiative called the Millennium Project and played a leading role in advancing stem cell research in the country, particularly in the early 2000s. An important characteristic of the Millennium Project was that it aimed to promote research areas that were not only of scientific significance but also of potential social as well as economic value. The project therefore was symbolic of what Shigeru Nakayama (2012) observed as the revival of technonationalism in Japan (see also Mizuno 2012), though I would rather consider it as the rise of technoscience nationalism, which not only reflects more precisely the emphasis of the recent slogan kagaku gijutsu souzou rikkoku 科学技術創造立国) (an advanced science-and-technology–oriented nation) but also is led chiefly by the Japanese Ministry of Education, Culture, Sports, Science, and Technology (MEXT) instead of the Ministry of Economy, Trade and Industry (see Mikami 2015b). The major pathway through which stem cell research was expected to deliver on this political promise was development of regenerative medicine, and when MEXT launched its Project for Realization of Regenerative Medicine in 2003, Shinichi Nishikawa, then

deputy director of the CDB, was appointed its project leader. Yoshiki Sasai also led its research stream on techniques for stem cell manipulation as one of its three principal investigators, together with Hiromitsu Nakauchi at the University of Tokyo and Hideyuki Okano at Keio University. Thus, since its establishment, the development of regenerative medicine has been one of the CDB's primary goals, if not the only goal.

In the early 2000s, the CDB produced many high-impact scientific articles but was not able to make as much progress in clinical applications of stem cell research, as the government had tasked it to do (Mikami 2015a). Unlike the two other leading groups of MEXT's project, which were based at university hospitals, the CDB was primarily a research center, and as suggested by its name, the Center for Developmental Biology, its remit was primarily to understand mechanisms of cell growth and differentiation. While it is adjunct to a research-focused hospital and has been part of the Kobe Biomedical Innovation Cluster, which aims to promote translational research, its research has not always had strong medical components. Strict regulations on both the creation and the research use of human ES cell lines introduced in 2001 also constrained the scope of its research, by not allowing clinical studies with human ES cells, despite the field of regenerative medicine thriving elsewhere in the world mainly in response to the establishment of the first human ES cell line in 1998 (see Franklin 2003; Hogle 2003). An example of research projects at the CDB is that of Teruhiko Wakayama, who led the Genome Reprogramming Group there since 2003 and studied mechanisms of nuclear transfer using not human cells but mouse cells.

As explained earlier, however, Yamanaka's success in developing the reprogramming technique and producing human pluripotent stem cells resulted in a dramatic change in the landscape of regenerative medicine research in Japan. The sudden availability of the new human iPS cells presented opportunities to investigate the relevance to human cells of what had been learned from mouse cells and to explore its medical utility. However, the government's decision not only to support his technique but also to endorse his vision of its further development made the technique *the* technical platform for regenerative medicine in Japan, despite the potential of other approaches, including nuclear transfer (e.g., Yamanaka and Blau 2010). Furthermore, in 2008, as the main promoter of iPS cell research, the Center for iPS Cell Research and Application (CiRA) was established at Kyoto University (Cryanoski 2008), and Yamanaka emerged not merely as the fourth principal investigator in MEXT's above-mentioned project, which entered its second term that year, but as the prominent figure in terms of both science of and policy for Japanese regenerative medicine research (Mikami 2015a). While a research collaboration platform called All Japan was introduced to improve the flow of both materials and information among researchers in the country and to compete against large research centers abroad, the CDB had lost the central position that it used to enjoy in this research area.

The shift in the political economy of Japanese regenerative medicine research did not mean that collaboration was scarce at the level of experimentation. A notable example of collaboration between the CDB and CiRA researchers is the clinical research on retina regeneration therapy using human iPS cells, led by Masayo Takahashi at the CDB. Already in the early 2000s, Takahashi and her colleagues developed a method of producing neural cells from primate ES cells potentially useful for treatment of retinal degenerative conditions (Kawasaki et al. 2002). The challenge was,

however, the regulatory environment in the country disallowing use of human ES cells for clinical study. She joined the CDB in 2006 and, immediately after Yamanaka produced human iPS cells in 2007, started working on an iPS cell therapy for age-related macular degeneration. In 2013 the government approved her clinical study, which was to be the first ever study to use human iPS cells for a therapeutic purpose (Cryanoski 2013). Therefore, it was expected that her study would be a proof of concept for regenerative medicine using iPS cells.

Nevertheless, the independent reform committee established by the director office of RIKEN in response to the STAP cell scandal suggested in its report, released on 12 June 2014, that the CDB's decision to hire Obokata as a research-unit leader reflected the research center's strong motivation to acquire her discovery of STAP cells, which could surpass the significance of iPS cells (RIKEN Reform Committee 2014; see also Cryanoski 2015a). The RIKEN Reform Committee (2014) explained that senior scientists at the CDB, including then director Masatoshi Takeichi and then deputy director Shinichi Nishikawa, recognized the potential importance of her work when they learned about it in early 2012 and offered her the job a few months later without following the normal selection procedure at the center. The RIKEN Reform Committee (2014) also revealed that Yoshiki Sasai, who became deputy director after Nishikawa retired in 2013, took a lead in preparing the press conference for the *Nature* publications but did not share details with RIKEN's public relations office in advance. Hence, the comparison between iPS cells and STAP cells that Yamanaka criticized was based on information that the researchers prepared (Suda 2014). Thus, the senior scientists at the CDB were aware that the success of STAP cells could introduce an alternative technical platform to Yamanaka's reprogramming technique, and that this would most likely put their center back in the driving seat of regenerative medicine research in the country, even though it might endanger its relationship with CiRA and the ongoing All Japan platform.

The success of STAP cells could equally be troublesome for some their colleagues at the CDB using iPS cells for their own research, and the senior scientists were most likely aware of this, too, but even so, they proceeded with announcing it in the most sensational manner. It is particularly remarkable that, by the time the announcement was made, Takahashi's group had already recruited the first patient to be treated with the iPS-cell therapy in its clinical study and had even started culturing the patient's iPS cells for transplantation. If STAP cells proved to be a safer and easier technical platform than iPS cells for regenerative medicine, revisions would have to be made to the study's protocol to adjust for this fact. At the same time, successful development of the better technical platform for regenerative medicine, as well as that of clinical application of stem cells, could potentially have invited the government to give the center more support than what CiRA received back in 2008. The timing therefore suggests the importance for the senior scientists at the CDB of the prescience of the potential for STAP cells to provide a new technical platform, while they seemed to have failed to give the science of the experiment close examination before its results were published. Hence, the RIKEN Reform Committee (2014) concluded that the STAP cell case was no less a failure of research governance than a matter of scientific misconduct and recommended the center be dismantled (Cryanoski 2015a). Responding partially to this recommendation, in November 2014, the CDB was restructured and restarted under new management.

4 Why Scientists Inferred the Doability of STAP Cell Research

So far I have examined the promissory aspects of the STAP cell case and demonstrated the ways in which the growing expectation for stem cell research in Japan and the institutional struggle of the CDB to reestablish its relevance in the national context, where science and technology are promoted by the state for the sake of national interest, allowed the situation to develop into a major national scandal. The success of STAP cells was expected to deliver exactly what people wanted: for both mass media and the public, a new heroic figure in Japanese science, and for the scientists at the CDB, a new technical platform for regenerative medicine. Although the *Nature* publications lost credibility after the misconduct was confirmed, this occurred not as quickly as one might expect. The situation remained confusing and controversial for more than half a year until RIKEN finally announced its conclusion in December 2014. In *Laboratory Life* (1986 [1979]), Bruno Latour and Steve Woolgar argue that credibility of scientific claims forms part of, and are simultaneously influenced by, a cyclical process of accumulating and expending one's credit as a scientist. The two publications on STAP cells gained credibility not only for the lead author, Obokata, who was, as explained above, still an early-career researcher, but also for her coauthors, in particular, the other corresponding authors, Teruhiko Wakayama, Yoshiki Sasai, and Charles A. Vacanti, who are all well established figures in their own fields. Their coauthorship made the publications more credible than Obokata alone could have done (see Maienschein 1993), and STAP cell research appeared doable to some corners of society because such coauthors were convinced by the STAP cell experiment.

The question then is why these scientists, as well as other senior ones at the CDB, who had access to the process of producing the scientific claims in which issues of complexity and uncertainty were addressed, remained convinced of the existence of STAP cells. RIKEN's Reform Committee (2014) reasoned that it was largely due to a failure of the research center to have a checking mechanism in place for the robustness of scientific claims made by its scientists, and this was a main reason that it recommended that the CDB be dismantled. In her book *The Scientist of Fabrication* (2014), Suda explains that the study of STAP cells by Obokata and her colleagues was so important for the CDB that it was kept secret from most other colleagues at the research center, despite the center having regular internal seminars where its scientists could discuss their unpublished results openly. Even so, at least a handful of senior scientists must have had a chance to challenge the robustness of her experiment in advance of the publication of its results, and yet none seemed to have looked into the research.

An important distinction to make, however, is that they seemed to have believed in doability of STAP cell research more than they actually did in the existence of STAP cells. The language used by Sasai substantiates this observation: when he spoke at a news conference on 16 April 2014, he described the STAP phenomenon as a "hypothesis," which "was worthwhile" but "still needed to be verified" (Nikkei 2014; see also Kameda 2014). According to Suda (2014), Hitoshi Niwa, who led RIKEN's postpublication study to examine the protocol of the STAP cell experiment, also shared this view up until a certain point. This was the view that they held *after* the results of the experiment were published in *Nature*, offering an interesting contrast to that of

Obokata and Vacanti, who kept insisting that STAP cells do exist (Cryanoski 2014b; Obokata 2016). While Fujimura (1987) argues that scientific research becomes considered doable where alignment of different levels, those of experiment, laboratory, and society, is achieved, doability of STAP cell research seemed to be inferred because the strong alignment at the institutional and societal levels—meaning the prefect fitness of its expected consequences to both the needs of the center and the visions of the government and the citizens—incited the scientists to think that STAP cells *ought* to exist. In other words, it appeared to them more logical to believe that the level of experiment was also aligned when it was not. And there seem to be two related reasons that they did not question this logic.

4.1 Partial Observation of the Experiment

The inference was not made out of the blue but with evidence suggesting that the level of experiment must also be aligned with the other levels. At the news conference where he described the STAP phenomenon as a hypothesis, Sasai stated that the project was conducted in an "unusual" environment involving multiple senior researchers (Kameda 2014) and clarified that he became involved in it only at the last stage of rewriting the article manuscripts for publication and had never produced STAP cells himself (Nikkei 2014). Although this account is inconsistent with the author contributions statements in the retracted publications (Obokata et al. 2014a, 2014b), this is not the point here but, rather, that he had only nominal involvement in the experiment. Furthermore, he explained that he was unable to check raw data or laboratory notes because Obokata was not a member of his laboratory and he only saw a video of STAP cells being created by Obokata (Nikkei 2014). According to Suda's (2014: 160–61) recollection, Niwa seemed to have been in a similar situation until he observed her making STAP cells in February 2014. Therefore, neither of them had seen the complete picture of the STAP cell experiment—what they saw was pieces of a jigsaw puzzle without knowing if they actually fitted together and presented a single picture.

More intriguing is the fact that this explanation also applies to both of the last authors listed in the publications, Teruhiko Wakayama and Charles A. Vacanti. The original idea of the STAP cell experiment—that is, inducing differentiated somatic cells to regain pluripotency by giving them some kind of stimulus—was developed while Obokata was a visiting researcher at Brigham and Women's Hospital, but at that time the main stimulus tested was physical stress caused by passing the cells through a very narrow pipette; the low-pH method described in the research article (and elaborated in the protocol published in March 2014) was developed after she started working at the CDB (Obokata 2016; Suda 2014). Therefore, Vacanti had not seen the STAP cell experiment explained in the retracted article in which he was named the last author. Wakayama, who was the last author of the letter and was the first among the corresponding authors to call for retraction of the *Nature* publications (Cryanoski 2014c), explained also that, although he was in charge of production of chimeric mice using STAP cells and of establishment of STAP stem cell lines, he used the cells handed over by Obokata and had never seen the entire process of their production (Suda 2014). He also confessed that he actually tried to replicate the results but never succeeded, and the

main reason for calling for retraction was because he feared that the cells he used might not have been STAP cells (Suda 2014: 69–70). Thus, there were certainly parts of the experiment that they observed, but again, they had never seen its entire picture.

As mentioned above, genetic analysis later revealed that contaminating ES cells were most likely responsible for the pluripotent behaviors of STAP cells described in the retracted publications (RIKEN External Investigation Committee 2014; Abbot 2014; see also Konno et al. 2015 for the genetic analysis) and therefore confirmed Wakayama's fear. More interesting, however, is that Obokata (2016) now claims in her book that even she had not seen the entire picture of the STAP cell experiment—as the experiment consisted of the two separate parts, she suggests, the first part, of which she was in charge, was genuine but she "does not know" what happened in the transition process to the second, which was done by Wakayama. The question of whether she had actually seen it or not is beyond the scope of this article, but either way, the picture of the STAP cell experiment presented in the *Nature* publications was produced by fitting together partial observations made independently by the individual researchers with a false assumption that they *ought to* fit together. It was much more straightforward for the international community of stem cell scientists to recognize inconsistency later, as they started from the whole picture and evaluated individual pieces in terms of their fitness.

4.2 Confirming the Dominant Ways of Seeing and Doing Stem Cells

The researchers were excited about the STAP cell experiment because some of the jigsaw puzzle pieces looked unusual compared to what they had seen before in their previous work on pluripotent stem cells. The most remarkable difference was STAP cells' ability to become placental cells (for the comments of Sasai, Niwa, and Nishikawa, see Suda 2014). It is, however, critical that, despite the unusualness, the researchers believed the experiment to be scientifically sound without raising serious doubts about it because it still confirmed what we might consider as the present paradigm in stem cell research. Thomas S. Kuhn (2012 [1962]) explains that a paradigm in science is a conceptual as well as material framework that allows scientists to conduct their research and interpret its results in a cohesive and cumulative manner. In other words, it refers to the dominant ways of doing and understanding science, and a locally specific version of these can be linked closely with Franklin's idea of a local biological in the context of stem cell research.

The research article on STAP cells begins by mentioning the similar phenomenon known to happen in plants and argues that it happens in animals too (Obokata et al. 2014b). As Austin Smith (2014) explained in his retracted commentary on STAP cells, de-differentiation of somatic cells is known to happen in some nonmammalian animals, such as lizards, and methods also exist to force it to happen in mammal cells, including nuclear transfer and Yamanaka's reprogramming technique. Furthermore, the article acknowledges that several groups—including Obokata and Vacanti's—had previously reported the existence of pluripotent cells, though in limited amounts, in adult tissues of mammals (e.g., Kuroda et al. 2010; Obokata et al. 2011). While the authors claimed that they controlled the phenomenon in vitro, the existing body of literature "naturalized" it conceptually as a biological mechanism that any organisms

potentially exhibit. Thus, the STAP phenomenon was supposed to fill a gap in the knowledge of cell biology rather than provide a novel understanding of stem cells.

The present paradigm in stem cell research also played a major role in a technical aspect. As Lena Eriksson and Andrew Webster (2008) point out, there has been no unique marker or set of markers to demonstrate pluripotency of cells. In discussing the similarity of laboratory-produced iPS cells to naturally derived ES cells, the community of stem cell scientists has developed acceptable and plausible methods of comparing pluripotent stem cells, in which the properties of ES cells are considered as the gold standard (Hauskeller and Weber 2011). For this reason, the argument for iPS cells tends to emphasize their clinical utility, rather than their equivalence to ES cells, and this tendency has been particularly evident in Japan (see Mikami and Stephens 2016). In the retracted research article, the authors demonstrated pluripotency of STAP cells and STAP stem cells by comparing them with ES cells (Obokata et al. 2014b). They then suggested that, just like iPS cells, STAP cells might not be the equivalent of ES cells but could be as good as and possibly better than iPS cells as tools for regenerative medicine because they were reprogrammed to the extent that they could even be placental cells. Because the previous discussions about iPS cells had established the necessary conditions of pluripotency, the STAP cell experiment was described as demonstrating that the cells met such conditions, and its significance was discussed in terms of their clinical utility.

The suggested superiority of STAP cells over iPS cells also reveals an ethical standard of local stem cell research in Japan. The very early stage of a fertilized egg has totipotency—the ability not only to become any type of cell in body but also to form the placenta, which plays a crucial role in developing an embryo in the womb. In the retracted letter piece, the authors argued that they managed to develop expandable cell lines from STAP cells without losing the ability to become placental cells (Obokata et al. 2014a). If this held true, STAP cells could have presented a new opportunity for (and simultaneously a danger of) doing reproductive cloning without involving any genetic manipulation. While the research was done only on mouse cells, the expectation was that the method would soon be applied to human cells. However, just as its science did not, the ethics of Obokata's "success" drew little attention from the senior scientists at the CDB. MEXT permits creation of germ cells from stem cells in its *Guidelines on the Research on Producing Germ Cells from Human iPS Cells or Human Tissue Stem Cells* (2010), and the government is monitoring the state of stem cell research to determine if created germ cells could be used to produce an embryo for research purposes (see Japan Cabinet Office 2015). As such an embryo could contain the genetic information identical to the donor of the cells used, the prospect that this may be allowed in the future made the ethics of the STAP cell experiment and the implications of broad developmental potential of the stem cells it produced much less contentious than they could have been otherwise.

Thus, the scientists involved found the results of the STAP cell experiment to be unusual in contrast to what they knew about other pluripotent stem cells but the presented argument overall was not contentious enough from conceptual, technical, and ethical perspectives—which together informed the local biological in Japan—to invite critical examination from the authors, or from the senior researchers at the CDB, in advance of their publication.

5 Conclusion

In this article, I examined the case of STAP cell scandal in Japan by situating it in the local context of stem cell research and demonstrated that it manifested some remarkable aspects of the social impact of the country's earlier success in human iPS cells. The two publications on STAP cells that appeared in *Nature* became a major national scandal as they were initially believed to deliver what the society wanted but were later revealed and confirmed to involve scientific misconduct in producing them. During this year-long process, many people in the country were left confused by the diverging opinions of the main authors, as well as by the confidence that some scientists had in the results of the STAP cell experiment. This article focused particularly on the question of what made these scientists become and then remain so confident, and argued that the local socio-institutional culture invited them to overstress the strong alignment exhibited at the levels of institution and society and to infer that this alignment extends even into the level of experiment, without paying sufficient attention to the science of the experiment and realizing its patchiness. Adopting Fujimura's (1987) concept of doability of scientific research, I argued that this was a case of inferred doability. As indicated in the actors' view that the STAP phenomenon was an interesting hypothesis that still needed to be verified, such an inference might be a common practice in the process of scientific research, but the experiment—as a means of its verification and hence assessment of the inference made—should have been done before its results were published and presented as a groundbreaking discovery. The STAP cell case developed into a major national scandal not only because the researchers involved did not undertake it adequately but also because they continued assuming that the alignment of the three levels—experiment, institution, and society—would become evident if they were given an opportunity to do it once again.

This understanding suggests that the vulnerability of local cultures of science to misconduct can be as problematic as, if not more than, the false intentions of individual researchers or inadequate research governance at a research center. As explained above, the changes in the relationship of science and society, in the focus of science and technology policy and in the political economy of local stem cell research in Japan after the hugely celebrated success of Shinya Yamanaka, were an important background to the STAP cell case. Allocation of blame on a particular individual—be it Obokata or Wakayama—and also on the host organization minimized the damage that it had on stem cell research in Japan but simultaneously jeopardized an invaluable chance to evaluate the implications of such changes. This offers an interesting contrast to Woo-suk Hwang's case in South Korea, in which the question of why he was able to represent himself as a national hero and the roles that the local culture of science in that country played in turning the case into a major national scandal have been the focus of much social science research (see, e.g., Chekar and Kitzinger 2007; L. Kim 2008; T.-H. Kim 2008).

The main argument in this article is that the STAP cell case corresponded closely to the local biological that emerged and was cultivated in Japan since Yamanaka's success in producing human iPS cells. As Franklin (2005) argues, however, stem cell research exhibits two mutually constitutive aspects—the local biological and the global biological. The former refers to practices of seeing and doing stem cell research embedded in and reflecting local values and cultures, while the latter highlights the tendency of

totalizing and assembling such local practices into a single grand enterprise (see also Mikami and Stephens 2016). Some practices in stem cell research discussed in this article are applicable across different locals and therefore are more global. An important feature of this global biological may be the expected speed of stem cell research. It only took about a year since its development using mouse cells for Yamanaka's technique to be applied to human cells, whereas there was a seventeen-year gap between Martin Evans and Matthew Kaufman's (1981) work on the first mouse ES cell line and James Thomson and colleagues' (1998) establishment of the first human ES cell line. A reason that the retracted publications on STAP cells drew considerable attention from stem cell scientists both in Japan and abroad was certainly the expectation that the work on mouse cells would soon be applied to human cells and could possibly be useful for regenerative medicine. As a result of stirring up their interest, they invested their time, money, and effort in testing whether the publications were genuine or fraudulent. While stem cell research as the global biological is a fast-moving and highly competitive field of science, this case therefore shows that, as much as there is strong desire to outperform others, the global biological is equipped with a mechanism of self-regulation. The reasons that the scientists at the CDB did not give close examination to the science of the STAP cell experiment might not be particularly unique, but it was also the delay in questioning their conviction about its results, in contrast to the efficiency of this self-regulation mechanism—a gap between the local biological and the global biological—that made this STAP cell case more confusing and controversial than it necessarily was.

Despite my emphasis on the local biological in Japan in understanding this STAP cell case, I do not consider the observed cultural vulnerability to scientific misconduct to be specific to that country. While Sasai explained that the manner in which the STAP cell experiment was conducted was "unusual," international collaboration involving multiple senior scientists is not uncommon in biomedical sciences, and considerable effort has to be made to ensure that they have the complete picture of their work before its results are published. Furthermore, as I have argued elsewhere (Mikami 2015b), it is not only scientists but also governments that are now desperate to outperform others in stem cell research, and Japan is a notable example in this regard. Yet, because the size of Japan's budget for scientific research and technological development is small compared to that of the United States and Europe, strategic prioritization of some areas of science and technology over others is considered inevitable. In this kind of a national context, there are high stakes for local scientists to have their research area prioritized and keep it as such, which also puts them under constant pressure to deliver returns on the government's investment. And as the literature on the Hwang case in South Korea illustrates (Chekar and Kitzinger 2007; L. Kim 2008; T.-H. Kim 2008), such a situation is by no means unique to Japan. Although reactions to a case of scientific misconduct more often than not stress the necessity of training in research ethics for individual scientists and also the need for a systematic approach to check the robustness of research within individual organizations (e.g., RIKEN External Investigation Committee 2014; RIKEN Investigation Committee 2014; RIKEN Reform Committee 2014), Fujimura's three levels of work organization in scientific research, that is, experiment, institution, and society, indicate that resource management at the societal level, which in this case incited the senior scientists at the CDB to acquire and promote Obokata's work, deserves as much scrutiny as do the levels of experiment and institution.

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