WORKING PAPER OF RISING POWERS RESEARCH PROJECT:

REPORT ON JAPAN AND REGGENERATIVE MEDICINE

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Report on Japan and regenerative medicine

Introduction

Japan has recently attracted substantial international interest with regards to its engagement in biomedical innovation. Until the mid 2000s, the country had attracted limited interest, but several developments have prompted changes to the landscape of biomedical innovation in Japan. First, Shinya Yamanaka's discovery of iPS cells in 2007, led to an award for the Nobel prize in medicine and substantial public support for stem cell research. Second, the Japanese government has been trying to support the development of knowledge intensive industries, and has identified the health care sector, as a means to rejuvenate its long stagnant economy. Third, the Liberal Democratic Party (LDP), newly elected into power in December 2012, has strongly supported stem cell research as part of a stimulus package aimed to lift the Japanese economy out of recession, with a commitment of 21.4 billion yen (over 220 million US dollars) this year for research in this field.

While critics have called attention to the need to temper the heightened expectations for regenerative medicine, the recent transformation of the landscape for Japanese stem cell research is important, not only because developments at the forefront of research puts to question the possibilities and limitations of research in this field. It also explores the flexibility and rigidities of domestic institutions, and the degree to which the domestic system coopts foreign institutions in favour of domestic institutions in a global research environment. Further, this research attempts to explore the evolution of multilevel governance, identify the role of governance structures at different territorial levels, and their impact on biomedical innovation in Japan. Later – as part of a broader agenda to reposition Japan within the global environment of biomedical innovation – this work hopes to articulate how Japanese governance structures have shaped and been shaped by biomedical governance structures overseas, particularly in the emerging Asian economies such as China and India.

Regenerative medicine

Regenerative medicine refers to an interdisciplinary field of research and therapy that focuses on the repair, replacement or regeneration of cells, tissues and organs to restore impaired function.[1] Two large concentrations of work in this field include cell therapy and tissue engineering. The potential for industrial development span a wide range of areas, such as biomaterials and scaffolds for tissue engineering; stem cell transplantation products; cord banks, cell processing centres, culture media, and other

[1]Heather Greenwood, Peter Singer, Gregory Downey, Douglas Martin, Halla Thorsteinsdóttir, Abdallah Daar, "Regenerative Medicine and the Developing World," *PLoS Med* 3, no. 9 (2006): e381.

operations that support this field; as well as materials for drug discovery. Innovation in this process of commercialization may be differentiated into two types: radical innovations led by new business models that will replace existing medicines and medical devices; and incremental or platform innovations in products that support research in regenerative medicine.

Regenerative medicine in Japan

Japan is an important contributor to global research in regenerative medicine. The country is equipped with leading research centres such as the Institute for Frontier Medical Sciences and the Center for iPS Cell Research and Application at Kyoto University (CiRA) at Kyoto Univerity, as well as the RIKEN Center for Developmental Biology in Kobe. In 2006, the government announced that while research in parts of the body such as the heart, liver, kidney, pancreas, retina, inner year, and digestive tract were still at the basic stage, research in skin, blood vessels, bone, cartilage, blood, cornea and nerves had moved to the clinical research stage—supported by government initiatives to support research in regenerative medicine.[2]

In 2012, the market for regenerative medicine in Japan was estimated at 12 billion yen (approximately 116 million US dollars). However, as of March 2014, there are still only two products currently approved for reimbursement under Japan's universal health insurance system (engineered tissue, Jace, and engineered cartilage, Jacc, both by Japan Tissue Engineering, Co.). The market is dominated by a range of self-pay treatments not covered by insurance, such as cancer immunotherapy, regenerative dentistry, and cosmetic medicine (such as the injection of dermal fibroblasts).[3] There has been a notable increase in the number of new companies entering this field, diversifying from sectors such as pharmaceuticals, food, and machinery. Most firms in Japan are engaged in the manufacture and sale of products that support research in regenerative medicine, such as culture media, reagents, and raw materials – rather than therapies.[4] Observers see the development of these related/supportive industries as an essential process of developing commercial therapies in regenerative medicine.

Winning in research and losing in business?

A much discussed concern for Japan, at least at the domestic level, is that whilst the country has very high levels of endogenous technological capacity in medical science,

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[2] Ministry of Education, Culture, Sports, Science and Technology (MEXT), *Wagakuni no Saisei Kenkyū ni tsuite* [Regenerative Research in Japan] (Tokyo: MEXT, 2006), 1.

[3] Ministry of Economy, Trade and Industry (METI), *Final Report on the Commercialization and Industrialization of Regenerative Medicine* (Tokyo: METI, 2013).

[4] Shigemi Takeuchi and Nobihisa Asano,"Saisei Iryõ no Genba kara [From the Field of Regenerative Medicine," *Right Now!* February (2007), 16-20.

the country's capacity to commercialise this capacity is weak. For example, Japan has the second largest markets in the world for pharmaceuticals and medical devices. Yet it is a massive net importer of both, and exports much fewer products compared to other developed countries such as the United States or Britain. Japan's relative weakness in translating its research capabilities to the clinic or to business is often associated with enduring problems in the domestic system. The following pages will discuss the financial system, the research and education system, and the role of government, in turn, in shaping this sector.

Financial system

One oft-cited problem is Japan's financial system. As Hall and Soskice have argued, market-based economies support more radical innovations, as a range of financial organizations can undertake risk and fund projects based on market selection. By comparison, bank-based economies – such as Japan – support incremental innovations, as banks acquire the experience and capacity to assess risk in projects for funding.[5] Crucially, Japan's financial environment long did not support small firm entrepreneurship to pursue radical innovation. Given the additional lending risks involved, Japanese SMEs were often disadvantaged in securing credit from large banks, and financed their operations through private banks dedicated to SME financing[6] and from government banks.[7] In addition, Japanese SMEs suffered from a serious lack of venture capital in the home market, as most Japanese venture capital firms were affiliated with banks, and seldom invested in new businesses or startups. This scarcity of venture capital further limited potential entrepreneurs of medical devices from pursuing their business ideas.

Following the collapse of the "bubble economy" at the end of the 1980s, Japan's financial system experienced considerable reforms toward a more market-oriented model. While the Japanese venture capital market developed alongside the creation of new stock exchanges for SMEs in the late 1990s, the market remained less developed compared to those of the United States or Europe. This relative lack of venture capital continued to prevent the growth of innovative sectors in Japan. Even in 2010, American and European venture capital firms respectively invested $23.3 billion and $5.1 billion, compared to the $1.4 billion invested by Japanese venture capital firms.[8]

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[5] Peter Hall and David Soskice, *Varieties of Capitalism: The Institutional Foundations of Comparative Advantage* (Oxford: Oxford University Press, 2001), 35

[6] Credit cooperatives and credit unions.

[7] These include Japan Finance Corporation for Small Business, National Life Finance Corporation, and Shōkō Chūkin Bank.

[8] European Private Equity and Venture Capital Association, *EVCA Yearbook* (Brussels: EVCA, 2011), table 9; National Venture Capital Association, *Yearbook 2010* (New York: Thomson Reuters, 2010), 25; Venture Enterprise Center, *Survey on*

The internationalization of capital, however, suggests that Japanese firms could have secured financing outside Japan, and that the greater bottlenecks to substantial innovation likely lay elsewhere.

Research and education system

Another barrier to translation lay in the research and education system. For decades, Japanese universities had supplied a steady number of science and engineering graduates, well above the OECD average. The universities also emphasized applied over basic research, which was suitable in an economy trying to nurture graduates capable of adopting and improving upon existing knowledge. The same qualities, however, were not necessarily conducive to generating breakthrough innovations. A more problematic issue lay with the *kōza* system, in which research professors ran hierarchical research teams comprised of associate and assistant professors as well as postdoctoral researchers.[9] The vertical rigidities of these research groups prevented, not only interdisciplinary research, but also hindered the commercialization of original, independent research from early-career researchers. Innovation in Japanese universities also suffered from low mobility among its researchers, and limited collaboration with industry.

It should also be mentioned that R&D for regenerative medicine, required not only greater collaboration between academia and industry, it also required continuous interaction between engineers, physicians, and other academics specializing in various fields of medicine. Innovation in regenerative medicine occurred between rather than within organizations, between rather than within a given discipline. Japanese organisations had previously pursued, insular, autarkic forms of R&D, but advances in science, technology and medicine – in areas such as regenerative medicine – has required the transition to a more network-based system of innovation. Indeed, leading Japanese universities and research organisations engaged in research in this field, particularly in Western Japan, are moving in this direction.

Healthcare system

The domestic health care system also requires mention, as the national context remains important in biomedical innovation despite globalisation. After all, for the most part, biomedical R&D cannot be isolated from the local organization of medical practice. Features of local healthcare systems such as universal health care; number of hospitals and clinics; and physician networks have shaped innovation. Japan's health care system has particularly faced the challenges of an ageing and declining population – especially in relation to cost containment.

Trends in Venture Capital Investment 2010 (Tokyo: Venture Enterprise Center, 2010), 13.

[9] Yoshinori Kumazawa, "Need for Change in Japan's Universities," *Nature* 388, no. 6639 (1997): 223; Cyranoski, David, and I-han Chou, "Winds of Change Blow Away the Cobwebs on Campus," *Nature* 429, no. 6988 (2004): 211-212.

Japan's universal health insurance, effective since 1961, helped support a large domestic market for medical products, whether pharmaceuticals or medical devices. Under this system, Japanese citizens have paid up to 30 percent of total medical care expenditures. Japan's fee-for-service system, tended to incentivize physicians to prescribe many examinations, to recoup the cost of expensive medical equipment that would attract patients to their practices.[10] Japan also had among the highest numbers of hospitals compared to other developed countries.[11] Such high figures led not only to high costs and coordination efforts to conduct clinical trials and the creation of complex, multi-tiered distribution networks, but also to the development of niche products customized to specific clients, which did not necessarily translate overseas.

It might be noted that Japan could support a much larger market for regenerative medicine if the government expanded the coverage of treatments for which mixed billing is allowed. Japan has a small market for private health insurance coverage that runs parallel to statutory insurance, but this coverage is generally limited to cash benefits for hospitalization or lump sum payment for surgeries. Indeed, over the past year, there has been ongoing discussion among major and mid-tier Japanese insurers to include regenerative medicine in such packages, or to offer specific products tailored to regenerative medicine. Japanese patients who have opted to purchase non-covered treatments have so far had to pay for their entire medical expenses out of pocket. With little demand for non-covered treatments, Japanese firms have faced significant barriers and limited incentives to develop breakthrough therapies in the domestic market. Re-evaluation of the practice of mixed billing is currently under debate.

In connection with this discussion of insurance, it is worth noting here that regenerative medicine treatments, particularly in the area of uninsured, private treatments, has encouraged the growth of private clinics in Japan offering stem cell treatments to self-paying patients – whether domestic or foreign. In fact, observers have raised concerns over Japan becoming a "therapeutic haven" for willing participants of experimental stem cell therapies – whether domestic residents or overseas stem cell tourists.

While academic stem cell research is regulated in Japan, private stem cell therapy has been effectively unregulated. The Japanese government allows for regenerative medicine treatment if administered under one of the following three categories i) approved therapies (which have undergone clinical trials) for insured medical treatments; ii) approved therapies (for clinical research) for insured medical treatments; iii) and therapies offered under a physician's discretion for uninsured treatments. The latter category is essentially a legal loophole for therapies that do not fill the first two categories and are of highly questionable safety and efficacy, and has

[10] Naoki Ikegami and John Campbell, *Containing Health Care Costs in Japan* (Ann Arbor: University of Michigan Press, 2006), 162-167.
[11] OECD, *OECD Health Data* (Paris, OECD, 1991-2012).

essentially allowed for the opening of unmonitored stem cell businesses. These include foreign firms, such as the Korean biotechnology company RNL Bio, which has sent over 10,000 patients to clinics in Japan and China to receive stem cell injections to treat a range of ailments, from diabetes, Alzheimers to arthritis.[12]

A NHK documentary recently reported that over 10,000 Japanese patients have experienced stem cell therapies at over 100 clinics across Japan.[13] Increasingly fearful of the potential break that a therapeutic tragedy might cause on the country's highly regarded academic stem cell research, these developments have also stimulated the government – particularly influenced by the academic community – to introduce radical reforms and develop regulation more suitable to support the development of a regenerative medicines sector in Japan.

Role of government

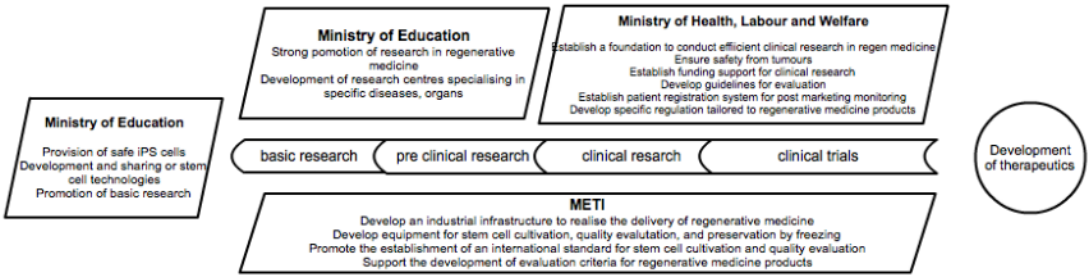

Figure 1. Japanese government bodies that govern the development of regenerative medicine

As Figure 1 above illustrates, three major government bodies govern the regenerative medicines sector. In principle, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) governs basic research to preclinical research while the Ministry of Health, Labour and Welfare (MHLW) governs later phases of development that often take place in industry. In the meanwhile, the Ministry of Economy, Trade and

[12] David Cyranoski, "Stem Cell Therapy Takes Off in Texas," *Nature* 483, no. 13-14, March 2012, http://www.nature.com/news/stem-cell-therapy-takes-off-in-texas-1.10133 (accessed 7 July 2013).

[13] NHK, "Tsuiseki, Saisei Iryō Toraburu [Investigation into Troubles in Regenerative Medicine]" 25 June 2013.

Industry's (METI) role has been to support the commercialisation of this sector throughout the development process.[14] In practice, however, governance has not been as cleanly divided; research funding, for example, has often been criticized for overlapping and lacking in strategy. In response, the government has recently drafted plans to create a Japanese NIH, modeled after the National Institutes of Health in the United States, to unify, clarify, and strengthen the efficacy of government policy toward biomedical innovation.[15] The so-called Office of Healthcare Policy, established in February 2014, however, has recently faced considerable public and media criticism as a much smaller, watered down initiative not comparable to its US counterpart.[16]

Policy support

Over the years, the government had tried to introduce policies that would harness Japan's endogenous technological capabilities in medical technology and support the development of a medical industry, which would in turn help to rejuvenate the long stagnant domestic economy. A combination of government measures began to support regenerative medicine from the mid-1990s. For example, the Japan Society for the Promotion of Science launched its project on regenerative medical engineering in 1996 as part of its Research for the Future program. Support for regenerative medicine was also included in the government's Millennium Project launched in 2000, a national research project that aimed to pioneer frontier technologies. In 2008, the government further introduced a super special consortia scheme to facilitate the commercialization of biomedical innovation via government funds, tax breaks, and looser regulation. Of the 24 projects selected for support, six relate to regenerative medicine.[17]

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[14] MEXT, "Special Report 2: New Developments in Regenerative Medicine and Drug Development Using Human iPS Cells," http://www.mext.go.jp/b_menu/hakusho/html/hpaa201301/detail/1338110.htm (accessed 6 March 2014).

[15] Cabinet Secretariat, "7th Industrial Competitiveness Council: Basic Outline of the Japanese NIH and Medical Excellence," 23 April 2013, available at http://www.kantei.go.jp/jp/singi/keizaisaisei/skkkaigi/dai7/siryou06.pdf, accessed 26 May 2013.

[16] Cabinet Secretariat, Office of Healthcare Policy http://www.kantei.go.jp/jp/singi/kenkouiryou/ (accessed 6 March 2014).

[17] Cabinet Office, "Sentan Iryō Kaihatsu Tokku (Sūpā Tokku) Saitaku Kadai no Ichiran [List of Selected Projects for Super Special Consortia for Medical Care]", available at http://www8.cao.go.jp/cstp/project/tokku/081117tokkusaitaku2_1.pdf (accessed 1 June 2013). Researchers leading the projects are: Shinya Yamanaka, Kyoto University; Eisuke Okano, Keio University; Mitsuo Okano, Tokyo Women's University; Tsuyoshi Takato, University of Tokyo, Misako Nakashima, National Center for Geriatrics and Gerontology; and Shinichi Nishiawa, Foundation for Biomedical Research and Innovation.

Regulatory developments

While scientists had previously complained that excessive bureaucracy in Japan seriously undermined stem cell research in the country,[18] Yamanaka's discovery of iPS cells accelerated reforms to facilitate research in this field. While clinical guidelines for stem cell research were established in 2006, these were revised in 2009; dedicated areas for R&D in advanced medicine has been created; and the Pharmaceutical and Medical Devices Agency has enhanced its efforts to bolster its review capacity and credibility through organizational reform, training and networking. As mentioned earlier, government reforms have taken further momentum with the Liberal Democratic Party's rise to power in December 2012, reversing the austerity of the previous administration with a commitment of 110 billion yen to iPS research over the next decade.[19] Perhaps the most transformative change were the two laws governing regenerative medicines passed in November 2013; the revised Pharmaceutical Affairs Law which allows for accelerated conditional approval has particularly attracted international attention.

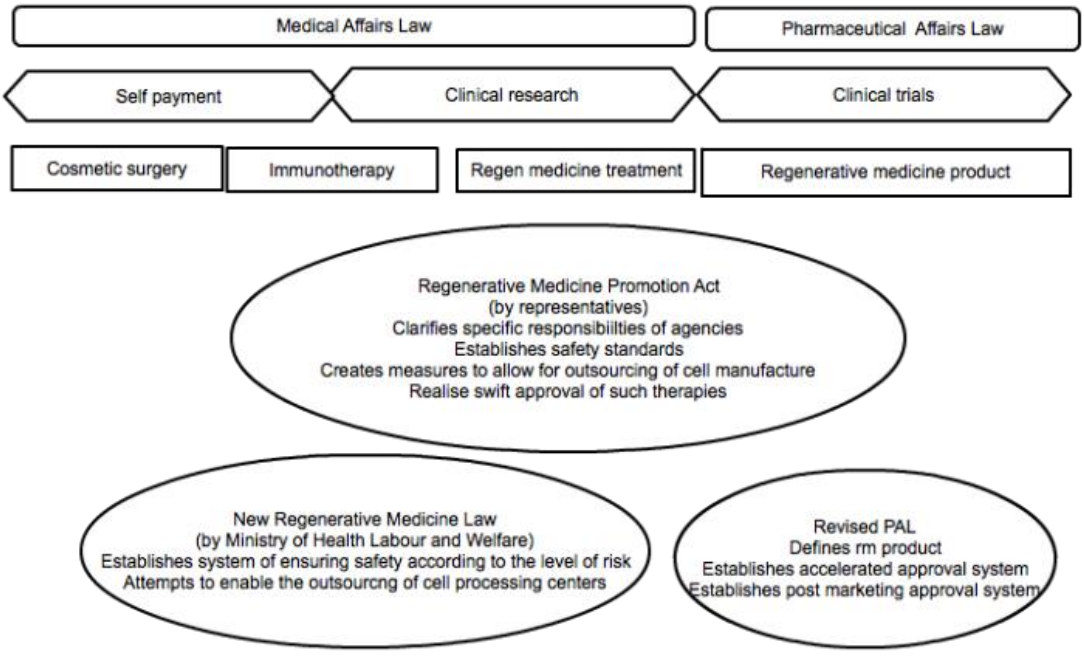

Figure 2. New Japanese legislation on regenerative medicine

The two new laws governing regenerative medicine that have attracted international attention are the New Regenerative Medicines Law and the revised Pharmaceutical Affairs Law (that latter is tentatively named the Law Governing Pharmaceuticals,

[18] Norio Nakatsuji, "Irrational Japanese Regulations Hinder Human Embryonic Stem Cell Research. *Nature Reports Stem Cells*, August 2007.

[19] "iPS Kenkū ni 1100 oku en Josei e [MEXT to Provide 110 billion yen to Support iPS Research]" *Asahi Shimbun*, 11 January 2013.

Medical Devices and Others). Both laws follow the Regenerative Medicines Act, which essentially clarifies the national intent to develop effective regenerative medicine laws.[20] Indeed, regulators are quick to note that the recent reforms are not about deregulation, but the reformulation of regulation tailored to the characteristics of regenerative medicine products.

The first of the two laws, the New Regenerative Medicines Law, is conceptually based on the Medical Affairs Law, governs medical practitioners and effectively closes the controversial loophole that allowed medical practitioner to administer cell therapies for clinical use. The new law requires all medical practitioners to gain consent for regenerative medicine treatments prior to administration. The level of approval required is differentiated according to three grades of risk: the first (considered high risk, involving the use of embryonic stem cells or iPS cells, for example) requires approval by an external, special designated approval committee and the Minister of Health; the second (medium risk, involving the use of somatic stem cells, for example) requires approval by the external, special designated regenerative medicine committee; and third (low risk, involving cell cultivation, for example) requires approval by an internal regenerative medicine committee. In addition, the New Regenerative Medicine Law will allow medical institutions to externalize and outsource their in-house cell processing centers, which is hoped to raise the efficiency of cell cultivation.

The second law refers to the revised Pharmaceutical Affairs Law, which governs corporations and the development of safe and effective therapies. The key development under the new law is the conditional approval of potential therapies after initial safety tests. This idea is to deliver potential therapies that are deemed safe but perhaps ineffective, as quickly as possible to patients who do not otherwise have viable therapies. The manufacturing and marketing approval for regenerative medicine currently requires firms to pass a clinical study phase and clinical trials; the new law will eliminate the third phase of clinical trials and approve therapies if safety and efficacy can be "surmised" in three years (rather than six). The products are required to establish safety and efficacy within a designated time, and up to a maximum of 7 years, after which their marketing approval will be further extended or withdrawn.[21]

It should be mentioned that one of the greatest impediments to biomedical innovation in Japan – whether pharmaceutical, medical devices, or regenerative medicine – has remained the high cost and lengthy time involved in the clinical trial process. It should be mentioned that under Japanese regulations, regenerative medicine currently falls under the category of medical devices until the new legislation takes effect in November 2014. Taking the example of medical devices, for example, the particularly

[20] METI, "On the New Regenerative Medicines Law," http://www.lifescience.mext.go.jp/files/pdf/n1183_09.pdf (accessed 6 March 2014).
[21] Ibid.

high barriers in Japan have led to a substantial device lag and device gap. In terms of the device lag, or time elapsed since first approval in another regulatory regime, in 2009, devices in Japan were approved 36 months after approval in the United States.[22] The "device" gap refers to devices used in other markets that are not introduced in Japan. In fact, the medical devices market in Japan was distinct for the relative unavailability of cutting edge technologies. Even in 2010, for example, the ratio of the number of devices available in Japan, Europe, and the United States, was 1: 1.9: 2.3.[23]

In the past, government efforts to upgrade the domestic institutional environment have been considerable from a domestic standpoint but limited in global perspective. For pharmaceuticals and device evaluation, for example, the government rapidly increased the number of staff, from 121 in 1996 to 605 in 2009 – which compared to 4,911 at the FDA.[24] Moreover, many reviewers have not been fully qualified to make safety and efficacy evaluations on medical products, which are increasingly complex and built upon interdisciplinary knowledge. Many reviewers were particularly reluctant to approve innovative therapies, as – unlike their FDA counterparts – Japanese reviewers were not indemnified for potential device failures. The cost, time, and uncertainty involved in the regulatory approval process posed severe disincentives to develop devices in Japan.

The creation of the two new laws governing regenerative medicine have been regarded as a major change, particularly as in the past, those engaged in developing regenerative medicine have faced even higher barriers to commercialization. Between 2001 and 2011, firms developing cell- or tissue-based products were required to conduct additional safety tests (*Kakunin Shinsei*) to gain permission to pursue clinical trials. In reality, few firms passed this stage; in fact, during this decade only one product was eventually accepted (Engineered tissue, Jace, by Japan Tissue Engineering in 2007). Partly in response to severe criticism from academia and industry, the government introduced an alternative procedure in 2011. Academic researchers and SMEs, in particular, have been asked to enter a new consultative process (*Yakuji Senryaku Sodan*), as a more accessible safety procedure that precedes clinical trials.[25]

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[22] Ministry of Health Labour and Welfare, "Iryō Inobēshon ni kansuru Shiryō [Information relating to Medical Innovation]," 19 May 2011, p. 15, available at http://www.mhlw.go.jp/stf/shingi/2r9852000001f1rr-att/2r9852000001f288.pdf (accessed 26 May 2013).

[23] L.E.K. Consulting, *IVD Review Time Clock Surveys, 2010, 2011*, American Medical Devices and Diagnostics Manufacturers Association, available at http://www.amdd.jp.

[24] Pharmaceutical and Medical Devices Agency (PMDA), *Annual Reports* (Tokyo: PMDA, 2004-2011).

[25] Mime Egami, "Saisei Iryō no Sangyōka to Kadai Kaiketsu ni Muketa Doryoku [Efforts to Resolve Barriers to Commercialisation in Regenerative Medicine," in

Intellectual property system

While Japan's patenting system in the post-1945 period prioritized technological diffusion at the expense of rewards for individual inventors, Japanese patent law was amended alongside international negotiations with the United States and Europe over subsequent decades as Japan acquired greater technological capacity. Product patents for pharmaceuticals and medical devices were recognized in 1976. In the 1990s, the government adopted a "pro-patent" policy, which, similar to earlier initiatives in the United States, was intended to foster innovative capacities, particularly in high technology sectors. These patent reforms included accepting applications in English (1995); ending third-party opposition to patent issue (1996) and recognizing the doctrine of equivalents (1998). The criteria for novelty were also made more stringent.[26]

Patent value can vary across nations and Japan's innovative capacities are difficult to assess, solely on the rising number of domestic patents. It may be worth noting that, Japanese inventors have been much less likely to patent their medical innovations abroad compared to American or European inventors. Between 2002 and 2006, for example, Japanese inventions in regenerative medicine accounted for roughly 63.2 percent of patents for therapeutics in Japan, but 11.2 percent and 13.1 percent in the United States and Europe, respectively.[27]

There is one further comment with regard to an issue with patents and incentives for innovation in regenerative medicine in Japan. Regenerative medicine products in Japan did not benefit from patent term extensions until this year. On 26 February, the government announced that, similar to pharmaceuticals, patent extension can be granted for up to 5 years; for the duration between registration for clinical trials or patent application and manufacturing approval (whichever is the longer).[28]

Specific case study, macular degeneration

Monozukuri Gijutsu kara Miru Saisei Iryō [Regenerative Medicine from the Standpoint of Manufacturing Technologies], CMC, ed. (Tokyo: CMC, 2011), 261-62.

[26] Kazuyuki Motohashi, "Nihon no Tokkyoseido to Kigyō no Inobēshon Katsudō: Puropatento Seisaku no Saihyōka [the Japanese Patent System and Innovation Activities among Firms]," *Hitotsubashi Univerity Innovation Research Center Working Paper* 03, no. 06 (2003).

[27] Japan Patent Office, *Tokkyo Shutsugan Dōkō Chōsa: Saisei Iryō* [Report on the Situation regarding Patent Applications: Regenerative Medicine] (Tokyo: Japan Patent Office, 2009), 7.

[28] Ministry of Economy, Trade and Industry, News Release: Summary or Patent Term Extension for Regenerative Medicine Products, 26 February 2014.

One project that has gained considerable international attention is Masayo Takahashi's pioneering research concerning the clinical application of iPS cells in macular degeneration. Takahashi, an opthamologist based at the RIKEN Center for Developmental Biology in Kobe, Japan, will pursue the world's first clinical application of iPS cells. Age related macular degeneration is an eye disease commonly found among elderly people, caused by damage to the macula, which controls central vision. Takahashi is attempting to treat the wet form of macular degeneration (commonly found in Japan) and not the subject of treatment by existing trials for the dry type (commonly found in Europe and North America). Existing therapies such as medication (ranibizumab) and laser therapy can prevent worsening of the condition for the wet type of macular degeneration, but these therapies are not curative. Takahahi's project follows clinical trials by firms, such as US-based Advanced Cell Technology to engineer retinal cells from embryonic stem cells and transplant these to patients.[29]

Takahashi obtained ethical approval from the Institute of Biomedical Research and Innovation (Kobe, Japan) and its parent RIKEN (Wako, Japan). Following approval by the MHLW, she has pursued clinical studies since August 2013. She commenced Takahashi's research team will select around six patients at the Institute of Biomedical Research and Innovation hospital, above the age of 50 who have not responded to conventional therapy. They will extract skin cells from several patients, create iPS cells from these over 10 months, develop them into retinal pigment epithelium, and transplant these into the patients next summer. The patients will be monitored every month or two following transplantation over three years.

Takahashi's objective in this clinical study is to establish the safety of this treatment; to prove that the treatment will not cause an adverse immune response or create tumours. While her initiative has attracted much attention, Takahashi remains cautious, as clinical studies in Japan are only a permit to conduct an experimental therapy for research purposes; they cannot lead to official approval as a standard therapy. Even if clinical studies are successful, researchers are hesitant to pursue Japanese clinical trials, which are lengthy and cost billions of yen. Further, even if safety and efficacy are established, and clinical trials are successful, the treatment would still need to be made affordable to be included on the official reimbursement list and utilized under the universal health care system.[30] Yet, what has been quite fascinating, are the recent reforms by the historically slow-moving Japanese government to support, promote and accelerate the development of regenerative medicine.

On multilevel governance and "Rising Powers"

[29] Masayo Takahashi, "iPS Saibō o Mochiita Mōmaku no Saisei Iryō," *Iyaku Jānaru* 47, no 10. (2011): 87-91.
[30] Takahashi, 89.

Governance structures have significant impact on advances in regenerative medicine and its industrialisation, because the development of this emerging field requires its support, whether in terms of the development of human capital, infrastructure, therapeutic method, financial systems, or new business models. As a heavily regulated sector, good governance structures are essential to guide, pull, and push the development of this field. With regard to the aforementioned case study, at the moment, the field of iPS stem cell therapy is focussed on Takahashi's group in Japan and the Japanese regulatory agencies to ascertain evidence of safety and efficacy. To this extent, this Japanese precedent currently has important implications on global biomedical governance and the reshaping of governance structures overseas. At the same time, various (Japanese) publications also reveal Japanese policymakers' research into biomedical governance structures in the United States, Europe, China and South Korea to enhance the domestic institutional infrastructure. Japanese policymakers do not appear to be looking at India for similar purposes.

Multilevel governance has become an increasingly topical issue with the opening, internationalization and regionalization of innovation in Japan. Supranational governance has progressed, often as a result of foreign pressure to deregulate the Japanese market. For example, over the decades, Japan's pharmaceuticals and medical devices sector has come under pressure from foreign industry and government organizations – such as the Pharmaceutical Manufacturers Association (PhRMA) the Health Industry Manufacturers Association (HIMA)[31] US Department of Commerce, or the European Business Council – to open access to the domestic market and harmonize standards in Japan with those of other countries.[32] In the area of regenerative medicine, the Japanese government is also involved in discussions with international bodies such as the International Standards Organization and International Stem Cell Forum to develop common standards.

Helped by government efforts to nurture clusters through national programs, such as METI's Industrial Cluster Program and MEXT's Knowledge Cluster Initiative, the governance of biomedical innovation at subnational levels has proceeded alongside growing supranational governance. This can be observed in industrial clusters, which are strongly supported by regional governments in Japan. While Japanese policymakers initially harboured considerable optimism for the interdisciplinary collaboration that could utilized for biomedical innovation from these cluster initiatives, observers now harbor guarded pessimism. Japanese clusters have been formed, more out of government administration rather than organic growth. As

[31] Advanced Medical Technology Association, or Advamed since 2000.

[32] Japan, House of Councillors, Official Report of Debates, Shōkō Iinkai [Commerce Committee]," 102nd Diet, 13th Session, 25 April 1985; Japan, House of Representatives, Official Report of Debates, Kisei Kanwa ni Kansuru Tokubetsu Iinkai [Special Committee on Deregulation]," 134th Diet, 3rd Session, 1 November 1995.

Casper has suggested from the failure of similar initiatives in Germany, Taiwan and elsewhere, government policies cannot orchestrate the development of science-based industries.[33] Foreign firms within these clusters have not invested heavily in R&D. Many Japanese firms report that the excellent transportation infrastructure within Japan diffuses the benefits that proximity may provide within clusters when compared to other countries. It remains unclear whether subnational governance will have much impact on innovation in regenerative medicine in Japan.

[33] Steven Casper, "Can New Technology Firms Succeed in Coordinated Market Economies? A Response to Herrmann and Lange," *Socio-Economic Review* 7, no. 2 (2009): 214.