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State-Supported Science and Imaginary Lock-in: the Case of Regenerative Medicine in Japan

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Introduction

The international race to develop regenerative medicine (RM) started at the beginning of the twenty-first century. Engaged in this race are not only Western countries but also many Asian countries, including China, South Korea, Singapore and Japan. The race is ‘international’ not only because scientists in these countries are undertaking cutting-edge research in this emerging field but also because the states have been politically committed to this global enterprise of stem cell science. As emphasized by the idiom of co-production (Jasanoff 2004), their commitments make some important contributions to the process of technological development, and social studies of stem cell science demonstrate that such commitments can vary in their styles and result in divergent research trajectories, reflecting their local values and social orders (e.g., Franklin 2005; Prainsack et al. 2008; Salter et al. 2009). Some studies also suggest that their policy decisions on biomedical research, including stem cell science, can be seen as national endeavors to re-construct nationhood (e.g. Jasanoff 2005; Kim 2008; Prainsack and Gmeiner 2008; Sperling 2008).

An important character of Japanese RM research is its strong emphasis on induced pluripotent stem (iPS) cells, which were originally created from mouse fibroblasts in 2006 by Shinya Yamanaka, followed by success with human cells about a year later (Takahashi and Yamanaka 2006; Takahashi et al. 2007). Anyone familiar with this national context would agree that a study of Japanese RM research should include some references to his achievement (e.g., Sleeboom-Faulkner 2011). The technique to create these cells was introduced as a potential solution for the ethical issue of human embryonic stem (hES) cells (Takahashi and Yamanaka 2006) and soon became recognized as an important achievement within the community of stem cell scientists (e.g., Cyranoski 2007a; 2007b). However, no consensus has been reached on whether these two types of pluripotent stem cells can be treated interchangeably, and no agreed-upon criteria for assessing their interchangeability are available (Eriksson and Webster 2008). For this reason, the therapeutic usefulness of iPS cells is yet to be confirmed, and in some western countries these cells are considered as the tools for basic research or modeling diseases in a laboratory, rather than the sources for RM (Hauskeller and Weber 2011). This divergence highlights the specificity of Japanese RM research, which dramatically shifted its focus towards the new stem cells after Yamanaka’s success.

This observation leads to the main questions of this paper regarding the roles of states in shaping research trajectories. The first question is ‘what roles did the Japanese government play in the development of iPS cell research?’ An important organization in this national context is the Ministry of Education, Culture, Sports, Science and Technology (MEXT), which launched the Project for Realization of Regenerative Medicine in 2003 and has since been the primary sponsor of RM research in this country. Therefore, it is crucial to understand how the Ministry reacted to Yamanaka’s achievement in 2007. The second question is ‘what implications did the strong commitment from the state have for the RM research in this country?’ Owing to the government’s emphasis on efficiency in science and technology (S&T) policy, the Ministry had to be accountable for its commitment to iPS cell research. In so doing, the scientific visions in the field became intertwined with the policy vision to bring about the transition to a *knowledge-based society*. Hence, this paper also examines the extent to which this science-policy intertwinement contributed to the strong emphasis on the particular trajectory of RM research in Japan.

This paper addresses these questions through qualitative analysis of 48 in-depth interviews with scientists, corporate actors and other professionals involved in the governance of RM research in Japan, along with ethnographic materials collected over four years between 2008 and 2011. Unlike those of laboratory studies, these materials did not derive from the observation of a specific research group or that of a single laboratory. Instead, ‘the field’ of this study is understood as the community of Japanese RM research, and hence the materials include academic and non-academic publications, minutes of government committee meetings and observations at conferences, public symposia and semi-closed study groups (cf., Hess 2001; Hines 2007; Marcus 1995). These data were then analyzed to present a historical account of Japanese RM research over the first decade of the twenty-first century.

The trajectory of Japanese RM research became so stable that other technical options, in which corporate actors showed more confidence, were reduced to ‘interim’ solutions in the pursuit of the ‘right’ visions of its development. This paper introduces the concept of *imaginary lock-in* and provides a detailed account of the intractable state of RM research, which resulted from binding a policy vision of the nation’s future with the visions of scientific advancement. This paper consists of three main sections. The first section introduces its analytical perspective, which is largely informed by Jasanoff and Kim’s (2009) concept of *sociotechnical imaginaries*; the second examines the significance of iPS cells in the history of S&T policy in Japan; and the third investigates the industry’s attempt to revitalize other trajectories of RM research in this country. These sections are followed by the conclusion, which summarizes the implications of the state interventions on Japanese RM research.

Sociotechnical Imaginaries and their Lock-in Effect

Stem cell science is argued to be a future-centric enterprise (Geesink et al. 2008). Both public and private investments are made to capitalize the clinical and economic values of living materials expected from this enterprise (Waldby 2002; Franklin 2003; Hogle 2003). Such expectations influence not only the pace of its progress but also its direction. For instance, the therapeutic promises of human embryos and hES cells were critical in making them available for research in some countries (Mulkay 1993, 1997; Rubin 2008). Similarly, the speculated potential of cord-blood stem cells underpinned the emergence of commercial cell banks (Brown and Kraft 2006). The power of these expectations to attract investment depends largely on their perceived feasibility, and scientists, who assert the legitimacy and attractiveness of their research, tend to be proactive agents in making future projections (Morrison 2012; Wainwright et al. 2006b). Also, corporate actors may reproduce such projections to substantiate their business models, sometimes altering research trajectories in the field (Martin et al. 2008; Petersen and Seear 2011; Wainwright et al. 2006a). In this future-oriented enterprise, however, nation states tend to be portrayed as more reactive agents, being enrolled in the emerging network of a projected future and providing public funds for its realization.

In contrast to this view, Jasanoff and Kim (2009) suggest that nation states proactively present a vision of ‘future’ in relation to S&T and in so doing define its trajectory. In their comparative study of the histories of nuclear power policy in the United States and South Korea, they argue that the states have been central to the production of ‘sociotechnical imaginaries,’ which they define as ‘collectively imagined forms of social life and social order reflected in the design and fulfillment of nation-specific scientific and/or technological projects’ (ibid.: 120). The US government, on the one hand, has envisioned acting as a responsible regulator of nuclear technology since the end of World War II, and this vision served to regulate its military use during the Cold War and its civil use more recently. In South Korea, on the other hand, the technology has been perceived as a powerful means to raise the nation’s technical and economic status to that of advanced countries, and hence the state attempts to advance it for national development. They demonstrate crucial differences in these policy decisions by characterizing their national imaginaries as ‘Atoms for Peace’ and ‘Atoms for Development’ respectively.

Jasanoff and Kim argue that national imaginaries are different from mere policy discourses because they ‘at once describe attainable futures and prescribe futures that states believe ought to be attained’ (2009: 120). For a state to commit to a particular trajectory of S&T, its imaginary needs to provide a collective understanding of benefit it offers in the future. In activating such collective consciousness, imaginaries

‘help create the political will or public resolve to attain them’ (ibid.: 123). This collective consciousness also enables the state to (re-)build the sense of nationhood (cf., Anderson 1991), while it demands constant maintenance of the perceived attainability of the future. Each imaginary has its own framings of the goals, priorities, benefits and risks that together account for this attainability, but some events and evidences may trouble such framings, inevitably casting doubt on its desirability and attainability. Therefore, the state must enact certain interpretations of the otherwise-jeopardizing events and evidences by exercising its political power. Through such political interventions, national imaginaries can ‘penetrate the very design and practices of scientific research and technological development’ (Jasanoff and Kim 2009: 124).

This also suggests that once a state makes its commitment to a particular trajectory of S&T, switching to other technical options can be exceedingly difficult. As Arthur (1989) argues, an initially attractive option, even though it may be inferior to others in the long run, can be a dominant choice because the experience of choosing it would increase the attractiveness of the same choice thereafter. Elaborating this argument, Cowen (1990; Cowen and Gunby 1996) suggests that this lock-in effect can also result from the increased confidence in evaluating the benefit of the choice already made in contrast to the uncertainty associated with the potential benefit of other hypothetical options. From the policy perspective, however, this kind of lock-in is undesirable. Referring it the ‘dilemma in social control of technology,’ Collingridge points out a challenge that ‘by the time a technology is sufficiently well developed and diffused for its unwanted social consequences to become apparent, it is no longer easily controlled’ (1981: 17-18). This undesirable level of inflexibility can be termed *imaginary lock-in*, where it results from the state’s early commitment informed by its vision of the nation’s future.

Although the state’s commitment to S&T can entrench the nation into its particular trajectory, the degree of resultant inflexibility may vary, and this variation seems to reflect the extent to which its research has become privatized. Privatized science is criticized for its excessive attention to intellectual property rights (e.g., Mirkowski and Sent 2002). The patent system allows an inventor of knowledge or a technique to own his invention, and an invention owned as one’s property may not only be ‘exchanged for other goods, service, or money’ but can also be ‘used to prevent, other, similar ideas from trespassing on its intellectual domain’ (Etzkowitz and Webster 1995: 483). Callon describes this market logic as ‘a powerful machine for constructing irreversibility and limiting the variety of technological options or the range of possible choices’ (1993: 410). Hence, the idea of privatized science represents the limited degree of circulation, or its exclusiveness, rather than simply referring to the legal state of its ownership. From this point of view, state-supported science can be *privatized* ‘in the sense that it does not circulate’ and ‘remains in private

hands' of certain individuals (Cambrosio and Keating 1998: 167).

Despite the fact that policy measures can be effective approaches to mitigate the problems of lock-in (cf., Cowen and Gunby 1996), imaginary lock-in thus indicates that the state's early commitment can make a field of science privatized, forcing it to advance within a closed network of certain actors. While this seems far from ideal to foster innovation (cf., Gibbons et al. 1994; Etzkowitz and Leydesdorff 2000), 'the level of market influence among public science labs' has long been observed internationally (Etzkowitz and Webster 1995: 484). Callon even argues that 'when the state intervenes, more and more often [science] takes the side of [privatized property and the retention of information]' (1993: 396). By examining how the state's early commitment to a particular trajectory of Japanese RM research resulted in the state of imaginary lock-in, this study therefore demonstrates this privatized nature of its research enterprise and the danger of intensive state support.

RM Research as a National Project

The policy vision to make a transition to a knowledge-based society appeared in Japan in the late 1990s and had a significant impact on recognizing Yamanaka's reprogramming technique as a valuable resource for the nation. The concept of 'a knowledge-based economy' was originally introduced in the context of international politics in the mid-1990s to cross-examine strong economies observed at local, national and regional levels (Cooke and Leydesdorff 2006; Godin 2006; Jessop 2005). The Japanese policy vision was a local interpretation of this concept, and it affirmed that the trend in the late twentieth century that S&T became 'deeply related to all aspects of society' would also prevail in the twenty-first century, emphasizing the importance of political initiatives to 'create new knowledge' (STA 2000: Part 1, Ch. 3). Another point of this vision was that S&T in the new millennium should be sustainable as well as socially responsible, suggesting that scientific knowledge ought to be utilized in the way it 'create[s] a path on which we can live in harmony with the earth' (ibid.: Part 1). In this view, therefore, there must be a 'right' course of S&T development distinctive from 'wrong' ones. This vision offered the basis of the national imaginary in this country, and this section demonstrates how it became intertwined with iPS cell research.

'A National Accomplishment, of which We are Proud'

In 1950s, the Japanese government started recognizing S&T as an important area of its policymaking and established several organizations for its promotion (Morris-Suzuki 1994). Since then, S&T has been seen as the main driver of Japan's national economy: the rapid recovery of the nation's economy in the 1960s

and its dramatic growth in the subsequent decades were largely led by research and development (R&D) activities in the industry with the political support from the Ministry of International Trade and Industry (MITI) (Freeman 1987; Low et al. 1999; Morris-Suzuki 1994). However, the burst of its economic bubble in the early 1990s drove the nation into a sustained period of serious deflation, often referred as ‘the Lost Decade’ (see Hayashi and Prescott 2002). This sharp economic decline caused significant downsizing in industrial R&D activities (Low et al. 1999) and urged the state to assume the task of promoting both basic and applied research.

In the mid-1990s, the change in S&T policy was called for. For example, the Science and Technology Agency (STA) argued in its 1995 annual report that ‘the government ought to actively undertake the reforms of policy systems to encourage creativity [in S&T] and to utilize its outcomes for the development of new markets’ (1995: Part 1, Ch.3). The lack of creativity was a criticism referring to weak academic science in the country at that time (Low et al. 1999), and the enactment of the 1995 Science and Technology Basic Law (CAO 1995) and the publication of the first Science and Technology Basic Plan (STBP) (CAO 1996), a five-year plan for research promotion and technological development between 1996 and 2000, aimed at addressing this issue. In 2001, the government undertook its structural reform, and the STA was merged with the Ministry of Education, Science and Culture, forming MEXT. In its final annual report, the STA again insisted that the country ‘must work to develop [its] own powerful knowledge’ to complete ‘the transition towards a knowledge-based society’ and ‘secure its position as one of the most developed countries’ (2000: Part 1, Ch.3).

This point was then picked up in the second STBP published in 2001. The document explicitly stated that S&T offers ‘inexhaustible intellectual resources’ for the country and that its ‘promotion might well be regarded as prior investment toward the future’ (CAO 2001: Ch.1, Article 3). This idea corresponds to some extent to the ‘obsessive concern about issues of resource security’ in postwar Japan (Morris-Suzuki 1994: 234). In the 1980s, under the slogan of ‘information society’ the government made its ‘endeavor to shift [the country’s] industrial structure away from reliance on traditional heavy industries and towards so-called “knowledge-intensive” industries’ (ibid.: 210). Yet, even stronger emphasis on the production of knowledge in this 2001 plan indicated that the performance of universities, rather than industries, would be critical for the nation’s future. For this reason, MEXT became more responsible for the promotion of S&T and hence for the investment toward the future, than the Ministry of Economy, Trade and Industry (METI), renamed from MITI in the 2001 government reform. The idea of ‘investment’ also demanded ‘efficient/effective resource allocation’ in its implementation (CAO 2001: Ch. 1, Article 3).

To achieve its goals, the government identified some prioritized areas of research and one such area was life science. In the second STBP, the government described its intention to promote stem cell science, ‘so as to achieve advances in organ transplantation and regenerative medicine’ (CAO 2001: Ch. 2, Article 1). Since 2000, stem cell science has been a target of the national investment and was enjoying the generous support within a national research program called the Millennium Genome Project. This research funding allowed the field to make substantial progress but the project was criticized in its mid-term assessment for poorly articulating its clinical and economic impacts (CSO 2003: 27-30). In response to this, MEXT in 2003 launched the *Project for Realization of Regenerative Medicine* with stronger emphasis on clinical applications. The Japan Science and Technology Agency (JST), a funding agency officially working with MEXT, also launched some research programs, endorsing this emphasis on clinical applications.

One such program of the JST supported Yamanaka’s project on cell reprogramming, in which he created ES-cell-like cells from differentiated mouse cells by introducing transcription factors (Takahashi and Yamanaka 2006). Cell reprogramming was not a novel idea in stem cell science, and reprogramming of differentiated cells was possible but only by using oocytes or ES cells (Hochedlin and Jaenisch 2006). Building on this knowledge, Yamanaka’s group developed the hypothesis that some genes maintaining the embryonic state of stem cells perform vital functions in cell reprogramming, and after a series of experiments they successfully identified the genes that function as the transcription factors. Their first publication of mouse iPS cells generated little public enthusiasm in Japan. When they announced their success on producing human iPS cells using the same technique (Takahashi et al. 2007), however, it was reported in various media, earning nationwide attention in the country (see Shineha et al. 2010).

With the creation of human iPS cells, Yamanaka triggered new policy dynamics in Japanese RM research. Hishiyama (2010), a former officer of MEXT’s Life Science Division, recalls that the Ministry responded to Yamanaka’s 2007 announcement with remarkable speed: no more than a month later, the Ministry published a document entitled ‘The General Strategy to Promote iPS Cell Research [*iPS Saibou (Jinkou-Tanousei Kansaihou) Kenkyu nado no kasokuni muketa Sougou Senryaku*].’ In this document, MEXT described Yamanaka’s achievement as ‘a national accomplishment, of which we are proud’ and listed its plans of support ‘to win the international competition’ in this field (2007: 2, the author’s translation). This enacted a certain interpretation of the series of events: while the value of Yamanaka’s reprogramming technique was recognized only after its successful application to human cells, it was his earlier success on mouse cells that gave his technique this ‘national’ identity; the simultaneous success in human iPS cells in the US reinforced the belief that this emerging field was already facing fierce international competition. Thus, this new technique became recognized as ‘our’ resource in this country (cf., Lock 2002).

The speed of MEXT's reaction also revealed its particular understanding of 'risk.' The potential of human iPS cells to replace hES cells and resolve the ethical issue of their research use made his technique an attractive candidate for a national project (see Sleeboom-Faulkner 2011). Yet, the Ministry was more concerned about the risk that the country might lose this potentially valuable intellectual resource, which is of vital importance for the resource-scarce country (cf., Low et al. 1999), to its foreign competitors. Thus, not only the Japanese identity of Yamanaka's technique but also the anxiety about losing this intellectual resource prompted the instant protection of and further investment in iPS cell research. While Jasanoff and Kim suggest that national S&T policies 'are useful sites for examining imaginaries at work' as they often 'balance distinctive national visions of desirable futures driven by [S&T] against fears of either not realizing those futures or causing unintended harm in the pursuit of technological advances' (2009: 121), the rapid reaction of MEXT gave it little time for deliberation before its commitment to iPS cell research.

Figure 1. The photo of the new research building of the Center for iPS Cell Research and Application at Kyoto University, opened in 2010 (taken by the author)

Making of an 'All Japan' enterprise

On December 25, 2007, the JST held a symposium 'The Impact of Induced Pluripotent Stem Cells - the Future of iPS Cell Research - [*Jinkou-Tanousei Kansaibou no Inpakuto - iPS saibou kenkyu no kongo* -].' In this symposium, Yamanaka argued that 'all researchers in this field should assemble and form Team

Japan,’ and welcomed MEXT’s proposal to set up a consortium for iPS cell research as a platform for its researchers ‘to share the latest research results and materials’ (JST 2008: 19, the author’s translation). He adopted the phrase of ‘Team Japan’ to stress the importance of such nation-scale collaboration to compete against his competitors abroad. This consortium was founded in 2008 but rather than inviting researchers to join the force, MEXT institutionalized the existing network of the researchers who had been part of its research programs. By early 2008, the Ministry also implemented its other plans to support iPS cell research. The Center for iPS Cell Research and Application was established at Kyoto University (Fig. 1), and Yamanaka was appointed its director, and a working group on stem cell science and RM research was set up under MEXT’s Life Science Committee. In April 2008, MEXT’s RM project started in 2003 also entered its second term and made the dramatic shift to iPS cell research.

In the first meeting of the working group held in January 2008, MEXT (2008) introduced the concept of ‘All Japan.’ Although the Yamanaka’s phrase of Team Japan emphasized the importance of collaboration among scientists, this concept highlighted the equal importance of commitments from non-research actors, mainly the government organizations, providing them with indispensable support for their research. The concept, just like the idea of ‘national accomplishment,’ reinforced the embeddedness of iPS cell research in the history of the nation’s S&T policy since the mid-1990s and portrayed iPS cells as the healthy return on the nation’s investment in S&T. In so doing, the Ministry legitimized its past investment and simultaneously became responsible for future exploitations of this intellectual resource for the nation’s economic recovery.

By assuming the leadership in promoting iPS cell research, MEXT was desperate to realize this All Japan concept and to turn it into a national project. However, for iPS cell research to fully achieve this status, MEXT’s commitment alone was insufficient. As an interviewee described, the government’s strong emphasis on ‘efficient/effective resource allocation’ was closely tied to the principle of ‘division of labor’ among ministries (Professional-3, on 13/09/2009). This interviewee then expressed as much confusion as irritation regarding the situation of RM research at that time where MEXT was ‘attempting to deal with both basic and applied [research]’ on iPS cells. Hence, the Ministry’s enthusiastic commitment to iPS cell research with the aspiration to develop clinical applications was considered unconventional. Furthermore, the ministerial division of labor had another implication for iPS cell research. The Ministry of Health, Labor and Welfare (MHLW) disallowed clinical studies of hES cells and also cells differentiated from them (MHLW 2006), and in principle this same rule was applicable to iPS cells. Therefore, there were some issues that MEXT alone could not resolve.

This situation changed when the Cabinet Office endorsed MEXT's decision to support iPS cell research. It first selected iPS cell research for its initiative to promote medical innovation in 2008, which provided no financial support but demanded close and effective liaison among MEXT, METI and the MHLW for its advancement. In 2009, it also launched a funding program - the Funding Program for World-Leading Innovative R&D on Science and Technology - and granted Yamanaka the total of five billion yen for his five-year project (CAO 2009). MEXT became responsible for the administration of this research grant, and this arrangement endorsed its authority in iPS cell research. As these initiatives set common goals for the ministries, urging the other two to ally with MEXT in its effort, the significance of the ministerial division of labor in this field was also played down.

Championed by this political mood, MEXT increased its funding for iPS cell research to 4.5 billion yen in 2008, a fifteen-fold increase over that of the previous year, and further to 14.5 billion yen in 2009 (MEXT 2009). In its document 'The Roadmap for iPS Cell Research [*iPS Saibou Kenkyu Rodomappu*],' MEXT stated that, given the substantial amount of investment it made in iPS cell research over the previous two years, it must be 'accountable' for its funding strategy and its outcomes (ibid.). This document then listed four main branches of iPS cell research as its focus: basic research on the mechanisms of reprogramming, basic research for defining technical standards for producing iPS cells, applied research creating disease-specific iPS cells for drug discovery and finally pre-clinical and clinical studies to develop RM using iPS cells. These branches of iPS cell research were consistent with Yamanaka's visions of its advancement, which he presented at MEXT's first working group meeting on RM research (MEXT 2008: 8-16), but the Ministry added a ten-year timeline to these visions, providing benchmarks for each branch.

Figure 2: The illustration of the Highway for the Realization of Regenerative Medicine (reproduced from MEXT 2011, 6)

Although developing RM using iPS cells is listed as one of the four main focuses, the timeline set in this roadmap concerns when clinical studies are to start, rather than when the technologies will be clinically available. This framing of the goals made MEXT's policy liaison with the MHLW particularly important because meeting the timeline depends critically on MHLW's approval of clinical studies of pluripotent stem cells. In 2010, the MHLW revised its guidelines and opened its doors for clinical studies on cells differentiated from pluripotent stem cells (MHLW 2010). Also in that year, the two ministries proposed a joint-research program – the Highway for the Realization of Regenerative Medicine – to enable the seamless transition from pre-clinical to clinical research and overcome the 'death valley' in RM research (Fig. 2). Thus, the idea of All Japan was realized by the enrollment of other ministries, the MHLW in particular, endorsing MEXT's emphasis on producing 'clinically-applicable' knowledge.

By 2011, the All Japan iPS cell research enterprise became comprised of the consortium of researchers and the inter-ministerial liaison supporting their activities. These science and policy actors teamed up to win the race against researchers abroad and to maximize the benefit of the national accomplishment of iPS cells. As Jasanoff and Kim (2009) emphasize, however, these actors needed to have the collective understanding of such benefit in order for the policy vision of initiating the transition to a knowledge-based society to be a national imaginary, and MEXT managed to develop it through its public engagement activities. MEXT frequently organized public symposia on its RM research project and invited Yamanaka to present his visions for iPS cell research, which were essential to MEXT's roadmap. The events were well attended and Yamanaka succeeded in presenting the therapeutic promises of iPS cells, similar to those of hES cells observed in some Western countries (cf., Rubin 2008). Despite the lack of public debate in Japanese stem cell science (Kato 2005; Sleeboom-Faulkner 2008), Yamanaka, as the creator of the 'ethical' stem cells and also as the young leader of Japanese RM research, became a heroic figure and endorsed MEXT's effort to turn iPS cell research into a national project (Professional-11, on 18/11/2010; also see Shineha et al. 2010; Sleeboom-Faulkner 2011).

RM Research as Privatized Science

In Japan, the differences between the reactions to iPS cells in many Western countries and that of MEXT seemed scarcely concerning. It was assumed that such differences arose from the country's ownership of Yamanaka's technique, rather than its policy decisions to support it intensively. As a result, this local enterprise became detached from its foreign counterparts (cf., Hauskeller and Weber 2011). Challenging its vision and proposing other trajectories of RM also became increasingly difficult in the country. The

growing concern, particularly among those not invited to the All Japan enterprise, was over what happens if its therapeutic promises fail to be fulfilled (Scientist-18, on 02/06/2009; Scientist-19, on 03/06/2009; and Scientist-23, on 28/12/2010). As Sleeboom-Faulkner notes in her study, some considered focusing on iPS cells at the expense of other approaches to RM ‘risky’ because ‘it threaten[s] the loss of current expertise’ despite the ‘unexplored presumption about the nature of [these] cells’ (2011: 237). However, MEXT and the other members of the All Japan enterprise were unable to address this risk because ‘risk’ in this imaginary was not framed as such. By exploring the initiative of the industry, this section examines why imaginary lock-in has become so evident in this Japanese context.

Japan as ‘the Nation of Craftsmanship’

Among the risks of RM identified elsewhere (cf., Faulkner et al. 2008), this local enterprise disregards most of the commercial ones because the issue of intellectual property rights is the only commercial risk for MEXT. Furthermore, the reluctance of pharmaceutical companies to engage in this field contributed to this situation too. Their reluctance resulted partly from the persistent deflation in the country, which made them unwilling to explore new market opportunities. It was also due to the perceived ‘inappropriateness’ of RM for their business models, characterized by large-scale manufacturing and nation-wide logistics (Scientist-1, on 21/04/2008). Therefore, the primary actors expected in this emerging market were start-up companies, who supposedly develop new business models for promising inventions. However, they badly struggled too. In 1999, the former Ministry of Health and Welfare introduced a process of pre-clinical assessment for cell- and tissue-derived medical products, requiring safety and efficacy of such products to be assessed before undertaking clinical trials (MHW 1999). This process, however, took years owing to the regulatory agency’s lack of experience in assessing the RM products, and the companies were not able to finance themselves during the process (Corporate-1, on 18/04/2008).

Despite this unfavorable regulatory situation, a few start-up companies remained active in RM research. In 2007, Japan Tissue Engineering Co. Ltd. obtained the first manufacturing authorization in Japan for its tissue-engineered product, which deploys a skin-regeneration technique originally developed in the US. Later in the same year, Yoshiki Sawa, a cardiovascular surgeon at Osaka University Hospital, announced that his team treated a cardiomyopathy patient with a novel technique called ‘cell-sheet engineering.’ This technique was developed by Teruo Okano, a biomedical engineer at Tokyo Women’s Medical University, in the 1990s (Okano et al. 1995), and a spin-off company had been exploring its commercial potential since the early 2000s. Its R&D projects were conducted in collaboration with medical professionals and some other business organizations, and Sawa’s success resulted from one such project.

These achievements were expected to mark significant milestones in Japanese RM research (Corporate-5, on 12/05/2009). The manufacturing authorization signified the development of expertise in the regulatory agency, indicating an improved regulatory environment. Sawa's success also represented the first clinical application of a 'made-in-Japan' technology in the field. However, they received little public attention, as they were overshadowed by Yamanaka's success on human iPS cells announced slightly earlier in that year. The two companies were not hampered by this situation, but METI, previously the main sponsor of their R&D activities, found it difficult to maintain the level of its support because iPS cell research became a national project and the Ministry was required to liaise with MEXT in its effort. While these companies had some connections to academic researchers, many of them were their clients (Corporate-6, on 26/09/2011) and did not function as effective channels to raise the concern about the commercial risks of RM in the national S&T policy.

Since 2007, the representatives of these companies have had several opportunities to speak at conferences but these events were different from the ones hosted by MEXT and their audiences were mostly businesspersons in related fields. In their talks, they not only stressed the need of the industry's engagement in RM for the nation's success but also disclosed some detailed information about their business operation, such as their facilities, personnel strategies and manufacturing protocols, which could potentially threaten their first-mover advantages in this emerging market. An organizer of an informal study group explained:

They do so because the field is still immature, and for Japan to establish a new industry around it and lead the international market, these companies must describe such unmet needs in their operations and present business opportunities for others. (Scientist-24, on 01/09/2011)

Despite the absence of a heroic figure like Yamanaka, these companies therefore attempted to develop a collective vision of RM at least within the industry.

Their vision emphasizes engineering techniques that allowed Japan to enjoy its international reputation as a high-tech country back in the 1980s (cf., Morris-Suzuki 1994). Such techniques can prove advantageous for automation of cell-culturing processes (e.g., Kino-Oka and Taya 2009) and in some cases have proven to be useful – for example, for designing a special container to deliver 'living' products (Corporate-2, on 08/05/2008). Some also suggest that a promising approach to establish international standards in this field would be to develop technologies guaranteeing the best quality and argue that Japan exhibits the potential to achieve this (e.g., Sengoku et al. 2011). This vision represents Japan as 'the Nation of Craftsmanship [*Monodukuri no Kuni*],' which differs markedly from that of MEXT: this alternative vision embraces the

nation's past to lead the world in many high-tech industries and seeks to replicate such prosperity with RM, while MEXT's vision discredits this past and pursues a new approach for economic recovery. Hence, this industry-oriented vision can be characterized as 'Cells for Revival' in contrast to the national imaginary intertwined with iPS cell research, which may be labeled 'Cells for Transition.'

As this alternative vision allowed various companies to operate in the prospective RM market with already-existing technical expertise, it soon became popular in the industry. In 2011, the companies sympathizing with the vision set up a cooperative organization - the Forum for Innovative Regenerative Medicine - to assess both technical and commercial feasibilities of various RM trajectories and to influence S&T policy based on such assessments (FIRM 2011). This initiative to set common goals and coordinate the voices in the industry resembles MITI's traditional approach in post-war Japan (cf., Low et al. 1999; Morris-Suzuki 1994). Their assessments suggest that in some cases 'less-potent' adult stem cells can be more promising sources for RM than iPS cells because they do not require the complex processes of reprogramming and re-differentiation, indicating both safety and cost effectiveness of their products (Professional-15, on 06/01/2011). Thus, the exclusion of these companies from the All Japan enterprise let their vision be a potential source for change: had it received some political commitment, its distinctive vision connecting the nation's past to its future could have marked the rise of a contending imagination in this country (cf., Jasanoff and Kim 2009).

'Privatization' of the State-Supported Science

The state did respond to this initiative. However, rather than adopting its alternative vision, it re-framed it so as not to contradict the national imaginary. In 2011, the Cabinet Secretariat's Office established the Office of Medical Innovation to increase coordination among the ministries (CSO 2011). The biomedical engineer Teruo Okano was appointed its deputy chairperson and several officers joined from the industry. However, this office did not focus on the area of RM and its influence on iPS cell research was unclear. Later in 2011, MEXT and the MHLW officially launched their Highway program and included a few non-iPS cell projects along with others focusing on iPS cells. These projects are expected to commence clinical studies either in three-to-five years or in five-to-ten years, with all the non-iPS cell ones categorized in the short-term group. Because the development of RM using iPS cells is unlikely to happen so soon, the non-iPS cell projects were included to cancel out its short-term disadvantage and to sustain the local enterprise until then.

A reason for the state's reluctance to enroll corporate actors in its RM enterprise and integrate their vision

may relate to the 2008 media report that a foreign company based in Japan outperformed Yamanaka in creating human iPS cells and even applied for its patent (Mainichi 2008). Kyoto University applied for the patent on Yamanaka's technique on his behalf in 2005 but at that time no one, not even Yamanaka himself, was certain about its applicability to human cells. Although the report did not reveal the exact dates of the company's success nor the nature of its application, this news caused public anxiety in Japan that this foreign company could be granted the patent and hence own the technique. The possibility of this corporate ownership, especially by a foreign company, presented a risk for the nation as it could limit the usage of this technology and inevitably its public benefit (see Yashiro 2008). The government eventually granted the patent to Kyoto University on the ground that the same technique works for both mouse and human cells, but this event reinforced MEXT's understanding of the commercial risk of RM and urged it to protect the national resource.

Furthermore, just like the growing distaste for the market influence on science in the US (cf., Mirowski 2011; Mirowski and Sent 2002), Japanese stem cell scientists tend to be averse to admitting their association with any commercial activities. For example, a university-based scientist, while listed as a scientific advisor of a start-up company on its website, explained:

I have no idea what [the company] is doing with the technique [that I developed]. [The people from the company] told me that they were interested in my research and wanted to use it, so I simply said 'ok.' I guess that is why my name appears on the website, but I have nothing to do with their business. (Scientist-13, on 13/05/2009)

However critical their contribution may be, the 'for-profit' nature of business organizations is frequently juxtaposed with the public benefit of RM, and hence their involvement is often considered inappropriate for this state-supported science.

Despite such insistence on being 'public,' Japanese RM research blindly follows the logic of market, as manifested in its language – *competition*, *investment*, *accountability* and *efficiency*. After all, this national imaginary was built upon MEXT's conviction that the nation must win this international race for its economic recovery. Although a similar logic was adopted by MITI in postwar Japan (Low et al. 1999; Morris-Suzuki 1994), MEXT in the new millennium acted like a mere industrial player investing in iPS cell research, seemingly the most rewarding trajectory of RM research from its point of view. Its decision might have reflected its belief that the industry was unable to undertake R&D activities to the extent required to win the race. However, its interventions have had different implications from the investment of ordinary business organizations: its early commitment to the trajectory gave authority to Yamanaka's scientific visions and its continuous investment then structured this research field, thereby ensuring the

visions.

This observation suggests that *imaginary lock-in* took place in two successive sequences. First, the state's policy vision became closely bound to the certain trajectory of RM as MEXT recognized the societal benefit of its future development. Lock-in at this stage was only 'imaginary,' as there was no material or financial constraint against pursuing other options. Then, lock-in started acquiring its material significance after the Ministry actively intervened in the field and Japanese RM research became locked into the imaginary, just like Collingridge's (1981) account of the dilemma of social control of technology. Soon after the creation of human iPS cells in 2007, MEXT assumed its leadership in this field and allocated the nation's limited resources primarily to the members of the All Japan research enterprise, even allowing them to retain their knowledge within this network. It was precisely this decision to retain such 'public' knowledge exclusively among its members that ironically reinforced the *privatized* character of Japanese RM research and accelerated its imaginary lock-in.

Conclusion

This study addresses the questions regarding the roles of the Japanese government in the rise of iPS cell research and the implications of its intervention in the field since 2007. The local enterprise of RM shifted its focus to iPS cell research dramatically after Yamanaka's creation of human iPS cells and this remains the focus, despite the uncertainty of their clinical usefulness. Rather than examining technical rationales for this shift, this study analyzed why the country is now entrenched in this particular research trajectory and explained it by introducing the notion of imaginary lock-in. Although the field of RM does not have a long history to allow a historical analysis of its imaginaries, which Jasanoff and Kim (2009) conducted for their original paper on sociotechnical imaginaries, this study instead identified the alternative vision of the nation's future and demonstrated the state's role in discrediting this vision in order to maintain the desirability and attainability of the state-supported science of RM research.

After the economic bubble burst in the early 1990s, the government began to place its emphasis on the production of knowledge and reformed its S&T policy with the aspiration to lead the country's transition to a knowledge-based society and to recover from the sustained deflation. Under MEXT's leadership, it began emphasizing the roles of universities as the primary targets of the nation's strategic investments. It was in this historical context that Yamanaka announced the creation of human iPS cells in 2007. MEXT saw his achievement as the return on its past investment and nationalized iPS cell research immediately. The Ministry's commitment to iPS cell research not only reinforced the embeddedness of his invention in

the S&T policy but also established its legitimacy in the field. The policy vision of the nation's future and this particular trajectory of RM thereby became intertwined and formed the national imaginary, which is characterized as 'Cells for Transition' in this paper.

This state intervention in iPS cell research had two implications. Firstly, this Japanese enterprise of RM research became somewhat detached from its foreign counterpart, and its exclusive focus on the iPS cell trajectory became legitimized on the basis that the reprogramming technique was 'our' intellectual resource. Secondly, other accomplishments, particularly those in which the industrial actors played key roles, were trivialized. While imaginaries should 'warn against risks or hazards that might accompany innovation' (Jasanoff and Kim 2009; 123), the exclusion of these actors made the All Japan enterprise inattentive to the commercial risks of RM, except the risk relating to the issue of intellectual property rights. The industrial actors then coordinated their voices by adopting a similar approach to the strategy of MITI in postwar Japan and presented the alternative vision 'Cells for Revival,' which appreciates the technical capability of various companies in developing a RM industry. However, the for-profit status of these actors has been juxtaposed with the public benefit of RM and this vision has been so far unable to become a contending imagination. Despite the fact that their initiative entails a remarkable extent of disclosure and free circulation of potentially appropriable information, the value of such knowledge has been mostly discredited.

Thus, the state's early commitment to iPS cell research has locked this Japanese research enterprise in the particular imaginary around Yamanaka's technique, devaluing knowledge produced outside the state-supported All Japan network. While it was not the legal owner of this technique, MEXT exercised its political power to mark its network out as the 'right' actors for the knowledge production. By legitimizing this publicly funded research network, the state intervention *privatized* RM research in this country. Here, the notion of 'privatization' is 'independent of the identity of the actors involved' (Callon 1993: 416). The reform of its S&T policy was an urgent task for the government and, as Jessop (2005) argues, it has been transforming itself in the attempt to define the meanings and practices of 'a knowledge-based society.' The danger of this kind of intensive state-support is, however, that, while the state may assume control over S&T development in the country, it can reduce its flexibility by undermining potential contributions of other-minded actors. While RM is just a section of the nation's S&T development, as the concept of sociotechnical imaginaries suggests, a similar challenge may well be present in other areas of S&T policy in this country.

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