6

Regulatory Redemption and the All Japan System

When the Spirit of the Regulation Is Not Reflected in Its Reforms

> The Ministry of Health, Welfare and Labour has been knocking on our door, asking when clinical application will begin!
>
> (personal communication iPS scientist)

For decades, Japan's regenerative medicine has enjoyed regulatory immunity due to a regulatory regime that put reputation first. But after the first report of the derivation of induced pluripotent stem cells (often abbreviated to iPCs) in humans in 2007, a number of regulatory changes were introduced to accelerate the translation of iPSCs into clinical applications. In 2012, a regulatory overhaul was announced that would revolutionise clinical trials to address the health issues of Japan's ageing population and Japan's slumping economy. Rather than being grounded in healthcare needs and scientific safety and efficacy, I show how the new regulation was predominantly concerned with economic and national considerations as expressed in the Health and Pharmaceutical Promotion Strategy and the 'All Japan System' (AJS). AJS ideology, emphasising its ability to save lives globally, made Japan's regulatory reforms redemptive to the life-saving therapies.

In this chapter, I show how a political strategy of this redemptive regulation harbours a discrepancy between the discursive aim of saving lives and that of regulatory protection of patients and good science. As explained in the introduction to Part III, the maintenance of such a strategy of redemptive regulation involves a continual misrecognition of what is actually going on in practice.

My examination of the dialectic between the international coproduction of Japan's regulatory reforms and its implementation sheds light on how both Japan's international research position has changed and how its science was affected at home, including scientific procedures and standards, research funding, priorities of clinical applications, structures

of governance and fundamental scientific choices. I visited Japan from March–May 2013 and October–December 2013, when the regulatory overhaul was announced and prepared, and from January–March 2016, when the initial effects of the regulatory and procedural changes started to materialise. I spoke with scientists working in the field of regenerative medicine, including iPSC research, in hESC-research, tissue engineering, rehabilitation and the production of biomaterials in the Kansai region (CiRA), Institute Frontier Medical Sciences (IMFS) and Institute for Integrated Cell-Material Sciences (*iCeMS*), the RIKEN Centre for Developmental Biology (CDB) and in the Kanto region (Keio University and the Women's University of Science and Technology). In addition, I spoke with experts in regulation, ethics and the social aspects of science and science communication. During these visits, we discussed the effects of regulatory changes and the AJS on their work, regenerative medicine in Japan and regulation in general.

Below I first describe the emergence of the AJS and the role of the state in the regulatory reforms. The second section examines how the regulatory politics of the AJS has affected the work of scientists by examining the collaboration among Japanese scientists, the frictions in the coordination of iPSC research, strategies used by scientists when planning clinical applications, constraints on scientific research and the ways in which scientists accommodate the AJS. After summarising the effects of the AJS on the work of scientists, the final section explains how the politics of regulatory redemption is based on a politics of misrecognition of what is actually going on and why this is important.

Regulatory Redemption and the Overhaul in Funding and Regulation

For years, in Japan, researchers had complained about the complex and time-consuming regulatory bureaucracy for stem cell research (Nakatsuji 2007). But when, in October 2006, Shinya Yamanaka and Kazutoshi Takahashi 'discovered' how to create iPSCs using mice (Takahashi and Yamanaka 2006), things changed. The notion of cell-reprogramming – it seemed to reverse biological development – was received with global excitement, and when the reprogramming method was applied to human iPS the following year (Takahashi et al. 2007), it propelled the government to action (interview Sato, 21/10/2008*; Hishiyama 2010).

IPS cells are made by 'reprogramming' somatic cells, such as skin cells. IPS cells closely resemble hESCs, which can be 'differentiated' into any of

the few hundred kinds of cells of the human body. The process involved the introduction of a limited set of (initially four) 'transcription factors' and feeder culture to 'fool' the somatic cells into reprogramming or 'reversing' their development. Japan's work on iPSCs not only showed the power of Japan's science, it was also advertised as ethical. Some scientists contrasted iPS research with research using hESCs, which requires donated oocytes and the destruction of embryos, iPS was promoted as an inexhaustible source for producing healthy cells (Nishikawa et al. 2008).

Even though Yamanaka and Takahashi were the first to 'discover' iPS, they had close competition from Jamie Thomson's group at the University of Wisconsin, Madison. In fact, they both published their results on human iPSCs in November 2007 (Takahashi et al. 2007; Yu et al. 2007). There was a realistic possibility that American researchers would claim a clinical first for iPS in humans. It was in this context that researchers asked for more funding for iPSC research and complained about Japan's regulatory disadvantage (Hishiyama 2010).

Nearly instantly, a suite of regulatory innovations was introduced to re-channel funding into what official documents referred to as the 'Japanese Research Team' for iPSC research and regenerative medicine, to reorganise the system for scientific funding, to make attractive collaboration with industry through re-regulation and to lower the regulatory threshold for clinical trials (MEXT 2007). The Ministry of Education, Culture, Sports, Science and Technology (MEXT) increased its funding for iPSC research to 45 billion yen in 2008, a fifteen-fold increase over that of the previous year, and to 145 billion yen in 2009. In 2013, Prime Minister Shinzo Abe's government committed ¥110 billion (about $1.1 billion) over ten years to iPSC research. Part of this amount was earmarked for 'Yamanaka's' iPSC bank at CiRA, Kyoto University (Philippidinis 2014).

Even before Yamanaka had received the Nobel Prize for his work on iPSCs in 2012, the Japanese government in 2010 had revised 'the guideline for clinical studies using human stem cells', expanding the coverage of the guidelines to include those for clinical studies using hESCs and iPSCs. In 2011, MEXT; the Ministry of Health, Labour and Welfare (MoHLW); and the Ministry of Economy, Trade and Industry (METI) had jointly launched the 'Highway to the Realization of Regenerative Medicine' to continuously promote research and development (R&D) for the realisation of regenerative medicine. This project culminated in the passing of the May 2013 Act for the Promotion of Regenerative

Medicine, which obliged the government to promote regenerative medicine. A researcher-cum-regulator explained: 'It is a political law meant to stimulate trust in the government and to stimulate industry to invest' (Imano, 9/3/2013*).

As explained in Chapter 2, two other acts followed: The Act on the Safety of Regenerative Medicine (RM Act) (2013 Act No. 85) and the Revised Pharmaceutical Affairs Law: The Pharmaceuticals and Medical Devices Act (PMD Act) (2013 Act No. 84), both of which were enacted in November 2014. These acts have altered the conditions for clinical application of regenerative medicine. The PMD Act introduced a specific regulatory framework for regenerative medicine products: it stipulates that the PMDA and the MoHLW provide for a conditional time-limited approval system for regenerative medical products. After exploratory clinical trials have demonstrated 'probable benefit' and 'proven safety', the product is given conditional, time-limited marketing authorisation (PMDA 2014; Azuma 2015). Allowing marketing without scientific evidence through conventional clinical trials, the new regulation attracted the interest of large companies, such as Sumitomo, Athersys, Mesoblast and Cytori Therapeutics, within a few months (Accesswire 2014).

Apart from regulatory innovations, new infrastructural policies were introduced to turn iPSC research into a success. The government promoted the creation of biomedical clusters, *Sūpā Tokku* (special disciplinary areas or networks), expanded IPR facilities and established support mechanisms for the collaboration between research institutions and industry. The new funding policies, formulated by the Headquarters of Healthcare Policy established in 2014 under the Cabinet Secretariat, integrated medical R&D budgets to concentrate on priority projects such as iPSC research proposals (Kantei 2013). The budgets of MEXT, METI and MoHWL were consolidated in the newly established Agency for Medical Research Development (AMED) from April 2015 (Sengoku et al. 2015). The new policies entitled 'Initiatives under the Project for Japan Translational and Clinical Research Core Centers' also promote specialised support for patent applications and education in translational research (Headquarters of Health Policy 2014) and the new Patent Act allowed the application for patent extensions for regenerative medicine for up to five years (Japan Patent Office 2014).

Crucially, according to the PMD Act, AMED allowed the reimbursement of newly approved regenerative medicine products, including conditionally approved products. NIH-insured treatment could also be combined with unapproved regenerative medicine products or 'evaluation treatment' if MoHWL assigns it 'Advanced Medical Treatment'

status (Health Insurance Act Article 86, cited in Azuma 2015: 126). Therefore, based on the *expectation* that the product works, Japan's insurance system covers part of the costs, and the patient contributes 10–30 per cent of the cost, albeit capped at around ¥100,000 (Anonymous 2015). Evidence for the conditionally approved therapy is required within a maximum of seven years, after which the regenerative product is unconditionally approved or rejected. According to Abe (9/03/2013*), these policies were expected to accelerate the application and commercialisation of regenerative medicine and iPSC research in particular.

Rather than maintaining its regulatory immunity, prioritising patient safety and science quality, the regulatory reforms were based on a polity of regulatory redemption that would shorten the regulatory pathways of regenerative medicine to the clinic. The financial and regulatory support for the commercialisation of science, including the introduction of a new insurance strategy and the shift from support for laboratory research to clinical research politically prioritised regenerative medicine above traditional branches of science and altered the standards and methods used in the production and evaluation of techno-scientific products. This organisational and material shift was accomplished through the political support for a vision for the AJS.

The Role of the State and the AJS

The prominent role of state governance in science, education and industry speaks for itself in Japan, known for its 'iron triangle' between government, bureaucrats and heavy industry (Johnson 1982). Since the introduction of the Japanese version of the Bayh-Dole Act in 1999, and the independence of Japanese universities in 2004 (Takenaka 2005), academia is encouraged to forge collaborations with industry. Nevertheless, until the introduction of the PDA Act in 2014, it had been difficult to tempt heavy industry to invest in medical innovation (Umemura 2011). In the context of the US, however, Mirowski and Sent (2002) regard a clear separation between 'pure' science supported by the state and 'applied' science as supported by industry as an untenable ideology, rejecting the notion of scientists as self-interested and science as market-driven (Mirowski and Sent 2002: 15, 23). But in the context of Japan, as we shall see, not taking into account this distinction would be unrealistic, as Japanese scientists observe major differences between 'pure' and 'applied' science and 'state'- and 'industry'-supported research settings. Although these separation-lines may seem artificial and subjective, the distinctions form an important point of orientation for

scientists and policy-makers with very real social and financial consequences for the way science is organised and practiced. It is this distinction that allowed the Japanese state to guide the science markets according to its own redemptive vision: the AJS.

The AJS was first formulated as part of the Health and Pharmaceutical Promotion Strategy and the five-year Medical Innovation Programme (MEXT 2012), which were to address the problems of ageing society and economic slow-down through regulatory reforms and make firm industrial and political commitments in support of regenerative medicine. Apart from turning Japan into the world leader of pluripotency, the AJS would be relied upon to boost the export of new medical products and devices to the Asian market (Headquarters for Healthcare Policy 2014) The All Japan System (オールジャパン体制) envisaged 'a system for All-Japan collaboration and co-ordination' and refers to the collective efforts to set up a structure for the advancement of a system for iPSC research (JTS 2008) supported by MEXT and the Stem Cell and Regenerative Medicine Strategy Working Group. Former Cabinet Secretariat Toshihiko Hoshino, professor and assistant director of the Basic Technology Research Division (MEXT), was tasked with building an all-Japan promotion system in collaboration with related ministries and agencies and industry to support regenerative medicine using iPSCs originating in Japan (CiRA 2012).

The AJS was to form a bridge between basic research in academia and industry to create new applications coordinated through national centres and universities; and it centred on Shinya Yamanaka's work on iPSCs. The AJS was led by Kyoto's Centre for iPS-cell Research and Application (CiRA), headed by Yamanaka, who was made responsible for the improvement of iPSC lines and culture technologies, including assays. The AJS network was built on four All-Japan pillars of iPSC research, involving Kyoto University, represented by Shinya Yamanaka (CiRA), who was to oversee the creation of technologies for the development of safe and efficient iPSCs, the development of iPSC proliferation control and for the evaluation of clinical response; RIKEN, represented by Yoshiki Sasai, responsible for developing technologies for cultivating and determining the efficacy of multipotent stem cells, including iPSCs; Keio University, represented by Hideyuki Okano, responsible for developing iPSC treatment with a focus on the central nervous system; and, Tokyo University, represented by Hiro Nakauchi, responsible for developing iPSC lines and treatment centered on blood cells (see Figure 6.1). Importantly, AJS made CiRA central to the

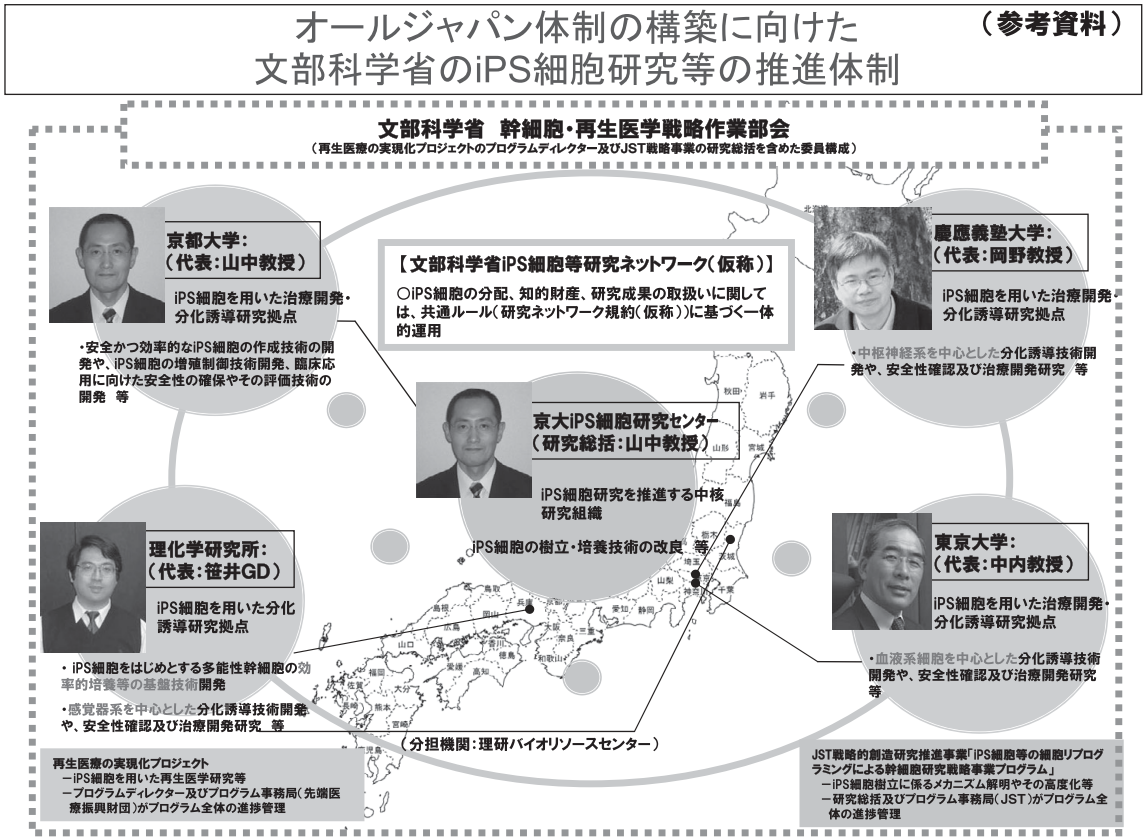

Figure 6.1 MEXT's promotion system for iPSC research toward building an All-Japan system.
Courtesy from the Japan Science and Technology Agency, reference material, https://www.jst.go.jp/keytech/h20-1sanko.pdf (22/1/2024).

distribution of iPSC lines, intellectual property and the handling of research results, and it stipulated that the tentative regulation of the research network of AJS was based on common rules. These policies, as we shall see below, restructured the science both organisationally and substantively.

In the following extract from a CiRA Newsletter (CiRA 2012), Professor Toshihiko Hoshino describes the AJS as the redemptive force behind the regulatory overhaul:

> In the future, cell therapy using iPSCs may be able to cure intractable diseases and lifestyle-related diseases. In order to meet the expectations and hopes of people who have such diseases and to realize life innovation originating in Japan, we will establish a system to bring together a lot of wisdom and promote iPSC research more effectively.
>
> (CiRA 2012)

A collective effort would mobilise resources in support of the long-term vision of iPSC cures.

> A long-term vision will enable us to systematically secure intellectual assets. On this basis, the results of short- and medium-term projects of 3 to 5 years, furnished with various competitive funds, will be organically linked and lead to even greater results. Thus, intellectual assets originating in Japan will be used by all humankind. In turn, the chances of Japanese assets being utilised will expand.
>
> (CiRA 2012)

The realisation of the AJS vision required overcoming institutional barriers to research promotion:

> We will work to improve the research base while securing intellectual assets and striving to overcome institutional barriers related to research promotion. We will promote all-Japan collaboration with related ministries and agencies and industry, and lay the foundation for returning the results of iPSC research to society.
>
> (CiRA 2012)

This plan made CiRA central to the iPS promotion strategy requiring other institutes to adjust, including scientific and ministerial ones, so as to realise the promise of iPSC research to society. Down-regulation was key to the realisation of AJS.

The re-brokering of Japan's regulation radically affected regulatory developments internationally (see Chapter 8); but in this chapter,

I focus how the regulatory reforms inspired by AJS affected Japan's iPSC research community.

How Did the 'All Japan System' Politics behind the Regulation Affect the Work of Scientists?

In July 2013, Masayo Takahashi from RIKEN-CDB received permission from the MoHWL to conduct a clinical iPSC pilot-study using iPSCs for age-related macular degeneration (AMD), news that soon spread across Japan and around the globe. In a few days' time, the study had recruited over one hundred patients, even though it was just a safety study; efficacy was to be tested in a next phase. According to a scientist working on the project: 'They are all in support of the study, because they want iPS to succeed!' (Ohashi, 29/3/2013*) This was the spirit of the 'All Japan System' speaking – the spirit that made the new regulation redemptive. But how did its politics regulate and affect the work of scientists?

This section explains how the AJS's politics of regulatory redemption affected research practice. It examines the dialectics between AJS and iPSC research in respect to: (a) research collaboration, (b) research coordination, (c) research options and considerations, (c) constraints on science and (e) working with and around AJS politics.

AJS and Collaboration

Scientists' competing interpretations of AJS provide nuance to dominant views of the regulatory reforms and show how AJS was designed to misread what was actually going on. My conversations with scientists on All Japan collaboration at CiRA, *iCeMS* and CDB illustrate this. Takayama, an administrator from CiRA, Kyoto University, gave his view of AJS:

> 'All Japan System' means that all the best scientists [in Japan] collaborate to produce good science applications in collaboration with the best scientists in the world.
>
> (Takayama, 5/11/2013*)

CiRA, an independent research institute, was one of the main beneficiaries of the life-science policy's focus on iPSCs and regenerative medicine. It is supported by the Japan Science and Technology Agency (JST), which funds science and technology targets created by the Japanese government (JST 2021) and is a main financial backer of the AJS. Kawa, a researcher

at *iCeMS*, Kyoto University, had a different view. *ICeMS* is supported by the World Premier International Research Centre Initiative (WPI), which was launched in 2007 by MEXT in a drive to build within Japan 'globally visible research centres that boast a high research standard and an outstanding research environment' (WPI 2020). Kawa said:

> The 'All Japan System' policy is a problem, as it likes to have everything from bench to bedside taking place in Japan. Hence, [the transplantation of iPS-] RPE cells is not important because of its value to the patient, but for creating a seamless line from bench to bedside in Japan.
>
> (Kawa, 30/10/2013*)

Kawa did not think that the AJS prioritised patients. He also emphasised the national focus of AJS. But the official version of the Health and Pharmaceutical Promotion Strategy had also announced collaboration with other Asian countries. Therefore, I asked about possible collaboration. Kawa said:

> There are too many political problems for collaborating with China now. Apart from that 90% of the JST focuses on All Japan, and as CIRA is the hub of All Japan, they cannot go to China. Nevertheless, Japanese researchers individually try to get overseas. Prof Shirakawa will go to Another [anonymised] University, where he wants to do translational research with overseas partners.
>
> (Kawa, 30/10/2013*)

In Kawa's interpretation of the Health and Pharmaceutical Promotion Strategy, Japan is hoping to export regenerative medicine products, while CiRA's iPSC activities develop them in Japan. As scientists frequently pointed out, at CiRA one in thirty PIs was not Japanese ('only one foreigner'), while *iCeMS* was required by its funder, WPI, to have 30 per cent foreign staff. But then, international collaboration is part of WPI's mission statement. Asking about CiRA's working relations with other institutions, such as the Medical School, Kawa responded:

> They do not collaborate! CIRA collaborates with FBRI [Foundation for Biomedical Research and Innovation] in Kobe. The Medical School does not accept iPS. Officially there are collaborations, but in practice, we do not see them. There has been no discussion about how to develop a clinical application of iPSCs in Kyoto, and Kobe is only two hours from here .... IPS does not benefit the traditional Medical School in Kyoto University.
>
> (Kawa, 30/10/2013*)

As repeatedly confirmed, the Medical School regretted the concentration of funding on iPSC research and CiRA. The Medical School wanted the funding to go to more urgent research, judging it too early for clinical applications using iPSCs. In 2013, these diverging views made collaboration difficult. According to an experienced legal scholar from Kyoto, Abe, the Japan Medical Association was also reluctant to support clinical applications using iPSCs:

> Currently safety and efficacy studies have to be done before clinical trials can start, but this is going to be reduced to safety studies alone. This is because iPSC applications are *expected* to be effective. The regulation will be about 'regenerative therapy' [saisei-chiryō] as 'regenerative medicine' [saisei yiryō] is not a correct expression: we do not know yet if it is regenerative [the emphasis is that of the interviewee].
>
> (Abe, 9/3/2013*)

The term 'regenerative therapy' gained currency, including in government documents. The term, in his view, reflects anxiety about the clinical application using iPSCs – not just about whether it will work but also about its safety, even in the case of RPE, which is supposed to be relatively safe, due to the low number of iPS-RPE cells involved and their traceability in case the eye socket is pierced. Nevertheless, being the first in-human study, there was much apprehension about Takahashi Masayo's iPS-RPE application.

The views above all pinpoint practices that have been mis-recognised by the AJS. First, the national focus on iPSC research as an all-Japanese iPSC production-line loses out of sight the plight of its poster-patients. Second, rather than a united effort of Japan's best scientists, iPSC researchers were privileged by the JST and AMED. Third, rather than the collaboration with Asian countries, the AJS-policy strategised to export therapy products to lift itself out of its long-term economic slump. Fourth, rather than unity among iPS experts, many preferred independence, and some paved their own way to collaborate with overseas researchers. In addition, the *will* to successfully innovate was translated into regulation that *presumed* a form of therapeutic efficacy not recognised by the medical community. In other words, critical observers recognised the AJS's misrecognition of what was going on in practice.

Friction in the Coordination of iPSC Research

Apart from misreading its collaborative dimension, AJS misread the smoothness of iPSC research coordination and the workload of scientists.

As illustrated below, although the AJS enabled iPSC research through regulation and funding, the very coordinative functions assigned to CiRA also had disabling effects. For instance, the AJS encouraged the use and development of 'Japanese' standards through CiRA's leadership. Most work on iPSCs involved collaboration with CiRA, and requesting iPSC-lines from its stock entailed the use of CiRA's standards and methods, because 'CiRA takes responsibility for the genome analysis involved and the user research centre for the tumorogenicity studies' (Azuma and Yamanaka 2016: 37). Thus, if a research centre derives iPSCs from sources other than CiRA for therapeutic use, the centre in question and CiRA would also have to characterise and analyse the differentiated cells together. Established researchers expressed frustration with the dependence involved in this 'collaborative' arrangement.

The examples that follow concern the research practice around the first clinical iPSC application in humans with AMD and the centrality of CIRA's strategy regarding the global standardisation of its methods. The clinical application took place at RIKEN-CDB, Porto Island, in Kobe, in collaboration with the Foundation for Biomedical Research and Innovation (FBRI) – next door – and CiRA at Kyoto University. Masayo Takahashi, the PI of this clinical application of iPS-RPE, had moved from the University of Kyoto, as she found its Medical School's 'conservative attitude' to iPSC applications disagreeable. According to a researcher on the project, she was happy about the regulatory reforms that had been formally announced:

> For the new regulation, the three ministries [MoHWL, MEXT, METI] are working together. After the clinical research, we can have a clinical trial, which will be easier than before. We can still do the research at the Hospital as Advanced Medical Therapy [sentan yiryo], which includes insurance of both patients and doctors.
>
> (Ohashi, 29/03/2013*)

A great step forward, the researcher explained, is that the RM Act facilitates the outsourcing of cell processing:

> Before the doctors had to process the cells themselves. This [RM Act] is a big step forward, as doctors have no time to do this. Now they can outsource. This is why she set up a company [Healios], and asked the company to take care of it. It also made possible to take things outside Japan, but that is not the purpose of the law.
>
> (Ohashi, 29/03/2013*)

Using a company seems to take pressure away from the PI. But as collaboration with a company introduces new possibilities, other pressures appear, as we shall see below. Of immediate importance to the pilot study was the availability of a Cell Processing Centre (CPC) at IBRI. Collaborating with CiRA, Takahashi uses Yamanaka's assays to test the autologous (from the patient) iPSC–derived neuron stem cells to generate RPE. A 'scientific mediator', who mediates between scientists on regulatory and coordinative issues, explains the centrality of CiRA in their work:

> We know now that using iPSCs you can create neurons effectively. The standardisation of CiRA's way of working concerns good methods of differentiation and multi-potentiality and checking whether the iPSCs have cancerous effects. CiRA is now looking into the safety of the iPSC derived neuronal stem cells.
>
> (Takamatsu, 14/11/2013*)

This collaboration was crucial to the AJS vision, as it was widely thought that the first successful iPSC applications would become a global standard. The same mediator explained:

> The standardisation of iPS is a very important topic of discussion now. There are two ways of thinking about standardisation: having the cell line as standard or having the assay as standard. Yamanaka Sensei had wanted to use one iPSC line as a gold standard and compare others to it. But this did not go very well, also internationally. But now, Yamanaka wanted to make the assay he uses standard. But it turns out that Life Technology's assay is strongest [more competitive]. Life Technology is an assay from American reagent producer Invitrogen. Applied Biosystems merged with Invitrogen (ABI), forming Life Technology. Life Technology has internationally the strongest assays. The reason for this is that there is the International Stem Cell Bank Initiative (ISCBI), run by Austin Smith [*sic*] and others in the UK; they use the methods created by ABI. And this now is naturally applied to iPSC research.
>
> (Takamatsu, 14/11/2013*)

In the context of AJS, the first successful in-human application of iPS would have had to make use of 'the Yamanaka assay'. But the development of assays is part of a long-term process of trial and error and something that scientists find important to experiment with. Without having a say in the use of assays, Kimura, a decision-maker in FBRI, where the clinical application takes place, commented that FBRI could not be held accountable for the iPS pilot-study (Kimura, 7/11/2013*).

The translational researcher in charge, Hashigawa, further clarified this stance in relation to how CiRA frequently changed protocols:

> For example, last year we finished the study, and the results seemed to be pretty good. But suddenly [they said] 'Okay, we made a new plasmid. You have to change it.' We needed to use a patent from their medical company [Academia Japan] to improve the efficiency of iPSCs by inhibiting the p53 function [a tumor suppressor] – AJ006. We should be All-Japan, and use a Japanese patent. But then we have to throw away the earlier test! They don't care: it [the test] should have nothing to do with their [wish to publish a] paper. I just have to follow suit.
>
> (Hashigawa 1/11/2013*)

This researcher summarised the AJS as 'A bad idea, promoted by the bureaucracy'. 'The power of Yamanaka and Takahashi', in his view, 'should be limited to their own field', that is, basic research. This researcher was clearly upset about 'having to use Yamanaka assays and feeders [when testing patients], just because these have to become world standard' (Hashigawa 1/11/2013*).

The symbolic violence with which the AJS created a Yamanaka-discourse and a Yamanaka personality-cult in the media also seemed to transcend the wish of Yamanaka himself. In fact, Yamanaka had tried to resist the media-rituals and bureaucracy that had turned him into 'Mr iPS'. Hiroshima, a vice-president of Academia Japan, the company that licenses and brands CiRA/Yamanaka products, explained that it is the mission of Academia Japan to advertise and turn Japanese iPS into a global success. The wide use of 'Yamanaka assays', 'Yamanaka cell lines' and 'Yamanaka methods', he related, was crucial to the company. Hiroshima laments:

> Yamanaka does not care what happens to his knowledge, or whether people in the USA use it – he is more in the USA than in Japan. There, he can also easily use embryonic stem cells. This is problematic, as Japan Academia tries to market *his* methods widely.
>
> (Hiroshima, 2/12/2013*)

These comments illustrate some of the frustrations generated by the conflicting demands of scientists and managers under the political requirements of the AJS.

The AJS spirit behind the regulatory reforms had been able to facilitate iPSC research applications but not without creating frictions through the coordination requirements that are part of its All-Japan vision. International collaboration is to serve All-Japan, while All-Japan

coordination means a hierarchic leadership headed by CiRA. AJS caused frustration: Academia Japan found marketing 'Yamanaka' brands hard; scientists disliked having to use assays just because they are to be patented by Academia Japan; medical institutions did not want to take responsibility for applying assays; and, the world was not waiting for Yamanaka iPSC lines and assays.

Scientists' Options and Considerations When Planning Clinical Applications

As well as being framed by the AJS, the regulatory reforms were aimed at encouraging the commercialisation of regenerative medicine through the industry pathway for clinical trials using iPS and methods from the CiRA. The iPSC bank at CiRA provides cell-lines for industrial research (in accord with Good Gene, Cell and Tissue Practice, GCTP) and company sponsored clinical trials (PMDA 2021). Even though some researchers prefer doing clinical research using their own processed cells through the RM Act first, the research pathway, the AJS vision favoured working on clinical trials with the financial backing of companies through the industrial, PMD pathway, oriented to the marketing of regenerative therapies. The RM Act regulates the use in research or in medical procedures of unapproved regenerative medicine products in medical institutions. It has lower integrity standards compared to those of the PMD Act pathway. For instance, clinical research does not require GLP – only GMP-like conditions – and resultant data do not count towards clinical trial approval under the PMD Act (Azuma 2015). The RM Act pathway is also considered cheaper, though this may depend on MoHWL requirements for a particular application (Azuma 2015; Azuma and Yamanaka 2016). The examples below illustrate how the introduction of regulatory measures supported by the AJS has shifted conditions for conducting clinical trials in such a way that they encourage making use of CiRA's iPSC bank, collaboration with industry and an orientation on marketing rather than on scientific research.

EXAMPLE 1

In 2013, a list of planned iPSC applications was announced at CiRA. It included Jun Takahashi's project to treat Parkinson's Disease (PD) using iPSCs. Takahashi was one of the many researchers who supported the use of the so-called Yamanaka-factors, -assays and -culture media, but, according to Tanabe, a researcher on the

(CONT.)

project, they also liked to have the freedom to experiment with his own (Tanabe, 15/11/2013*). In 2014, Takahashi received permission from MoHWL to use iPSC-derived dopamine neurons (iPS-DN) in a *clinical study* for Parkinson's Disease, initially involving autologous iPSCs. His team had resolved problems related to the mass-culturing and safety of cells for transplants, and with the help of the large pharmaceutical company, Dainippon Sumitomo, he hoped to receive the go ahead for a clinical trial in 2015 through the PMD Act (Yamasaki and Arai 2014). But for scientifically unclear reasons, it was decided to use a different cell source for his *clinical study*: The major histocompatibility complex (MHC)-matched iPSCs from CiRA's homozygous iPSC stock. According to Tanabe, the application of iPS-DN was likely to create only a minor histocompatibility antigen (MHA), which is known to cause problems of immunological rejection much less often than that of MHC. The new situation created a dilemma for Takahashi: He had wanted to forge ahead with a clinical study using autologous iPSCs to create a proof of principle. But, conform the AJS-vision, it was decided that the clinical study had to use CIRA's iPSC-line stock, which made turned this into an allogeneic application. Tanebe explained that this decision had not satisfied the Medical School and Kyoto University Hospital (KUH): KUH had had in mind an autologous application, and it had major reservations about using allogeneic iPSCs (Tanabe, 12/02/2016*). Though some colleagues ascribed this reservation to the 'conservative' attitude of KUH, others said KUH feared the enormous reputational risk if the *first in human* applications of iPS-DN would fail.

EXAMPLE 2

Although the guidelines for clinical studies are thought to be less stringent than those for commercial clinical trials, the cell lines used in Masayo Takahashi's clinical pilot study of age-related AMD using autologous iPS-RPE, the world's first in human clinical trial, required whole-genome sequencing: the original cells, those differentiated, and those in vivo, all had to be sequenced, and a listing of all their mutations had to be provided to make sure that the cells were stable and safe. But once given permission, the cost for quality control amounted to 50 million Yen ($500k), which was covered by MoHWL. But in late March 2015, it was announced that the RPE-cells of Masayo Takahashi's second patient showed mutations, after which the clinical study was halted (IBRI 2015). By then, it had become policy to use allogeneic cells from Yamanaka's iPSC bank. Using autologous cells, it was generally argued, takes much time and is expensive. But Takahashi declared that it was she who had decided to stop the autologous pilot-study: not so much because of the mutations, which she had expected to occur, and not because she had been told

(CONT.)

to do so, but because of the new regulatory options supportive of clinical trials that had become available since November 2014 (Knoepfler 2015).

Other researchers, however, argued that in her place they would have continued to conduct *clinical research* first, but now using allogeneic iPS-derived RPE-cells to avoid genetic tumorigenicity. Paid for by CiRA and MoHWL, she could use CiRA's GCTP-accredited cells for clinical research, process them with Haelios, the company she worked with, and create a proof of principle. But Takahashi went ahead with the clinical trial supported by the pharmaceutical giant Sumitomo Dainippon Pharma Co. Of course, a colleague explained, industrial companies rarely make large investments for the sake of a scientific study alone (Kodama, 6/3/2016*). Industry likes to focus on factors related to safety of the production process and marketing; they like to have reliable starting materials (Umeda, 27/2/2016*).

The advent of the AJS-vision, then, has meant that an increasing number of scientists decided to use iPS in addressing conditions in collaboration with industry. As the ultimate aim was commercialisation and mass-production, there was a push not just for the clinic but also to collaborate with industry and to use 'off the shelf' allogeneic cells, preferably from Kyoto's iPSC stocks. To accelerate this effort scientifically, and to facilitate the ideal of All-Japan production, CiRA methods, resources and standards were shared.

The 'choice' between the pathways of clinical research and clinical trials depends on various factors, ranging from the planned medical intervention and the PI's location and collaborating hospital to the PI's relation with CiRA. Decisions involve complex considerations, including issues related to cell sourcing and use (autologous, allogeneic), access to funding (through government funding, industry investment, grants.), management (e.g., engaging a company or not), use of culture media, assays, vectors, etc., ease of acquiring authorisations, availability of facilities and their quality and the onerousness of regulatory pathways.

Constraints on the Conventions of the Science Community

Research leaders in main iPS-hubs, though aware of its benefits, expressed doubt that the vision of AJS was conducive to conducting basic science; they were acutely aware of rebellion against CiRA's central role in iPSC research and its standard-setting role. In particular, there was anxiety about the expected commercialisation of regenerative medicine and its distraction from basic science. Although working with industry may provide the funding and conditions for marketing to scientists working on regenerative therapies, such collaborations play havoc with 'traditional' modes of scientific research among academic colleagues.

The intense negotiations and skills involved in the acquisition of resources, the application for funding, permissions and certificates, maintaining relations with CiRA and accommodating the visits of audits and collaboration with hospitals take up much of a PI's time and can be nerve-wracking. Many iPS scientists prefer to leave such pressures to company CEOs if they can. Nevertheless, being tied to a company places constraints on the conventional activities of the scientific community. One scientist involved in an iPSC application, Kishi, explains:

> On Thursday-mornings all lab leaders have to present their work in Japanese and in English. Before this was very useful. But there is a lot of competition. Also, many have links with companies, so they are bound to secrecy. Some do not even want to reveal the molecules they are working on.
>
> (Kishi, 12/2/2016*)

Collaboration with companies encourages secrecy and hampers scientific exchanges. When I met scientist Sumida, who uses iPS reprogramming to create cardiomyocytes at Keio University, I asked him why he did not collaborate with another scientist, who engaged in very similar research. He said:

> I have a company and he has a company. We are in competition, so I need permission to collaborate.
>
> (Sumida, 29/11/2013*)

This scientist does not use CiRA's iPC reprogramming methods, both because he is tied to a patent used by the company he works with but also because in his view his vectors are better:

> The Sendai virus works outside of the nucleus, but Yamanaka uses an episomal plasmid, which in principle can be integrated into the chromosomes.
>
> (Sumida, 29/11/2013*)

As such integration could lead to tumourisation, Fukuda does not see any reason to give up the Sendai vector. In fact, he prides himself of spending only twenty-five days on reprogramming and differentiation – 'much faster than other methods'. When asked, Fukuda said he would also use the Sendai vector for clinical applications. But others who work with CiRA, such as Yanagishi from an Osaka-based research group that used CiRA iPSC lines to differentiate into cardiomyocytes, claim that the episomal plasmid is much better (Yanagishi, 3/12/2013*).

A number of researchers have experienced 'suffocating influence' through the AJS. Kishi aims to use iPS reprogramming to generate HLA- (human leukocyte antigens) and HPA- (human platelet antigens) controlled platelets for allogeneic transfusion. Kishi was diversifying his regulatory pathways for strategic reasons. He had begun preparations for a pilot-study at CiRA:

> The design of the iPS-pilot at CiRA will provide authority, and this will help with getting PMDA permission for the clinical research/trial. Using the same design, we can do a PI-led IND (Investigational New Drug) application.
>
> (Kishi, 12/02/2016*)

Kishi planned to make platelets using his own assays: 'You do not need to test for gen- mutations: we can use irradiation to eradicate any contamination.' This allowed him to work relatively independently. So, Kishi was going to use three different protocols for cell processing: one for a clinical pilot-study with KUH to produce platelets in the laboratory under GMP-like conditions, one for the generation of iPSCs with a specific HLA of GMP-grade cells for clinical investigation following the RM Act and one for large-scale production of GMP-grade platelets for industrial use with Megacaryon and Toray using the PDA Act. The combination of managerial and scientific work involved Kishi found taxing:

> Today I had to go to a managerial meeting with companies, then to a medical department meeting at the Medical School, and then we had team meetings. Now, I meet you and I also need to speak with my assistant about CPC as he needs to leave early.
>
> (Kishi, 12/2/2016*)

Apart from experiencing organisational difficulties, Kishi was also frustrated with AJS for what he regarded as ethical reasons: 'Despite the low level of blood donation in Japan, Japan does not support the production of platelets: they believe that it is a social problem.' Thinking that the US does not have these issues, Kishi was wondering whether to go for clinical trials in Japan or in the US. Europe was not an option, he reflected: it has good systems for blood donation.

The AJS-vision introduced new constraints and dilemmas in the work of scientists. First, scientists were pitted against one another insofar as they are encouraged to work with companies: competition between companies hampers scientific exchanges on research methods and academic collaboration. Second, the pressure to work with CiRA created

dilemmas: some scientists used their own vectors for reprogramming, because they worked in their research or because they had commercial contracts that require their use. Third, scientists missed chances to experiment with assays and to develop their own theories about suitable standards. And fourth, increased competition and pressure to commercialise has pushed scientists to adjust their research designs and to collaborate with industry. In short, researchers' attention to patient needs and scientific quality had shifted towards regulatory options and marketing.

Working with and around AJS Politics

The financial resources, responsibility and authority that came with research funding made CiRA vulnerable to critique and conflict about funding, priorities and methods. New modes of working affected the science itself.

Researchers have moved away from CiRA to other institutes for various reasons as a direct or indirect result of the implementation of the AJS-vision. Some objected to the hierarchic organisational structure at CiRA, rejecting political interference. Immunologist Shirai, who moved to Kobe, wanted to collaborate internationally in iPSC applications to counteract forms of cancer. Shirai explained why he left CiRA:

> CiRA is run hierarchically: the top decides what PIs do and with whom they collaborate. CiRA also tries to determine what happens in other labs that use iPS. This is because Yamanaka wants his own products standardized. But it is important to participate in the International Stem Cell Banking Initiative (ISCBI), to discuss how to define pluripotency. Yamanaka was not interested even though Japan paid for Japanese scientists to be part of it.
>
> (Shirai, 8/11/2013*)

The ISCBI aims at the global harmonisation of quality control, safety and efficacy of human pluripotent stem cell banks and their derivative cell therapy products. Shirai believed that CiRA was only interested in setting Japan's standards for the world to follow. His new institutional environment, by contrast, encouraged participation in this international initiative as it favours 'real' international collaboration.

Many researchers are disturbed by the focus on iPSC translation. For instance, one researcher of autologous iPS-derived MSCs for muscular skeletal conditions in, for instance, multiple sclerosis and rheumatism,

concluded that the method does not offer prospects to patients over the age of thirty-eight. For this reason, he moved to another research centre to concentrate on physical rehabilitation. This, he believed, would be crucial to the success of any cell therapy for muscular skeletal disorders (Hameda 28/3/2013*). Other researchers, such as Nakatsuji Norio, openly argued that a focus on iPS drug-screening is the most viable use of iPS methods, but he preferred to use less costly methods from biochemistry to emulate cell functions using biomaterials and tissue engineering (Nakatsuji 2015: 101). Tissue engineers, such as Tanida from IFMS, felt they were passed by unwisely: 'You need scaffolds to get the cells to work.' Tanida had developed a sponge to deliver growth factors to the affected tissue. Like other leading tissue engineers, such as Okano and Iwata from Tokyo, Tanida said, tissue engineers have lost out to medical professionals that translate iPSC research too early:

> Tissue engineering gets little grant money for research: it all goes to iPS. But researchers from CiRA come to my lab for advice …. I do not get money for that!
>
> (Tanida, 15/11/2013*)

Tanida decided to work on iPSCs to get funding that would also support his research. But he felt uncomfortable doing so, as his main expertise is making the cells work through scaffolds. He explained that 'assays and vectors are predetermined', criticising government policies and the Forum for Innovative Regenerative Medicine (FIRM) for mainly investing in large companies that will take the industry abroad to make profit. Other researchers echo this critique. Although Tanida supported a policy that encourages collaboration with industry, the AJS neglects small specialised companies even though 'you need them for ideas to create devices useful for both the lab and the science' (Tanida, 15/11/2013*).

Some researchers criticised AJS for the practical consequences of its emphasis on using the same vectors and assays, while others were more worried about scientific classifications of pluripotency and international banking standards. Cell biologists pointed out that science is universal and requires universal standards for measuring pluritpotency across the fields of hESCs and iPSCs (see also Nishikawa, Goldstein and Nierras 2008). Fierce supporters of this stance were leading researchers of hESCs. One expert lamented the ethical halo of iPSC research:

> Yamanaka should never have spread doubt about the ethics of ESC by comparing his daughter to an embryo. hESC-lines are the

> Gold Standard for iPS; they were there first. So you do need to research them.
>
> (Tsuji, 22/11/2013*)

Until iPSC research became the focus of attention, hESC-research had slumped, due to strict regulation and ethical issues of oocyte donation (Slingby et al. 2004). A leader in hESC-research and regulation commented that policy-makers decided rather late that encouraging hESC-research would support the iPS venture (Umeda, 27/2/2016*). Another leader of hESC-research criticised CiRA's iPSC bank as a waste of money and efforts, because allogeneic applications still require immune suppressants. Instead, he recommended emulating Pfizer's example:

> Just use one good cell-line can produce lots of cells for all patients all the time. This solves both issues of costs and storage. Later you can work on further technological improvements regarding assays, efficacy – in the meanwhile you use immune-suppressants. You can always switch to iPS afterwards.
>
> (Tsuji, 22/11/2013*)

Many scientists were in favour of conducting hESC research but did not think Japan's regulatory climate made it viable.

Another reason for opposing AJS related to the need for international industrial standards for production. Hashigawa, from Kobe's FBRI, did not just work on clinical applications of iPS research but also on those of MSCs, T-cells and gene therapy. He worked in both laboratory and clinic and acted as business consultant on international standardisation. Hashigawa said that he could not find international collaborative partners in Japan due to the national focus of the AJS. This is why Hashigawa and his team had started to work on new industrial standards in the context of the International Alliance for Biological Standardization (IABS) (cf. Abbot et al. 2018) and the ISCBI. He compared it to ICH-guidelines for good clinical practice in the pharmaceutical industry, providing guidelines for GMP and risk-management in regenerative medicine:

> There are some rough standards for classifying pluripotency, but there are no standard measures for infections: In a chemical drug, it is very easy to disinfect, but we cannot kick out any germ out of a cell or a biological . . .. You cannot use the same template as for drugs. But with the use of IT, sensing technology, and other methods you can measure all the parameters and mediums to check the metabolome, PH-sensors, CO2-sensors, and so on. By combining the results, we can assure the quality of the product.
>
> (Hashigawa, 4/3/2016*)

In the meantime, PMDA leaders had also realised that the international isation of regenerative therapy necessitates the creation of such a system. But there are researchers who object to the hijacking of Japanese science through companies that move abroad. One research-leader, for instance, fiercely opposed the collaboration of Takahashi Masayo with Healios, believing its establishment of a branch in the US was an omen of selling out iPS to the US (Yamaguchi, 14/11/2013*). Other researchers, however, claimed that a nationalist emphasis on the Japaneseness of iPS had set the scene for the scandal around STAP (Stimulus-triggered acquisition of pluripotency)-cells at RIKEN-CDB (Tsuji, 05/2/2016*; Takehara, 26/2/2016*), which involved the attempt to create pluripotent stem cells by applying stress to ordinary cells (Cyranoski 2014). For a few weeks, STAP-cells shook the world, as it was thought that they were even easier and quicker to produce than iPSCs (Suda 2015). Its dismantling left RIKEN-CDB considerably weakened (Normile 2015). In fact, the STAP scandal resulted in the closure of the CDB (Osaka, 27/1/2016*) and its and reassignment of many of its former labs into a new institute, the Centre for Biosystems Dynamics Research.

The AJS has made iPSC research central to Japan's quest for 'regenerative therapies'. Funding and infrastructure support emphasised iPS over other branches of science such as tissue engineering and hESR. AJS' encouragement of collaboration with industry took resources away from basic research and hampered collaboration with small specialised companies. Many researchers used the AJS-vision as an opportunity, but others viewed it as a hindrance. Of the latter, many grudgingly adjusted their research focus and methods, but others moved to different fields. There was conflict especially around the focus on Japan. Some researchers advocated for CiRA's international leading role, while others emphasised the importance of more fundamental collaboration in industrial and scientific standard setting, while again others criticised AJS for making iPSC research vulnerable to profiteering companies that go abroad.

The Politics of Regulatory Redemption as a Politics of Misrecognition of What Is Going On

Insight into the AJS politics of regulatory redemption sheds light on how the regulation of regenerative medicine misrecognised the scientific reality effected by the regulatory reforms as collective and collaborative, as a Japanese scientific feat and an attempt to save the world to the glory of

Japan, as a panacea for an ageing society and as rescue for patients disabled by serious medical conditions ranging from AMD to PD.

We saw how the AJS matched the regulation with its organisational policies but could only do so by misrecognising what was going on in the field. Rather than a united effort of the 'Japanese Research Team' on the road to scientific success, we saw the rise of a regulatory framework for clinical trials whose approval mechanism presumes the success of applications developed in the hierarchically organised, privileged iPS-hubs. In addition to the hurry to bring iPSC therapies to the clinic, we also saw an insistence on branding 'Yamanaka methods' as knowledge assets, a move that frustrated many of those involved in the research applications to the extent that hospitals distanced themselves from taking responsibility for applying them.

The new regulation aimed to facilitate both clinical research and clinical trials in the field of regenerative medicine and beyond. Although the regulation may have become more 'permissive', it is no less complex. It required researchers to acquire expertise in a wide range of areas related to the new politics of cell-sourcing and use, access to funding under AMED, extended administrative management, the tactics of using culture media, assays and vectors politically, becoming savvy about acquiring knowledge assets, the complex rules for applying for authorisations, the negotiation of regulatory pathways and the lobbying for the required laboratory-facilities. In the light of the AJS vision of global success of iPSC research and the wide range of skills and efforts needed for clinical iPS applications, scientists were pushed into the arms of industry and the application of 'off- the-shelf' allogeneic cells using CiRA's iPSC stocks. Although collaboration with industry might mean financial and managerial support, the pressure can distract their focus on research, and contracts are likely to include secrecy clauses that shackle scientific discussion. The various rules introduced around iPSC line usage, assays, feeders and culture media led to obligatory collaboration, on the one hand, and precluded possibly fruitful exchanges with other scientists, on the other. As a result, important scientific discussions stopped taking place, pushing scientists to join more internationally oriented institutions and discussions. As it focused on presenting the world with life-saving regenerative therapies, the AJS-vision blinded its proponents to the scientific and professional needs of researchers, without reflection on whether patient needs were best addressed through iPS or other technologies.

All in all, an orientation to basic research, the cultivation of a wide range of life-science disciplines in the field of regenerative medicine and collaboration with specialised companies made space for a research orientation to clinical iPSC applications in collaboration with large industry and venture capital. The reconfiguration of funding and resources, the leadership of CiRA and the obligation to follow Yamanaka methods had the effect of alienating other leading researchers in the field of regenerative medicine. Scientists in iPSC hubs said they enjoy conducting scientific research and take pride in contributing to their team, to science and to human health. If needed, they spend evenings and weekends to attain their goal. They like getting their heads around all aspects of their research tasks, exploring alternative methods, honing their skills and getting feedback from colleagues. Becoming part of an iPS production line for Corporation Japan, however, was not what most of them had signed up for.

The imperative to translate (Harrington and Hauskeller 2014) research outcomes into clinical applications forces scientists to make a strong case for their experimental models to compete for funding. Although regulation for clinical iPS trials has become more permissive, there is an extreme pressure to be successful, as failure would reflect disastrously on the institutions involved and, crucially, on Japan's regulatory system. It would also mean letting down the 'Japanese Research Team' and the death-knell of Japan's already weakened regulatory immunity. The pressure on scientists to engage in the clinical translation of iPS research, on the one hand, and the stringent checks and verification of the research protocol, on the other, create great pressures along the translational pathway. The resultant rollercoaster of forced promise and necessary failures together with the scientific and organisational constrictions imposed by AJS cannot be conducive to the kind of scientific understanding that Yamanaka had acquired before he became Japan's scientific saviour.

Nevertheless, since the introduction of the regulatory reforms, now ten years ago, there has been a gradual move away from overhyping iPS and other regenerative medicine products. PMDA review reports (PMDA undated) show that the clinical studies that were used to justify conditional approvals suffer shortcomings. Cyranoski et al. (2023) show how deficiencies in trial design undermine the rationale for both on-market clinical use and insurance reimbursement, rendering it unclear as to whether trial effects (including severe adverse reactions and deaths) are

a result of biomedical intervention or the, often, invasive operation itself. Furthermore, the long period of post-marketing studies that proponents of conditional approval believe can generate proper evidence usually lacks randomisation, blinding and independent analysis, potentially lengthening a period of experimentation. There is evidence that the PMDA has started to take a stricter stance on regenerative medicine product approvals, demanding more evidence and giving far fewer regenerative medicine products conditional approval (Nomura 2021; Cyranoski et al. 2023). This makes the question of whether accelerated regulation helps company profit, scientific knowledge or patient health even more poignant. Posing it becomes crucial to the issues of why and how a society might want to fund and support the science community. If doubts are shoved aside amidst feverish global competition, one might have to ask what countries that compete by brokering their research regulation to their own advantage have to offer to patients. What do patients want, and more importantly, need?