

Report

Positioning Asia in the Japanese Regenerative Medicine Industry:  
The Case of China and India

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## 1. Introduction

### 1.1 Background and purpose of report

The purpose of this report began as an attempt to investigate the activities of Japanese regenerative medicine companies, and their activities in broader Asia – particularly in China and India. Japanese firms are widely regarded as having strong capabilities in basic science, but their capability to develop or commercialise such technologies has been rather limited. In addition, Japanese firms have largely conducted autarkic forms of biomedical innovation,<sup>1</sup> improving upon imported technologies at the firm level, rather than engage in knowledge exchange across organizational boundaries.

In recent years, however, the Japanese government has made considerable efforts to improve the domestic environment to facilitate firms' engagement in innovation at the technological frontier. Part of this effort involves support to commercialise biomedical technologies as a means to revitalize its economy through high technology industries. In an age of globalisation, government, academia, and firms have tried to advance a highly complex technological field and develop this industry through international collaboration and open innovation.<sup>2</sup> Governments, for example, have discussed the harmonization of regulation, as well as introduced policies to support (collaborative) research in this field. Academics are working, not only with foreign academics in home institutions but also across national borders on a regular basis. Japanese regenerative medicine firms are expanding overseas, whether for markets, raw materials or knowledge; via acquisitions to joint ventures. This report considers the position of China and India in the internationalization of Japanese regenerative medicine firms, as well as the role of government and academia in this process.

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<sup>1</sup> Kneller, Robert, "Autarkic drug discovery in Japanese pharmaceutical companies: insights into national differences in industrial innovation," *Research Policy* 2003 vol: 32 (10): 1805-1827

<sup>2</sup> Globalisation here refers to as the phenomena of increasing interconnectedness and interdependence of different regions in the world, and recognizes a range of factors – from trade to information flows – as contributing to this process. In this report, the term does not refer to the international expansion of firms into foreign markets.

## 1.2 Summary findings

- The Japanese government has played an important role in facilitating Japanese expansion in Asia, whether through regulatory harmonization or policy initiatives. A recent prominent initiative involves supporting Japanese firm expansion in China to take advantage of the ease of commercialization and large market potential in China to develop Japanese industry. Similar initiatives in Thailand are, in the long run, intended to support the expansion of Japanese regenerative medicine in broader Asia, including China and India.
- Until recently, Japanese academic research had limited collaborations in China or India. Even in the early 2000s, collaborations were limited to foreign researchers who were working in Japanese universities or other research organisations. In the past few years, Japanese academic researchers have actively been collaborating with researchers in Asia, particularly those based at Chinese academic organisations. Indian collaboration exists, but is much more limited.
- Despite interest in Asia, the Japanese regenerative medicine sector itself – whether in terms of therapeutics, medical devices, or supporting fields – currently has relatively limited presence in China or India. There are a number of firms, from Japan Tissue Engineering, Regience and T&C Holdings, that have expanded to different extents in China, but these are not representative of the majority of Japanese regenerative medicine firms.
- Japanese regenerative medicine firms that have expanded into China and India are varied, and range from those offering therapeutics, research tools, to consulting services. A number expand into Asia (including China and India) using imported technologies or licensing agreements with Western firms. Many more expand into China than India.
- The relative lack of expansion into Asia may partly be due to the promotion of the Japanese regenerative medicines industry as a “national” project that is hoped to, in some respects, “regenerate” the Japanese economy. The government and industry preference is for Japanese firms to collectively “upgrade” their innovative capacity, which may involve utilizing overseas institutional

environments in Asia – primarily China – for initial commercialization. Following export to these markets; improved delivery of therapies; and adjustments to the business model, Japanese firms aim to expand further in Asia, and more globally.

## 2. The broader context

### 2-1. The Japanese context and the impetus for overseas expansion

The expansion of Japanese firms into Asia needs to be placed in the broader context of why there has been such strong and particular interest in developing a regenerative medicines industry in Japan. This section examines the broader context of: relative economic stagnation; an aging population; and relative decline in biomedical innovation.

#### Relative economic stagnation

One motivation to nurture an industry at the technological frontier comes more than two decades of relative economic decline. Following a high rate of growth since the mid 1950s, Japan has experienced a long period of relative decline since the 1990s. The so-called “Lost Decades” that followed decades of impressive growth, not only generated a crisis of confidence, but also a sense of urgency to “upgrade” the domestic environment to facilitate radical innovation at the technological frontier – and recover from a long economic slump. Thus, when Prime Minister Abe was elected in December 2012, he introduced a now much widely-debated programme, called Abenomics, that was comprised of monetary, fiscal and structural reforms to revive the economy. Indeed, part of Abenomics’ structural reforms targeted specific sectors, including the biomedical industry. The reforms incorporated widespread changes to domestic institutions: from the introduction of mixed billing to regulatory reforms concerning approvals for therapeutics.

#### An ageing population

Another motivation to nurture the regenerative medicines industry comes from Japan’s rapidly ageing population. As shown in the tables Japanese life expectancy at birth (83.3 years) is longer than the US (78.8 years) or the UK (81.0 years) and substantially longer than China (75.4 years) or India (66.5 years).<sup>3</sup> Moreover, as both the immigration rate (1.6% foreign born)<sup>4</sup> and the fertility rate (1.4) are considerably lower than most developed countries, the percentage of the population over age 65 is not only much higher (25.1%) than most countries, but also continues to grow rapidly. This ageing population has placed immense pressures on Japan’s universal health care system, under which the government subsidises healthcare provision. Regenerative medicine

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<sup>3</sup> The World Bank, "World Development Indicators." Available at <http://data.worldbank.org/data-catalog/world-development-indicators>, accessed 20 April 2015.

<sup>4</sup> OECD, “Foreign-born population (indicator).” Available at <http://dx.doi.org/10.1787/5a368e1b-en>, accessed on 21 April 2015.

has been considered a potentially attractive and cost effective alternative to conventional medicine, as – in the future – it might offer a short-term curative treatment rather than long-term symptomatic treatment of chronic illness.

Table 1. Life expectancy at birth

	1973	1993	2013
India	51.0	59.5	66.5
Japan	73.8	79.3	83.3
China	65.0	70.0	75.4
United Kingdom	72.3	76.4	81.0
United States	71.4	75.4	78.8

Source: The World Bank, *World Development Indicators*.

Table 2. Percentage of Population Over Age 65

	1973	1993	2013
India	3.4	4	5.3
Japan	7.5	13.4	25.1
China	4.3	6	8.9
United Kingdom	13.6	15.8	17.5
United States	10.1	12.6	14

Source: The World Bank, *World Development Indicators*.

Table 3. Fertility rate

	1973	1993	2013
India	5.2	3.6	2.5
Japan	2.1	1.5	1.4
China	4.5	2.0	1.7
United Kingdom	2.0	1.8	1.9
United States	1.9	2.0	1.9

Source: The World Bank, *World Development Indicators*.

#### Lost Potential? Relative decline in innovative capacity

The third reason behind such strong Japanese interest in regenerative medicine is also related to its positioning as an industry at the technological frontier, and is motivated by the desire for Japan to pioneer such an industry. Similar with many Japanese technologies, there had been worldwide expectation in the 1980s that Japan would

pioneer innovation in high technology industries, including biotechnology.<sup>5</sup> By the millennium, it had become rather clear that Japan was losing the biotechnology race – if the country had ever been a real contender. In the meanwhile, Japan also began to lose footage in other technology sectors. Japanese companies such as Sony, Panasonic, or Hitachi had been leading global consumer electronics companies in the 1980s but struggled to compete South Korean firms such as Samsung and LG by the millennium. While the automotive sector fared better, Toyota, Honda or Nissan competed in the global market with Asian rivals as Hyundai or Kia. More generally, by the millennium, there was a growing sense that Japan could only catch-up in established industries – where it would have to compete with Asian rivals in the global market. Japanese observers suggested that while Japanese firms could excel in manufacturing, it could not pioneer industries at the technological frontier.

However, to many Japanese leaders – whether in government, industry and academia – such news was unfortunate, as the inability of Japanese firms to take a leading role in the biomedical industry was consequence of a poor domestic environment to support commercialization, rather than the caliber of Japanese academic science. Some articles pointed to the caliber of Japanese basic science, if not the supporting institutions for clinical research.<sup>6</sup> In an age of growing scientific and technological complexity and globalisation, leading Japanese scientists began to call for open innovation, particularly in Asia, to advance these frontiers. Indeed, scientists such as Ken'ichi Arai called upon the importance, not only of institutional reforms that would facilitate academic entrepreneurship or provide financing for promising research, but also of collaborative research beyond Japan. In particular, he emphasized the potential leadership role that Japan could play in the countries that originated from Chinese culture (that used Chinese characters) in the Northeast Asia region.<sup>7</sup>

As discussed above, Japan's interest in the regenerative medicine industry stems from three major aims. The first aim is revive the Japanese economy by developing a

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<sup>5</sup> See for example, "Commercial Biotechnology: An International Analysis." Washington, D. C.: U.S. Congress, Office of Technology Assessment, OTA-BA-218, January 1984.

<sup>6</sup> While Japan was fourth in basic research articles, it was fourteenth in clinical articles. Rahman, Mahbubur, and Tsuguya Fukui, "A Decline in the U.S. Share of Research Articles." *The New England Journal of Medicine* 347, no. 15 (2002): 1211-1212. See also, Takashima, Toshirō, "Wagakuni ni Okeru Rinshō Igaku Kenkyū no Genjō to Kokusai Hikaku [The Current Status of Clinical Research in Our Country in Comparative Perspective]," *Seisakuken Nyūsu* 25 (2008): 18-23.

<sup>7</sup> "Seimei Biggu Ban Fōramu [Life Sciences Big Bang Forum]," *Sankei Shimbun*, 28 November 2001, 13.



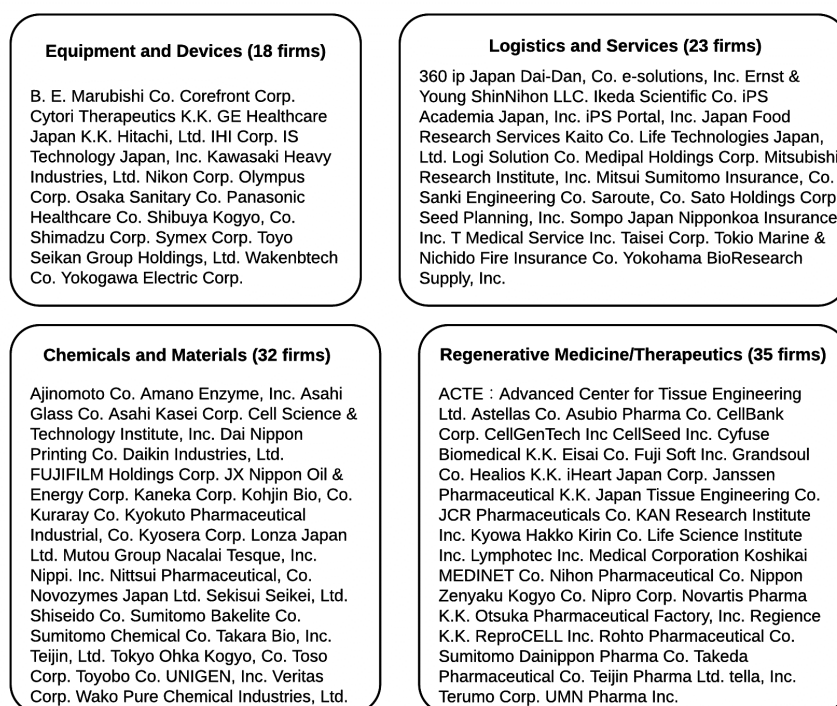
competitive high technology sector beyond manufacturing. The second aim is to find a means to contain healthcare spending amid an ageing population. The third aim is to realise the commercialisation of highly sophisticated Japanese academic research and pioneer an emerging industry. The Japanese interest in Asia arises from this idea that, in order to achieve these aims in a highly complex field in a global age, collaboration with Asian partners and expansion in more favourable institutional environments is important.

## 2-2. The regenerative medicine industry in Japan

### Regenerative medicine companies, a definition

The Japanese regenerative medicines industry is comprised of a range of firms, from those that offer autologous or allogeneic therapies; provide platform technologies (such as assays), to those that deliver services (such as capital, insurance). Formally, many of these companies are members of FIRM (the Forum for Innovative Regenerative Medicine), the industry association for regenerative medicine in Japan. Unlike its parallel organization in the United States and Europe, Alliance for Regenerative Medicine, whose members are primarily engaged in therapeutics, FIRM is comprised of firms that span a range of sectors, from insurers, logistics providers, construction companies, machinery companies, to therapy providers are all members of this “industry association,” which now number more than 100. The range of FIRM members are indicated in Figure 1 below.

Figure 1. The Japanese Regenerative Medicines Industry, FIRM membership, 2014



108 firms as of 14 October 2014

Source: FIRM, 2014<sup>8</sup>

<sup>8</sup> FIRM, “Chūō Shakai Hoken Iryō Kyōgikai Sōkai Iken Chunjutsu Shiryō [Central Social Insurance Medical Council General Council Opinion Statement Document],” 22 October 2014.

#### FIRM: The regenerative medicine industry association

It is worth noting that, in the Japanese context, “industry associations” have played an important role in industrial development over the decades. The industry association has played a prominent role as a communicative forum between government and industry, as well as a forum for cross-sectoral collaboration for industrial development. During Japan’s catch-up phase, Japanese industry associations were primarily comprised of leading firms in a given sector, engaged with government officials, and shared imported technologies from the developed countries – so as to cooperate and catch up with the more developed countries at the time. The industry association for regenerative medicine is a reformulation of this traditional industry association.

The new industry association is similar with the old model in several ways. For instance, the government has been collaborating and cooperating with Japan’s leading large businesses to nurture the development of a world-leading industry, to rejuvenate the Japanese economy – much as it had done in earlier decades. Now, the government’s efforts are intended to support the formation of a domestic industry at the technological frontier, rather than guide an industry to growth. The government that once prided itself for nurturing “monozukuri,” or Japanese manufacturing, now endeavours to nurture “kotozukuri,” or, in the post-manufacturing era, “phenomenalisation.” The new industry association for regenerative industry is different in that its members cross sectors and include some small to medium size enterprises. The new industry association also has foreign representation, such as the Swiss biotechnology company Lonza Group; Swiss pharmaceutical company Novartis AG; American medical devices company Cytospor Therapeutics; and Singaporean intellectual property and fund management company 360ip. However, there is no Chinese or Indian representation.

#### Government initiatives

The Japanese government began to launch state-sponsored initiatives to spur open-innovation in biomedicine – including regenerative medicine since the 2000s. The significant attention and emphasis centered on this sector was prompted by Shinya Yamanaka’s discovery of iPS cells in 2007, which led to an award for the Nobel prize in medicine and substantial public support for stem cell research. Government support for regenerative medicine largely comes from three different ministries: the Ministry of Education, Culture, Sports, Science and Technology (MEXT), primarily in academic research; the Ministry of Health, Labour and Welfare (MHLW), primarily in clinical

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application; and the Ministry of Economy, Trade and Industry (METI), primarily in industrialisation. As mentioned earlier, METI has long played an important role in supporting Japanese firms; has established a dedicated regenerative medicine committee group; and demonstrates a constant presence at Japanese academic or industrial conferences in this field (ex. Japan Society for Regenerative Medicine, Expo for the Industrialisation of Regenerative Medicine).<sup>9</sup> Since 2008, METI has introduced three large-scale projects (P08030; P10027; P14006) through its project agency, NEDO, to support commercialization in regenerative medicine through teams of Japanese firms and universities.<sup>10</sup>

Perhaps one of the most transformative changes that has attracted global attention to the Japanese regenerative medicines industry, has been the introduction of two laws governing regenerative medicines that were passed on 27 November 2014. The two laws are the New Regenerative Medicines Law and the revised Pharmaceutical Affairs Law.<sup>11</sup>

The first of the two laws, the New Regenerative Medicines Law, requires all medical practitioners to gain consent for regenerative medicine treatments prior to administration – a response to criticism over unapproved stem cell therapies administered in Japan under physicians' discretion. The New Regenerative Medicine Law will also allow medical institutions to outsource their in-house cell processing centers to private firms. The second law is the revised Pharmaceutical Affairs Law, and allows for the conditional approval of potential therapies after initial safety tests. The revised PAL offers adaptive approval for a given therapy after safety has been established and efficacy is surmised; after completion of Phase 2 trials. Firms are permitted to market their therapies whilst conducting further safety and efficacy tests for a maximum period of 7 years, after which they will be expected to apply for final approval. The law

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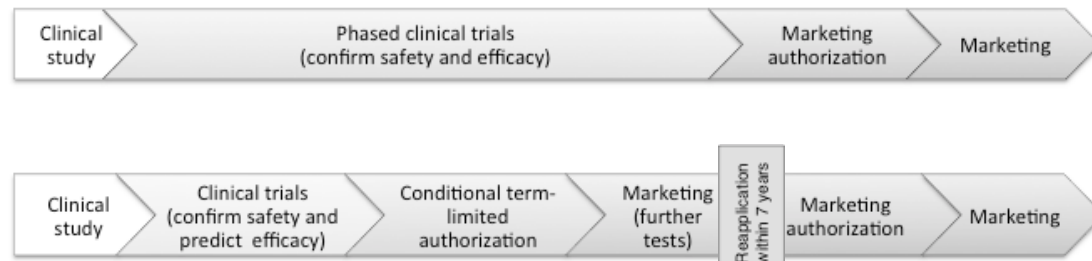
<sup>9</sup> METI, "Saisei Iryō no Jitsuyōka/Sangyōka ni Kansuru Kenkyūkai [Research Committee to Consider the Application and Industrialisation of Regenerative Medicine]." Available at [http://www.meti.go.jp/committee/kenkyukai/mono\\_info\\_service.html#saisei\\_iryō](http://www.meti.go.jp/committee/kenkyukai/mono_info_service.html#saisei_iryō), accessed 5 May 2015; See also NEDO, "Jigyō Ichiran [Activities List]." Available at <http://www.nedo.go.jp/content/100186623.pdf>, accessed 5 May 2015.

<sup>10</sup> METI, "Saisei Iryō ni Kanuru Keizai Sangyōsho no Torikumi o Shōkai Shimasu [Introducing METI's Engagement in Regenerative Medicine]," METI press release, 25 October 2012. Available at <http://www.meti.go.jp/press/2012/10/20121026001/20121026001-1.pdf>, accessed 5 May 2015.

<sup>11</sup> METI, "On the New Regenerative Medicines Law." Available at [http://www.lifescience.mext.go.jp/files/pdf/n1183\\_09.pdf](http://www.lifescience.mext.go.jp/files/pdf/n1183_09.pdf), accessed 6 March 2014.

aims to accelerate the approval and commercialisation of regenerative medicines, and deliver potential therapies as quickly as possible to patients without viable therapies.<sup>12</sup>

Figure 2. Conventional therapeutic development process (above), and the Japanese alternative (below)



Source: Adapted from Pharmaceutical and Medical Devices Agency (PMDA), Japan, 2014.<sup>13</sup>

#### The Japanese market for regenerative medicine

Japan's Ministry of Economy, Trade and Industry (METI) estimated the therapeutics market for regenerative medicines as 9 billion yen in 2012, with projections for 95 billion and 1 trillion yen in 2020 and 2030, respectively. METI estimated that the market for supporting sectors (services, consumables, and devices) as 17 billion yen in 2012, with growth potential of 95 billion yen and 550 billion yen. Currently, however, there are 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. In addition, four clinical trials are underway. These are: Terumo's cell sheets for cardiac regenerative therapy; JCR Pharmaceutical's (Mesoblast's Japanese partner) for GVHD prevention; Kobe's Foundation for Biomedical Research and Innovation's autologous cartilage; and Japan Tissue Engineering's autologous cultured corneal epithelium.<sup>14</sup>

At present, the market is dominated by a range of self-pay treatments not covered by insurance, such as cancer immunotherapy, regenerative dentistry, and cosmetic

<sup>12</sup> Ibid.

<sup>13</sup> PMDA, "Saisei Iryōtō Seihin: Jōken oyobi Kigentsuki Shōnin [Regenerative Medicine Products: Conditional and Limited Approval]," 25 November 2014, 22. Available at <http://www.pmda.go.jp/files/000199506.pdf>, accessed 5 May 2015.

<sup>14</sup> Sawa, Yoshiki, "Saisei Iryō Seihin no Hoken Teikiyō ni kansuru Kangaekata [Considering the Application of Insurance to Regenerative Medicine Products]." Representing the Japanese Society for Regenerative Medicine at MHLW Committee Hearing, 22 October 2014. Available at <http://www.mhlw.go.jp/file/05-Shingikai-12404000-Hokenkyoku-Iryouka/0000061894.pdf>, accessed 5 May 2015.

medicine. There has been a notable increase in the number of new entrants in this field, diversifying from sectors such as pharmaceuticals, food, and machinery. However, as shown in the table below, as of 2013, most firms in Japan have 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. This situation is similar to Europe, but the reverse of the United States, and also of Asia, in which most firms have focused on therapeutics.

Table 4.

Location and sectors in which firms using stem cell technologies are based, 2013

	RM/cell therapies	Pharmaceuticals	Medical devices	Supportive sectors	Other	Total
Japan	27	7	17	38	1	90
US	99	25	11	71	1	207
Europe	29	11	7	43	1	91
China	5	0	0	0	0	5
South Korea	12	1	0	0	1	14
Other	22	2	0	10	1	35
Total	194	46	35	162	5	442

Source: Mitsubishi Techno-Research Corporation, as cited in Japan Patent Office, 2013.<sup>15</sup>

#### Key players in the Japanese market

As noted briefly earlier, most large Japanese pharmaceutical firms, whether Takeda, Astellas or Eisai, now have regenerative medicine divisions and have made investments in smaller regenerative medicine companies to follow developments in this new technology. As well, consumer electronics companies and precision instruments companies such as Panasonic and Nikon are applying existing technological capabilities to the development of new products that support research in regenerative medicine, such as cell processing workstations or highly sophisticated microscopes. Companies in Japan are currently offering supporting technologies such as cell culture media or iPS cell derived cardiomyocyte or neurons as drug discovery tools, but most regard iPS cell derived cell therapy as a product that may be realised about a decade into the future. In the meanwhile, foreign companies such as the American firm Cytori have expanded their

<sup>15</sup> Japan Patent Office, “Tokkyo Shutsugan Dōkō Chōsa Hōkokusho: Kansaibō Kanren Gijutsu [Report on Patent Trends: Stem Cell Related Technologies].” Tokyo: Japan Patent Office, 2014.

operations in Japan since the early 2000s and are already generating a large proportion of their revenues in Japan. Australia's Mesoblast is planning to offer the first official allogeneic stem cell treatment in Japan. The November reforms in regenerative medicine have prompted considerable discussion on an international level, and have created greater opportunities in the Japanese market.

### 3. Government

#### 3-1. Relevant government bodies

As touched upon earlier, the Japanese government have strongly supported the regenerative medicine industry for various reasons: containing health care costs; controlling unregulated cell therapies; compensating for the lack of organ donors; to taking advantage of the country's world leading research capacities represented by Yamanaka. The key government players in supporting the regenerative medicines industry are MEXT, MLHW, and METI. MEXT is primary concerned with basic research and is most widely recognized for its "Network Program," creating academic research hubs and networks in regenerative medicine.<sup>16</sup> MLHW is primary concerned with clinical application, and has been concerned with support for establishing safety procedures for clinical research; supporting drug development using iPS cells; and relevant personnel to develop this field.<sup>17</sup> METI is concerned with industrialization, from supporting the development of medical equipment and devices to support research; to helping to form a regulatory environment to facilitate commercialization.<sup>18</sup> Such government initiatives are inherently domestically oriented, and few involve overseas players.

The government has been following regulatory and other developments overseas in order to improve the domestic environment and advance Japan's regenerative medicine industry – as well as to aspire to become the standard-setter in Asia. In Asia, government interest has centred more on South Korea and China (the Northeast Asian region) rather than India (although they are aware of developments in the country). The government has also shown some interest in developments in Taiwan, Singapore and Thailand. This may be due to the relative geographic and cultural proximity of these countries to Japan.

#### 3-2. Government initiatives

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<sup>16</sup> MEXT, "Saisei Iryō Kenkyū no Suishin ni Kansuru Monbu Kagakushō no Torikumi ni Tsuite [On MEXT's Engagement in Promoting Research in Regenerative Medicine]." Available at

[http://www.lifescience.mext.go.jp/files/pdf/n1296\\_03.pdf](http://www.lifescience.mext.go.jp/files/pdf/n1296_03.pdf), accessed 5 May 2015.

<sup>17</sup> MHLW, "Kōsei Rōdōshōni okeru Saisei Iryō ni Kansuru Torikumi ni Tsuite [On MHLW's Engagement in Regenerative Medicine]," MEXT, 22 February 2013.

<sup>18</sup> METI, "Saisei Iryō ni Kansuru Keizai Sangyōsho no Torikumi o Shōkai Shimasu [Introducing METI's Engagement in Regenerative Medicine]," METI press release, 25 October 2012. Available at <http://www.meti.go.jp/press/2012/10/20121026001/20121026001-1.pdf>, accessed 5 May 2015.



### Regulatory adjustments

By the mid 2000s, Japanese leaders became acutely aware of the relative loss of leadership in biomedical innovation, even within Asia, to countries such as South Korea, China, and India. The institutional rigidities in Japan and subsequent hollowing out of clinical trials from Japan to Asia had severe implications on access to cutting edge medical innovations and the lowering of R&D calibres among Japanese biomedical companies. In response, government initiatives began to support the sharing of clinical trial data across Asian countries. In 2008, for instance, the government prepared 52 million yen toward collaborative clinical research with China and South Korea, and annual meetings by the health ministers are held on an annual basis.<sup>19</sup> Similar initiatives have involved discussions among Asian representatives to harmonise the method of manufacture or means of differentiation in iPS research. Such efforts are ongoing.

### Projects to develop the industry through Asia

As mentioned earlier, Japanese government initiatives to develop the regenerative medicines industry have expanded upon the post war model of government and large business working in tandem to develop a world-leading sector (This was, for example, the case of Japan's semiconductor industry in the 1980s). However, the new initiatives have adopted a more international perspective to take advantage of the more flexible institutional arrangements available in Asia compared to Japan. As with most initiatives, these are introduced by METI and are comprised of a consortium of leading Japanese firms.

One prominent initiative in regenerative medicine involves the government project to realise regenerative medicine in China and Thailand.<sup>20</sup> There are several aims of the project. These include: exporting Japanese regenerative medicine; establishing Japanese regenerative medicine standards as de facto standard; improving the delivery of regenerative medicine products; and improving the regenerative medicine business model.

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<sup>19</sup> "Kōrōshō, Kakushintaki Iyakuhin/Iryōkiki Sōshutsu no Suishin Shisaku o Kakujū [MHLW Enhances Policies to Cultivate Innovative Medicines and Medical Devices]," *Kagaku Kōgyō Nippō*, 15 January 2008, 8; Sato, Takeyuki, "Kokusai Kyōdō Chiken no Genjō to Kadai [Current Status and Problems of International Collaboration in Clinical Trials]," presentation for Medical Platform Asia, 11 July 2013.

<sup>20</sup> METI, "Chūgoku, Tai Ōkoku ni okeru Saisei Iryō Jitsuyōka Purojekuto [Project to Realise Regenerative Medicine in China and Thailand]," MEXT, February 2014. Available at [http://www.meti.go.jp/policy/mono\\_info\\_service/healthcare/kokusaika/downloadfiles/fy25kobetsu/outbound\\_11.pdf](http://www.meti.go.jp/policy/mono_info_service/healthcare/kokusaika/downloadfiles/fy25kobetsu/outbound_11.pdf), accessed 5 May 2015.

The government identified China as a favourable location to expand for several reasons. For example, China has a large and growing market; its science and technology is developed; similar products are available, but has had limited market penetration. Officials also hoped that many Chinese patients/consumers would pay additional fees for foreign “quality.” While Japan Tissue Engineering’s two regenerative medicine products have a relatively small market for very severe burns in Japan, the firm plans to cater to a much larger market in China that offer products to both burns and cosmetic surgery patients. In addition to the centralized approval system by the China’s Food and Drug Administration (SFDA), the Japanese parties wished to take advantage of the accelerated approval system in Shanghai. Indeed, the project identified Shanghai as an optimum location to expand for its local advantages. The SFDA requires five to nine years for market approval, including Japanese approval as a precedent. However, in Shanghai, products characterized as a New Medical Technique (NMT) require approximately three for a geographically limited approval – and does not require Japanese approval as precedent.

The Japanese firms involved in the government’s recent China project are: Japan Tissue Engineering Co., Fujifilm Corp., Sumitomo Bakelite Co, and Wako Pure Chemical Co. All are members of the aforementioned industry association, FIRM. As mentioned Japan Tissue Engineering is the only firm in Japan whose regenerative medicine products are approved and covered by universal health insurance: tissue-engineered skin and cartilage. Building upon technologies developed from its photography business, Fujifilm has recently made major investments in regenerative medicine. The firm is a majority shareholder of Japan Tissue Engineering and recently acquired the US firm Cellular Dynamics.<sup>21</sup> Sumitomo Bakelite is a plastics company that has developed research tools such as BlotGlyco with Hokkaido University that can be used in regenerative medicine. Wako Pure Chemical has also developed a range of culture media and reagents to support research in this field. Through the project, the Japanese government and firms seek to develop regenerative medicine products and strengthen business operations in China, then expand into other countries.

In practice, the China project involves the creation of a Fujifilm-Japan Tissue

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<sup>21</sup> Cellular Dynamics International, “Fujifilm Holdings to Acquire Cellular Dynamics International, Inc.,” Cellular Dynamics International, press release 30 March 2015. Available at [http://www.cellulardynamics.com/about/press\\_releases.html](http://www.cellulardynamics.com/about/press_releases.html), accessed 5 May 2015.

Engineering joint venture Fujifilm Tissue Engineering (Shanghai) Co., which is also supported by local Chinese government. This joint venture will utilize various equipment and materials supplied by Japanese firms and develop manufacturing facilities at Zhangjiang Hi-Tech Park, a technology park in Shanghai comprised of firms from the life sciences to information technology. The therapies will be delivered through a partnership formed with Shanghai Jiatong University hospitals as well as other local hospitals to Chinese patients. Physicians from St Marianna University in Tokyo will travel to impart knowledge regarding the administration of the cell therapies/tissue engineered products in Japan.

It should be mentioned that the government's initiatives in Thailand adopt a similar model – but intended to deliver to medical tourists as well as the local population. The Thai initiative also aims to become an indirect path to expansion in broader Asia, including China and India. For example, a government project administered by NEDO involves the adaptation, installation and use of automated cell processing machines developed by Kawasaki Heavy Industries, Ltd. in Thailand. Kawasaki has used their firm's expertise in robotics to diversify into medical devices that support the development of regenerative medicines. In addition to Kawasaki, the Japanese members for this project includes Mukogawa Womens' University, Osaka University and DSPResearch, Inc. while the Thai members of this project includes Chulalongkorn University, Srinakharinwirot University, Mahidol University and AESKULAP Clinic (Asia) Co. In the long term, the Japanese planners hope that this Thai project will allow Kawasaki's product to expand into the large potential markets of China and India – and beyond.<sup>22</sup>

#### The role of cluster programmes

Indirect government support for the regenerative medicines industry also arises from the government's cluster projects over the years. These include the Industrial Cluster Project and Knowledge Cluster Initiative of the late 2000s to the more recent regional innovation cluster programmes. The government cluster projects have been dedicated to the development of knowledge intensive industries in Japan. Some such clusters have

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<sup>22</sup> Yumitori, Shuji, "Saisei/Saibō Iryō Gijutsu oyobi Seizō Infura Saitekika no Kenkyū Kaihatsu: Tai de Saisei/Saibō no Jisshō Shiken ga Honkaku Shidō [R&D of Regenerative/Cell Therapy Technology and Optimisation of Manufacturing Infrastructure: Experimental Study of Regenerative/Cell Therapy in Thailand Begins]," NEDO press presentation, 30 September 2013. Available at <http://www.nedo.go.jp/content/100537721.pdf>, accessed 5 May 2015.

formed overseas alliances, either at cluster or firm level. The Kobe Biomedical Cluster, for example, has formed an alliance with China Medical City alongside other overseas clusters such as Medicon Valley (Denmark/Sweden) and FlandersBio (Belgium). The latter is China's only official medical cluster comprised of approximately 260 pharmaceutical companies in Taizhou, Jiangsu province. The Kobe cluster is located close to Riken CDB, one of Japan's leading research organisations in regenerative medicine, and the cluster is home to a number of firms engaged in regenerative medicine, including Healios K.K. and Sumitomo Dainippon Pharma Co.<sup>23</sup> As in the case of the Kobe cluster's alliance with China Medical City, other Asian linkages have also been initiated by foreign governments. For instance, Taiwanese policymakers have been keen to promote collaborative R&D with Japanese firms via Taiwan's nonprofit Industrial Technology Research Institute – which historically played an important role in supporting the development of leading Taiwan's high tech semiconductor companies such as TSMC and UMC.<sup>24</sup>

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<sup>23</sup> Cabinet Office, Japan, "Hyōgo Kōbe Gurōbaru Raifu Inobēshon Tokku: iPS de Sekai o Kaeru [Hyogo Kobe Global Life Innovation Special Zone: Change the World with iPS Global Life Innovation Special Zone: Change the World with iPS]." Available at [http://www.kantei.go.jp/jp/singi/tiiki/kokusentoc\\_wg/pdf/45-hyogokobe.pdf](http://www.kantei.go.jp/jp/singi/tiiki/kokusentoc_wg/pdf/45-hyogokobe.pdf), accessed 5 May 2015.

<sup>24</sup> "Baio/Iryō de Nihon ni Neshisen: Taiwan Keiyu Chūgoku Shinshutsu mo Shien, Taiwan Kōgyo Gijutsu Kenkyūin [Strong Interest in Japan: From Taiwan, Also Supporting Expansion into China, Industrial Technology Research Institute]," *Yakuji Nippo*, 12 September 2014, p 4.

## 4. Academia

### 4-1. Relevant academic organisations

Research in regenerative medicine is carried out across universities in Japan, but the leading research organisations tend to be in Western Japan. These include the Institute for Frontier Medical Sciences at Kyoto University; the Riken Center for Developmental Biology (Riken CDB) in Kobe.<sup>25</sup> These organizations have been the source of leading academic startups and both have strong ties with leading biomedical companies in Japan. Academic startups include: iPS Academia Japan (intellectual property management company, Kyoto University) and Healios (iPS cell therapy firm for macular degeneration, Riken Center for Developmental Biology). Kyoto University conduct collaborative research in this field with Japanese firms such as Takeda, Astellas, and Reprocell; Riken has done with Regience and Dannippon Printing. In addition to such prominent research organisations, star scientists are scattered across Japanese universities, such as Teruo Okano at Tokyo Women's Medical University. Okano has launched Cellseed, a startup dedicated to commercializing Okano's cell sheet technology.<sup>26</sup> Among the abovementioned companies, iPS Academia have recently shown interest in China, participating in BioChina 2015 held in April this year.

### 4-2. Trends in academic collaboration

The Japanese academic community have been keenly observant of developments in the forefront of biomedical innovation, as well as those in Asia. In the field of regenerative medicine, Japanese scientists in the early 2000s noted that while it was much easier to advance stem cell research in the United States and India, for example, where it was possible to transplant the retina of embryos to patients, whereas ethical and practical limitations prevented similar research in Japan.<sup>27</sup>

In the early 2000s, the geographic focus of collaborative research for Japanese academics was focussed on Western – primarily American and European – partners. For instance, the Japanese biotechnology community in Silicon Valley established a community network in 2002 that involved cross-border consulting services through

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<sup>25</sup> See Institute for Frontier Medical Sciences, Kyoto University at <http://www.frontier.kyoto-u.ac.jp/eng/>; Riken CDB at <http://www.cdb.riken.jp/>.

<sup>26</sup> See CellSeed, Inc., "Kiban Gijutsu [Basic Technology]." Available at <http://www.cellseed.com/technology/003.html>, accessed 20 April 2015.

<sup>27</sup> "Shinsēki Kenkyū Mappu, Kyoto Daigaku Igakubu Fuzoku Byōin Tansaku Iryō Sentā Jokyōjyu Takahashi Masayo san Mōmaku Saisei [New Era Research Map, Kyoto University Medical Hospital Medical Research Centre Assistant Professor Takahashi Masayo, Retinal Regeneration]" *Kyoto Shimbun* 20 December 2001, 7.

firms such as Gallasus. Yet by the mid 2000s, a growing consensus emerged over the need to pursue collaborations with greater Asia, particularly China. A 2004 report by the Japan Health Sciences Foundation found that the commercialisation of commercialisation of highly sophisticated technologies were undeveloped compared to North America and Europe, but also that Japan was not losing ground to competition from Asia, whether Australia China or India.<sup>28</sup> Such views were echoed by reports by the Japan Science and Technology Agency a few years later. As the realisation of relative Japanese decline accompanied those of the rise of Asia, Japan also began to demonstrate greater interest in and collaborate more with Asian partners.

These trends can be observed in publication counts. For example, the growing research in regenerative medicine can be observed in the extraordinary rise of publications in this field. While recognising that other search terms for this field exist, a sample search of the term "regenerative medicine" in ISI Web produced 8 hits in 2000, but 2,369 in 2014. Database results also suggest that Japan has remained one of the leading countries for research in this field, given the number of publications that originate from the country. However, while Japanese publication counts were roughly equal to those of the United States in the early 2000s (In 2001, publication counts from Japan and the United States were 4 and 7, respectively), Japan lost the momentum for publication compared to the United States by 2014 (In 2014, publication from Japan and the United States were 193 and 677, respectively). The rise of Asian research in regenerative medicine was also evident. While China and India had one publication each in 2005, in 2014, India produced 55 while China produced 237; even more than Japan.

The growing collaboration in research with Asian partners was also evident. In the early 2000s, the few collaborations with China or India were in the context of Chinese or Indian scholars based at Japanese institutions. However, Asian collaborations grew over time, initially more with scholars working on multinational projects that included Japan, India and China as well as scientists in the United States and/or Europe. More recently, Japanese collaborations with Asian countries have become common, particularly with China. Some such projects include multi national projects that included the US National Institutes of Health, Japan Society for the Promotion of Science, Okayama University and Tianjin University. Other projects were cross-country pursuits by Japanese and Chinese

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<sup>28</sup> Japan Health Science Foundation, "Kokugai Chōsa Hōkokusho: Posuto Genomu Jidai no Gurōbaru Kenkyū Kaihatsu to Senryaku [Overseas Research Report: Global R&D and Strategy in the Post Genome Era]." Tokyo: Japan Health Science Foundation, 2005.

scientific teams at: Beihang, Tsinghua and Hokkaido Universities; Osaka University, the Chinese Academy of Medical Science, and Zhejiang University; as well as the Tokyo Institute of Technology, Tianjin and Nankai University. Such active international collaboration with Chinese partners in pursuing research regenerative medicine is expected to continue.

Smaller scale collaborations do exist in India. For instance, the Nichi-In Centre for Regenerative Medicine is an Indo-Japanese initiative affiliated with the Tamil Nadu Dr. M.G.R. Medical University, an Indian government university dedicated to the health sciences located in Chennai, Tamil Nadu. The Centre was established by Dr Samuel JK Abraham, a medical graduate of India who completed his doctoral training at Yamanashi University. In addition to services such as stem cell banking, cord blood banking and stem cell research services, the Centre holds Indo-Japanese conferences in this field and maintains ties with Japanese universities such as Yamanashi University and Waseda University.<sup>29</sup>

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<sup>29</sup> Nichi-In Centre for Regenerative Medicine, "Global Network." Available at <http://www.ncrm.org/global.htm>, accessed 20 April 2015.

## 5. Industry

### 5-1. Relevant companies

The Japanese regenerative medicines industry is comprised of therapeutics; devices; chemicals and raw materials; logistics and other services companies. Many of these firms, from Hitachi, Asahi Glass, The Tokio Marine and Fire Insurance, and Eisai have overseas operations. However, these are not necessarily in regenerative medicine -- particularly in the Asian context. For instance, the Japanese pharmaceutical firm Rohto has a dedicated regenerative medicine group in Japan, but Rohto's work in this field is not conducted in China or India.

Leading biomedical companies, such as the pharmaceutical giant Takeda have prepared for internationalisation with internal reorganisation, and have shown commitment to regenerative medicine. In the case of Takeda, for instance, the company has a regenerative medicine division; has invested in the American regenerative medicine Fate Therapeutics;<sup>30</sup> and, in April, formed a substantial alliance of 10 years of over 20 billion yen with Kyoto University's Center for iPS Research and Application (CiRA) on iPS research.<sup>31</sup> Yet Takeda's activities regarding regenerative medicine in Asia appear negligible compared to its interest in North America and Europe; and the trend is similar to many leading therapeutics companies in Japan.

Devices companies such as Nikon, Canon and Olympus, all part of the FIRM group, also have a presence in India and China. While there may be indirect use of their medical devices in those countries, as researchers conduct research in regenerative medicine, such activity is difficult to trace and is not made explicit among the companies. Where pertinent to regenerative medicine, logistics and other services companies are also, for the most part, dedicated to services in Japan. Many Japanese firms in this field express interest in China and India as future potential markets for their regenerative medicine

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<sup>30</sup> Takeda Pharmaceutical Co., "Takeda Benchā Tōshigaisha ni yoru Saisei Iryō ni Kakakru Fate Therapeutics sha e no Senryaku Tōshi ni Tsuite [Takeda Ventures Makes Strategic Investment in Regenerative Medicine, Fate Therapeutics]," Takeda Pharmaceutical Co. press release 9 May 2011. Available at [https://www.takeda.co.jp/news/2011/20110509\\_4782.html](https://www.takeda.co.jp/news/2011/20110509_4782.html), accessed 5 May 2015.

<sup>31</sup> Takeda Pharmaceutical Co., "Kyoto Daigaku iPS Saibō Kenkyūjo (CiRA) to Takeda Yakuin no iPS Saibō Kenkyū ni kansuru 10 nenkan no Kyōdō Kenkyū ni Tsuite [Kyoto University's Center for iPS Research and Application (CiRA) and Takeda Pharmaceutical Sign 10-Year Joint Research Agreement]," Takeda Pharmaceutical Co., press release 17 April 2015. Available at [https://www.takeda.co.jp/news/2015/20150417\\_6963.html](https://www.takeda.co.jp/news/2015/20150417_6963.html), accessed 5 May 2015.



related business, but these plans are not currently active.

## 5-2. International expansion, China and India

Japanese regenerative medicine companies do have a global perspective, given the foreign origins of many of the technologies, ongoing international collaborative research, as well as the lure of greater market opportunities overseas. While limited and rather recent, a number of Japanese regenerative medicine companies – whether engaged in therapeutics, devices or services; reputable or less so – have expanded into China and India. The reason and means of expansion into China, India, or indeed other Asian countries, are varied. Motivations range from access to resources; pursuit of collaborative R&D; and certainly, market access. Expansion may be on a short-term, project-basis or more permanent, such as acquisitions of local companies. The following paragraphs illustrate several examples.

### Seeking markets

Services: CMIC Holdings Co.

CMIC Holdings is a Tokyo-based contract research organisation in Japan, established in 1985 as one of Japan's pioneering firms in this field. Over the years, the firm had developed comprehensive consulting services for pharmaceuticals, from clinical trials to pharmaceutical registration. In China, CMIC established a fully owned subsidiary in 2004 to assist Japanese pharmaceutical firms operating in China to develop products in the country. CMIC further strengthened its clinical development capabilities in China by establishing a joint venture with the Beijing-based CRO GDP ClinPlus, forming GCP CMIC Clinplus in 2011<sup>32</sup>. In May 2015, CMIC announced their expansion of consulting services to regenerative medicine, incorporating a team of specialists to provide consulting services<sup>33</sup>. Aside from China, CMIC have office across Asia, from Malaysia, Singapore to South Korea.<sup>34</sup>

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<sup>32</sup> CMIC Holdings Co., "Chūgoku ni okeru Rinshō Shiken Shien Taisē no Kyōka ni Tsuite: Chūgoku CRO to no Gōben Keiyaku Teiketsu no Oshirase [Strengthening Clinical Trial Capacities in China]," CMIC Holdings Co. press release 22 February 2011. Available at <http://www.cmic-holdings.co.jp/corporate/press/2011/0222.shtml>, accessed 26 May 2015.

<sup>33</sup> CMIC Holdings Co. "Saisei Iryōmuke Consarutingu Jigyō no Kyōka ni Tsuite [Strengthening Consulting Services in Regenerative Medicine]," CMIC Holdings Co. press release 11 May 2015. Available at <http://www.cmic-holdings.co.jp/corporate/press/2015/0511.shtml>, accessed 13 May 2015.

<sup>34</sup> CMIC Holdings Co., "CMIC Gurūpu ni Tsuite [On the CMIC Group]." Available at <http://www.cmic-holdings.co.jp/corporate/group/index.shtml>, accessed 13 May 2015.

### Regenerative Medicine/Drug Development Tools: Reprocell

Reprocell is a Yokohama-based company established in 2003 that offers a range of pioneering products using stem cell technology. For instance, the firm offers reagents for human ES/iPS culture and human iPSC-derived cardiomyocytes, neurons and hepatocytes. Many of the firm's technology were developed by two of Japan's star stem cell scientists Norio Nakatsuji (Kyoto University) and Hiromitsu Nakauchi (formerly University of Tokyo, now Stanford University). The company has been the first in the world to be able to commercialise some of its advanced products, such as the human iPSC-derived cardiomyocytes and neurons. Reprocell has a global operation, and established a US subsidiary in 2011 for sales to American pharmaceutical firms and universities.<sup>35</sup> While its iPSC cell business is centred on Japan, the United States and Europe, the firm acknowledges the large market potential of emerging markets. Reprocell sells its products in China and India through local distributors. The firm has three Chinese distributors across seven offices and one Indian distributor, and plans to strengthen as well as expand its presence across global markets.<sup>36</sup>

### Therapeutics: Biomaster, Inc.

Biomaster Inc. is a Yokohama based cell therapy company established in 2002. Somewhat similar to firms such as the US company Cytori Therapeutics, Biomaster develops devices and cell therapy using stem cells in adipose tissue. The firm also manages a clinic in Yokoyama that offers cosmetic treatments, such as breast augmentation, using these technologies. Biomaster harvests stem cells from adipose tissue from patients' stomach or thighs and re-inserts them in the intended location, building upon expertise developed with the University of Tokyo, a leading Japanese university. The firm argues that their technology helps avoid post-operation hardening of blood vessels that tend to arise from the lack of stem cells.

Biomaster is a unique case, as it is the only joint stock corporation that took advantage of government deregulation measures in 2002. The government allowed private enterprises to offer medical services in specific zones, for highly specialised and sophisticated medical treatments for which patients would bear the full medical cost.

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<sup>35</sup> Reprocell, Inc., *Yūka Shōken Hōkokusho* [Annual Securities Report], 2014.

<sup>36</sup> The Chinese distributors are: Boppard (Hong Kong, Shanghai, Beijing, Guangzhou); Miao Tong ( Shanghai ) Biological Science & Technology Co. Ltd (Shanghai, Hangzhou); EastLakeCell Co.,Ltd.(Wuhan). The Indian distributor is: GeneX India Bioscience Pvt. Ltd. See Reprocell, Inc., "Branches and Distributors." Available at <https://www.reprocell.com/en/contact/branches-distributors/>, accessed 26 May 2015.

The existence of Biomaster in the Kanagawa Biomedical Industry Zone has the subject of criticism from a range of communities, from local residents to the Japan Medical Association, who dislike the firm's provision of cosmetic surgery as well as its profit-making approach to medicine.<sup>37</sup> Aside from the dampening of patient demand due to Japan's long economic stagnation or the negative sentiments borne by different communities, Biomaster also faces a limited market in Japan due to strong advertising restrictions for its services. Biomaster has thus formed medical alliances with foreign firms for technology transfer as well as to welcome foreign patients to its clinic. For example, in 2009, Biomaster formed an alliance in China's Beike Biotechnology, which involved technology transfers to Beike as well an opportunity for Biomaster to invite Chinese patients to its clinic.<sup>38</sup> Biomaster's technology is already available in a Shanghai clinic. The company has also been trying to expand its services in Southeast Asia.

#### Building upon imported technologies

In quite a few cases, Japanese firms have expanded into Asian markets based, not on in-house technologies, but on advanced technologies developed in North America and Europe – as well as Japanese universities. Perhaps one of the most prominent examples is the aforementioned Japan Tissue Engineering, with the only officially approved regenerative medicine products in Japan. Japan Tissue Engineering's autologous cultured epidermis, *JACE*, is based on Harvard scientist Howard Green's technology developed in the 1970s. With Fuji Film, the company has been preparing to offer this product in China. The company's autologous cultured cartilage, *JACC* is based on Hiroshima University scientist Mitsuo Ochi's technology, and is being developed for the Thai market. While currently still in development, Japan Tissue Engineering's

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<sup>37</sup> Cabinet Office, Japan, "Heisei 19 nendo Kōzō Kaikaku Tokubetsukuiki Suishin Honbu Hyōka/Chōsa Iinkai Iryō/Fukushi/Rōdō Bukai, 4 kai Giji Gaiyō [4<sup>th</sup> Summary Minutes of 2007 Structural Reform Special Zone Promotion Evaluation/Inspection Committee, Medical/Welfare/Labour Section]." Available at <https://www.kantei.go.jp/jp/singi/tiiki/kouzou2/hyouka/chousa/iryoubukai04/gijigaiyou.pdf>, accessed 13 May 2015; Japan Medical Association, "Iryō ni okeru Kabushikigaisha Sannyū ni Taisuru Nihon Ishikai no Kenkai [Views of the Japann Medical Association on the Provision of Medicine by Joint Stock Companies]," 24 December 2009. Available at [http://dl.med.or.jp/dl-med/teireikaiken/20091224\\_3.pdf](http://dl.med.or.jp/dl-med/teireikaiken/20091224_3.pdf), accessed 22 May 2015.

<sup>38</sup> "Baioimasutā, Chūgoku Kigyō to no Teikei de Kaigai Fuyūsō e no Jiko Shibōyurai Kansai Chiryō no Kakudai o Nerai [Biomaster Aims to Expand Therapies Using Adipose Derived Autologous Stem Cell Therapies to Affluent Patients through Alliance with Chinese Company]," *Nikkei Biotech*, 7 December 2009, 14; "Baioimasutā, Shibōnai Saibō de Nyūbō Saiken, Chūgokusha to no Teikei mo [Biomaster Conducts Breast Reconstruction, Also Forms Alliance with Chinese Company]," *Nihon Keizai Shimbun*, 2 July 2010, 26.

autologous cultured corneal epithelium is based on technology developed at the Italian Veneto Eye Bank and two scientists based at Modena University.<sup>39</sup> With the Veneto Eye Bank, the company has acquired technology transfer rights to all of Asia, including China, India and Singapore.<sup>40</sup>

Another prominent example of Asian expansion using imported technologies is the Cambridge MA based Broad Institute's collaboration with three Japanese firms: Wako Pure Chemical Industries, iPS Academia Japan and the Institute of Immunology. Wako Pure Chemical Industries, is a chemical company established in 1922 in Osaka to supply laboratory chemicals and reagents to scientists; the Tokyo-based Institute of Immunology Co. was established in 1979 to develop diagnostic reagents, while iPS Academia Japan is Kyoto University spinoff formed in 2008 that specializes in IP management and the distribution of iPS cell lines established at Kyoto University. The alliance combines Broad Institute's technology to produce various cell types; iPS Academia Japan's capacity in iPS cell technologies and Wako Chemicals sales strengths in related services – so as to provide genetically modified animals and modified human iPS cells using the latest genome editing technology in East Asia.<sup>41</sup>

Medinet Co., too, is expanding into Asia using established technologies by negotiating greater licensing rights. Established in 1995, the Yokohama based company provides a range of services related to cancer immuno cell therapy in Japan. These include: managing cell processing facilities; biotechnology for cell culture and processing; as well as provision of reagents and other consumables. In 2010, Medinet acquired the Asian licensing rights of electroporation technology from the US biotechnology firm MaxCyte. While the firm had acquired the Japanese license since 2007 for cancer therapy, the 2010 licensing arrangements allowed Medinet to apply MaxCyte's technology to more different types of cells; to a broader range of indications, from infections to drug development; as well as to Asian markets beyond Japan, such as China, Australia, Singapore, Thailand and Taiwan. Medinet has also strengthened its presence in China

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<sup>39</sup> Japan Tissue Engineering Co., Company Presentation for year ending March 2015. Available at [http://www.jp-te.co.jp/ir/library/index\\_seminar.html](http://www.jp-te.co.jp/ir/library/index_seminar.html), accessed 26 May 2015.

<sup>40</sup> "J-TEC ga Jigyō Keikaku, Saisei Kakumaku Jyōhi, Ajia Zen'iki ni [J-TEC Business Plan to Provide Autologous Corneal Epithelium throughout Asia]," *Nikkei Sangyo Shimbum*, 27 August 2008, 15.

<sup>41</sup> "Wakō Junyaku: Tokushu Men'ekiken, Idenshi Kaihen Dōbutsu nado no Jutaku Sakusei Sābsu Kaishi [Wako Pure Chemicals, Institute of Immunology, Begin Contract Research Services for Genetically Modified Animals]," *Kagaku Kōgyō Nippō*, 22 April 2015, 1.

through the acquisition of the Chinese medical device company BioOne in 2012. Through its Chinese subsidiary, Medinet has endeavoured to provide cell therapy services to Chinese medical institutions, as it has done in Japan through, for instance, Tokyo or Kyushu Universities.<sup>42</sup>

Some Japanese biotechnology firms simply act as Asian distributor for existing products. Takara Bio Inc. is one of Japan's leading biotechnology firms established 2002, and is based in Shiga Prefecture. In addition to sales of research reagents and equipment and equipment, the firm also conducts R&D in cell therapies. In 2012, Takara Bio signed an agreement with the Danish biotechnology firm Exiqon AS to sell Exiqon's miRCURY LNA products in Asia, which, in addition to Japan, includes China, Hong Kong, South Korea and India. The firm also provide contract research services using this technology.<sup>43</sup>

T&C Holdings is a Jasdac-listed (3832), Tokyo-based medical company that is involved in medical device manufacturing, management, and medical tourism. The company entered the medical business in 2013, and currently provides a range of services, from medical technology to consulting services and offers these two services in China. T&C have focused their internationalization efforts in China. In regenerative medicine, T&C collaborates with He Eye Hospital in Shenyang, China to conduct clinical research, and provides the hospital with regenerative medicine technology for a fee. If clinical research in China begins, T&C anticipates licensing arrangements with the hospital or another biotechnology company. The firm plans to establish a local joint venture if the technology is commercialized.<sup>44</sup>

T&C also have a China subsidiary, T&C Beijing, Ltd., through which are also planning to provide anti-ageing and immunotherapy to affluent Chinese patients with an emphasis on "growth factors" – either through Chinese medical institutions or through the recruitment of Chinese patients to Japanese clinics. In China, for example, T&C will send physicians with regenerative medicine expertise to the Beijing based Sansei Science and

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<sup>42</sup> "Medinetta, Bei MaxCyte sha to no Erekutoroporēshon Gijutsu Raisensu Keiyaku no Han'i Kakudai [Medinet Expands Licensing Rights to US MaxCyte's Electroporation Technology]," *Nikkei Sokuhō News Archive* 1886, 9 April 2010.

<sup>43</sup> Takara Bio Inc., "Exiqon sha no Idenshi Seigyo o Shiraberu tame no Kenkyū Shiyaku o Nihon, Chūgoku, Kankoku, Indo de Hanbai Kaishi [Sales of Exiqon's Gene Expression Regulation Product Begin in Japan, China, South Korea and India]," Takara Bio Inc. press release, 17 October 2012.

<sup>44</sup> "T&C HD Chūgoku no Ganka Iin wa Saisei Iryō no Ganka Ryōiki ni okeru Rinshō Kenkyū de Teikei [T&C Holdings, Alliance China's Eye Hospital for Clinical Research in Ophthalmology]," *Nikkei NEEDS Kigyō Senryaku Jōhō*, 16 May 2014.

Technology Group, while the Chinese firm will send trainees to T&C.

An emerging alliance form?

The Japanese company Regience actively seeks technologies from external organisations – whether in academia or industry – to develop them into potential therapies. Regience was originally established as KnowledgeSolution in 2000 by a former investment banker and biotechnology entrepreneur Masanori Murayama. The firm was renamed as Regience K.K. in 2008. Regience is a unique firm dedicated to the development of regenerative medicines and has endeavoured to take advantage of the implementation of the two regenerative medicine laws to commercialise Japanese advanced technologies. The company has licensed in a wide range of technologies for a range of different ailments across universities.<sup>45</sup> The firm has also licensed in technology from a Shanghai based company with CPC facilities for vitiligo, for which clinical studies are already under way.<sup>46</sup> The increasing attraction of China shown by Regience, not only as a market, but also as a source of knowledge and knowledge exchange is also reflected in iPS Academia's recent exhibition at ChinaBio 2015.<sup>47</sup>

The India dimension

As the foregoing paragraphs indicate, Japanese firms show growing interest in China, particularly in the last few years. However, this level of interest is not replicated in India. In the past, the now bankrupt Fuji Biomedix Co, once invested in Asian CROs, including the Indian CRO Accutest Research Laboratories India and the South Korean CRO Biototech Co. in the hopes of becoming Asia's leading CRO<sup>48</sup>. In 2007, Fuji Biomedix had also invested in the development of its regenerative medicines, particularly through an alliance with Mediclude Co., through which there is another China connection. Mediclude is a Japanese firm that operates a chain of Seishin Cosmetic Clinics across Japan, and have offered regenerative cosmetic treatments incorporating stem cells in adipose tissue. Seishin Cosmetic Clinics not only welcome affluent Chinese patients, they also have a branch in Shanghai.

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<sup>45</sup> Regience KK., "Regience to wa [About Regience]." Available at <http://regience.jp/company/>, accessed 18 May 2015.

<sup>46</sup> Murayama, Masanori, "Towards A Leading Company In Regenerative Medicine." Presentation, Kyoto, Japan, 10 November 2014.

<sup>47</sup> iPS Academia Japan, Inc., "Chaina Baio ni Sanka Shite Imasu [Participating at ChinaBio]." iPS Academia Japan, 16 April 2015, available at [ips-cell.net/j/topics/](http://ips-cell.net/j/topics/), accessed 18 May 2015.

<sup>48</sup> "Fuji Baio, Kankoku CRO to Gijutsu/Shihon Teikei [Fuji Bio Forms Technology/Capital Alliance with South Korean CRO]," *Nikkan Yakugyō* 14 December 2006, 7.

Another example with regard to the Indian expansion of a Japanese biomedical business is Nagase Sangyo. Nagase is a Tokyo and Osaka based chemicals and cosmetics trading company, which acquired the bankrupt biotechnology company Hayashibara in 2012, and strengthened its biomedical business. Nagase invested in the Indian chemical company ZCL Chemicals in 2009, and has sold various pharmaceutical ingredients, chemicals, reagents, and other medical materials around the world, including China and India. The firm is conducting R&D on chemically defined materials that can support advances in regenerative medicines. The firm is also developing cellular adhesives using siRNA.

Jellice's Indian expansion was motivated by access to raw materials.<sup>49</sup> Jellice is Japan's leading gelatin supplier that commands 80% of the gelatin market in the country. Established in 1941, the Miyagi prefecture based firm expanded into India (Pioneer Jellice India Private Limited) and China (Jellice Pioneer Private Limited Taiwan Branch) for access to raw materials, namely the bones of cows. While Jellice historically specialised in food products, the firm has diversified to produce gelatin for a range of medical and industrial purposes.<sup>50</sup> In regenerative medicine, their expertise is applied to cell cultivation media; and the firm is seeking other means of diversification in this field beyond applications of gelatin.

Another Indian collaboration involves the use of Indian expertise in information technology. The MediBIC group, established in Tokyo in 2000, offers a range of services in the healthcare sector, utilising information technology for gene analysis, big data analysis in preventative health care, clinical trial support, and regenerative medicine<sup>51</sup>. In 2004, the firm formed an alliance with India's Strand Genomics Pvt Ltd to take advantage of the high IT technology capacities in India to jointly develop informatics and support services for the Japanese market.<sup>52</sup> By 2006, the firm had formed further alliances with Indian medical firms and took part in an India Forum that urged Japanese

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<sup>49</sup> "Shinshun Intabyū: Jellice, Inai Ken'ichi Fukushachō [New Year Interview: Jellice Vice President Kenichi Inai]," *Nihon Shokuryō Shimbun* 19 January 2005, p 13.

<sup>50</sup> Jellice, "Kaisha Jōhō [Company Profile]." Available at <http://www.jellice.com/company/info>, accessed 26 May 2015.

<sup>51</sup> MediBIC Group, "Keiei Rinen [Corporate Mission]." Available at <https://www.medibic.com/corporate/mission.html>, accessed 26 May 2015.

<sup>52</sup> "MediBIC, Puroteōmu Kaiseki Sābisu Kaishi [MediBIC Begins Proteome Analysis Services]," *Kagaku Kōgyō Nippō* 16 September 2004, p 9.

firms to take greater advantage of the opportunities of alliances with Indian IT and biomedical companies<sup>53</sup>.

A further unique venture is the GN Corporation based in Yamanashi Prefecture. GN Corporation was established in 2002 by an Indian scientist then based at Yamanashi University. The firm is affiliated with the India-based Nichi-in Center for Regenerative Medicine mentioned earlier, which trains researches as well as conducts research activities in regenerative medicine. GN Corporation not only offers consulting services to Japanese biomedical firms interested in expanding into India and other South Asian countries, they also help export medical equipment, devices as well as cell cultivation technologies from Japan.<sup>54</sup> GN Corporation is also affiliated with the India-based Indo-Japanese joint venture established in 2000 that is also related to the Nichi-In Center, and dedicated to technology transfer between Japanese and Indian organisations, which include the area of regenerative medicine<sup>55</sup>. While less explicitly related to regenerative medicines, and a rather small initiative, it may also be worth mentioning that Indo Japanese joint ventures such as Medi Nippon Healthcare Pvt Ltd, offer – in addition to acting as trading agent– consultancy services for Japanese biomedical firms regarding the Indian market and medical tourism services for Indian patients in Japan.<sup>56</sup>

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<sup>53</sup>“FDA Ninka Shisetsu wa Yaku 60 Shisetsu mo: Kōhinshitsu, Teikosuto, Indo no Gijutsusha o Katsuyō Seyo [More than 60 FDA Approved Facilities: Utilise High Quality, Low Cost Indian Technicians. MediBIC Group. India Forum],” *Medical Academy News*, 11 August 2006.

<sup>54</sup> See GN Corporation, “Kaisha Hōshin [Company Concept]” GN Corporation. Available at <http://www.gncorporation.com/gncorp/concept.html>, accessed 20 April 2015.

<sup>55</sup> See Nichi-In Bio Sciences Pvt Ltd., “About Us.” Nichi-In Bio Sciences Pvt Ltd. Available at <http://www.nichiin.com/aboutus.htm>, accessed 20 April 2015.

<sup>56</sup> See Medi Nippon Healthcare Pvt Ltd., “Services.” Medi Nippon Healthcare Pvt Ltd. Available at <http://www.medinippon.com/services/index.htm>, accessed 20 April 2015.