The commercialization of biotechnology in Japan

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This exploratory study examines the role of large pharmaceutical companies, the government, universities and dedicated biotechnology firms in the commercialization of biotechnology in Japan. Based on secondary data, as well as primary qualitative data, we conclude that, in particular, the low level of basic research and deficiencies in the technology transfer from universities to the private sector have inhibited the commercialization of modern biotechnology in Japan. Several of the formal barriers have been removed recently and there are already weak signals of a bio-boom in Japan, as indicated by the increasing number of newly founded dedicated biotechnology firms. A change in the mindset of university professors towards entrepreneurship will be essential for the success of commercial biotechnology in the long run.

The early years

In the early 1980s, many Japanese companies acknowledged the potential of biotechnology. Interestingly, it was not only the traditional pharmaceutical, chemical and food processing companies that stepped into biotechnology, but also many companies with totally unrelated core businesses, such as steel manufacturers and even construction companies. In contrast to the developments in the USA, these enterprises were mainly large companies or part of an industrial group. As a result of the oil crisis and diminishing profits in their core businesses, these companies conceived biotechnology as an opportunity to diversify their business.

The main focus in the 1980s was in bioprocess engineering because Japan possesses a strong competitive position in fermentation technology [1]. In fact, the biggest share of research funding was channeled into bioprocess engineering rather than into basic research in molecular biology [2]. This strategy turned out to be successful in some applications of biotechnology, for instance, in the production of amino acids, antibiotics and vitamins [3]. The downside of this strategy was that Japan lags several years behind the USA in 'modern' biotechnology, such as genomics, proteomics and bioinformatics.

In the following, we analyze how certain core elements (large pharmaceutical companies, the government, universities and dedicated biotechnology firms) of the institutional environment have inhibited the commercialization of 'modern' biotechnology in Japan, and how recent developments have started to change the situation. This analysis is based on secondary data, such as government reports and annual reports from pharma companies, as well as primary qualitative data derived from interviews with entrepreneurs and industry experts (consultants, technology transfer managers) in Japan.

Biotechnology and large pharmaceutical companies

Most pharmaceutical companies in Japan have previously neglected the importance of biotechnology for research and development on drugs. Their strategy was mainly focused on 'me-too' products, such as generics, for which efficient low-cost manufacturing was established. However, this strategy has turned out to be less successful. Although Japan is the second largest market for pharmaceuticals in the world, there are no Japanese pharmaceutical companies in the worldwide top ten in terms of sales. The largest pharmaceutical company from Japan, Takeda Chemical Industries (Osaka), ranks only 14th globally. One explanation is the lack of biotechnological research know-how. Although Japanese pharmaceutical companies have significantly increased their R&D budget in 2001 (see Table 1) with a special focus on biotechnology, the combined R&D budget of the ten largest Japanese pharmaceutical companies (473 billion Yen, which is ~12% of 2000 sales) is in the same order of magnitude as GlaxoSmithKline's R&D budget (representing 14% of 2000 sales), which clearly shows the backlog of the Japanese pharmaceutical industry.

Some major pharmaceutical companies have started to reorganize their efforts in biotechnology and have put greater emphasis on research activities. To obtain a window on innovative technologies, which will eventually result in new products, large pharmaceutical companies are looking overseas for new opportunities. Recently, many Japanese pharmaceutical companies entered into different types of collaborations, such as research contracts, joint ventures or licensing agreements with leading US universities or specialized small- and medium-sized biotech companies

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Table 1. R&D budgets of the ten largest pharmaceutical companies in Japan

Company	R&D-budget plan March 2001 (in billion Yen)	Increase (%) compared with fiscal year 1999–2000
Takeda (Osaka)	89	15.3
Sankyo (Tokyo)	73	13.4
Yamanouchi (Tokyo)	56	2.2
Esai (Tokyo)	53	13.5
Fujisawa (Osaka)	51	11.8
Chugai (Tokyo)	42	5
Daiichi (Tokyo)	40	11.6
Shionogi (Osaka)	29	8.1
Welfeid (Osaka)	20	6.2
Tanabe (Osaka)	20	2.6
Total	473	10.1

(Table 2). In 1982, these collaborations still had their focus primarily in marketing [4] for obtaining a rather rapid access to market. Nowadays, there is a clear tendency towards an increasing significance of R&D partnerships. In addition, research centers and subsidiaries of these Japanese pharma companies were established abroad to monitor recent developments in leading biotechnology clusters, as well as to facilitate collaborations with researchers.

However, sourcing technology from abroad, a classic catch-up strategy, will only partially offset the lack of innovativeness at home. To evaluate and implement the potential of the technologies

Table 2. Selection of recent collaborative activities of major Japanese pharmaceutical companies in biotechnology (from http://www.recap.com)

Company	Partner	Year	Type of collaboration
Takeda (Osaka)	Celera Genomics (Rockville, MD, USA)	2000	Licensing
	Affymetrix (Santa Clara, CA, USA)	1999	Licensing
	Human Genome Sciences (Rockville, MD, USA)	1995	Licensing
Eisai (Tokyo)	Incyte Genomics (Palo Alto, CA, USA)	2001	Licensing
	Neurogenetics (San Diego, CA, USA)	2001	R&D collaboration
Fujisawa (Osaka)	CV Therapeutics (Palo Alto, CA, USA)	2000	R&D collaboration
	Arena Pharmaceuticals (San Diego, CA, USA)	2000	R&D collaboration
	Discovery Therapeutics (Richmond, VA, USA)	1999	Licensing
	GeneLogic (Gaithersburg, MD, USA)	1999	Licensing
	Quark Biotech (Cleveland, OH, USA)	1999	R&D collaboration
	Protein Design Labs (Fremont, CA, USA)	1999	
Chugai Pharmaceuticals (Tokyo)	Immusols (San Diego, CA, USA)	2001	R&D collaboration
	Protein Design Labs (Fremont, CA, USA)	2000	Licensing
Sankyo Pharmaceutical (Tokyo)	GeneLogic (Gaithersburg, MD, USA)	2001	Licensing
	FibroGen (South San Francisco, CA, USA)	2001	R&D collaboration
	Incyte Genomics (Palo Alto, CA, USA)	2000	Licensing
	Genetic Institutes (Cambridge, MA, USA)	1999	R&D collaboration
	Affymetrix (Santa Clara, CA, USA)	1999	Licensing
	Quark Biotech (Cleveland, OH, USA)	1999	R&D collaboration
	ArQule (Woburm, MA, USA)	1997	R&D collaboration
Taisho Pharmaceuticals (Tokyo)	Pharmagene (Royston, UK)	2001	Licensing
	Arena Pharmaceuticals (San Diego, CA, USA)	2001	R&D collaboration
	IDEC Pharmaceuticals (San Diego, CA, USA)	2000	Development
	EpiGenesis (Cranbury, NJ, USA)	2000	Licensing
	Neurocrine Biosciences (San Diego, CA, USA)	2000	Development
	FibroGen (South San Francisco, CA, USA)	2000	Development
	Vertex (Cambridge, MA, USA)	1999	Development
	Quark Biotech (Cleveland, OH, USA)	1999	R&D collaboration

offered by the partner, it is necessary to build up an in-house expertise in the field of interest. According to Cohen and Levinthal [5], this so-called absorptive capacity broadens the internal know-how base and enhances the ease of adoption of external innovations because new technological knowledge can be better absorbed and applied with a basic understanding of the technology. Therefore, it is arguable whether the Japanese pharmaceutical industry can take advantage of these collaborations in the long term, without having a strong internal research base in biotechnology.

Initiatives of the Japanese government

In Japan, the central government has an important role in the commercialization of biotechnology [6,7]. There are several ministries concerned with biotechnology, most notably the Ministry of Economy, Trade and Industry (METI, formerly MITI), the Ministry of Education, Science, Culture and Sports (MEXT, formerly Monbushu and STA), the Ministry of Health, Labour and Welfare (MHLW, formerly MHW) and the Ministry of Agriculture, Forestry and Fisheries (MAFF), which promote and guide research in industry, universities and other national research institutions. In the past, these ministries have acted in a rather fragmented and reactive approach to promote biotechnology. No integrated policy among these institutions harmonized the efforts and, often, there existed a competition between different projects in biotechnology launched by each ministry. However, the different ministries have in common that they prioritized applied sciences in the private sector rather than basic research in universities or other public laboratories [8–10].

A unique feature of the Japanese industrial policy are research associations and research companies in which up to one dozen enterprises work together in a field of common technical interest. These R&D consortia are aimed at raising the level of understanding about new technologies and enabling cross-fertilization between companies. The Japanese government encourages these types of inter-firm collaborations and has a guiding and coordinating role in the distribution of information through its different ministries. Although the main focus is geared to explicitly commercial purposes, some projects have also been conducted in basic research by these R&D consortia. As an example, the ERATO projects (Exploratory Research for Advanced Technology), organized by STA (Science & Technology Agency) and launched in 1981, encompassed projects in basic research, such as research on bioadhesives, glycobiology and brain mechanisms, for an average period of five years [10,11].

Although these R&D consortia had an important role of disseminating new projects and technology in some industry sectors (e.g. in the electronic industry), this approach has failed in biotechnology. Because the rationale behind these associations has been more a broad diffusion of information and know-how rather than the fostering of innovative research, these inter-firm associations are often little more than a distributor of funds to large, already existing firms. This strategy has turned out to be less successful in biotechnology, as one can see from the weak position of the pharmaceutical industry. In the past few years, however, some promising new initiatives in industrial policy have been introduced by the Japanese government, which are outline below.

After the burst of the economy bubble in 1990, the Japanese government rediscovered biotechnology as one of the 15 key sectors for future industrial development under its Action Plan for Economic Structural Reform in 1997. In contrast to the 1980s, the Japanese government has acknowledged the dynamism of small entrepreneurial businesses in high-technology sectors. There exist several supporting programs for entrepreneurial activities providing no-interest loans and grants for individuals who want to start their own businesses.

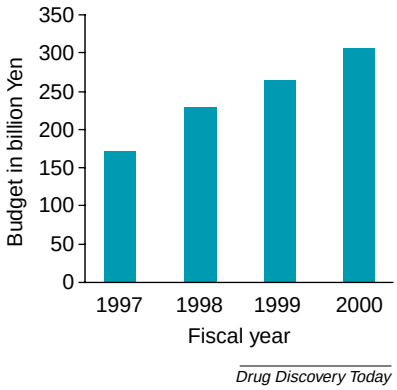

Figure 1. The Japanese government's Life Sciences budget (data from the Ministry of Trade and Industry; see http://www.meti.go.jp).

Another important element of the structural reform is to push forward basic research. Given the low level of basic research in the modern Japanese biotechnology industry [12], the Japanese government has recently promoted research carried out in public laboratories. As seen in Fig. 1, the total funding on Life Sciences for research institutions has increased steadily to about 300 billion Yen for the fiscal year 2000, which is then channeled into specific projects.

Previously, each arm of the government has launched their own projects in an isolated manner for different areas of biotechnology [13]. To change this situation, the ministries concerned with biotechnological research formulated a joint 'basic guideline for the creation of a biotechnology industry' and set up the Life Science Council in 1999. One of the first inter-ministerial projects in biotechnology was the 'Millennium Project', which was initiated by former Prime Minister Keizo Obuchi in December 1999. The main objective of this project is to promote human and rice genome research including efforts to decode disease-related human genes and to

Table 3. Japans 'Millennium Project' budget for promoting biotechnology

Project name	2000 fiscal year (in billion Yen)	2001 fiscal year (in billion Yen)
Analysis on human genome	33.8	60.6
– Post-genome sequence		(28.1)
– Analysis of genome sequence		(32.3)
Tissue engineering	10.8	13.1
Analysis of rice genome	5.6	7.3
Assurance of safety in biotechnology	0.4	0.6
Others	13.5	13.7
Total	64.1	95.3

develop a new cancer treatment. In addition, the project is intended to facilitate the collaborations between academia, industry and the different bio-related ministries. The total budget of this project is ~95.3 billion Yen in the fiscal year 2001 compared to 64.1 billion Yen in 2000 (+ 49% growth) as shown in Table 3.

The success of Japan's biotechnology sector will strongly depend on the degree to which the results of research projects can be transferred to the private sector for commercial development. The Japanese government has, therefore, promoted the technology transfer from research institutions and universities to the industry. In August 1998, Technology Licensing Organizations (TLOs) were established by the Ministry of Education, Science, Sport and Culture (MEXT) to encourage the patenting of university research and to facilitate technology and knowledge transfer between universities and the industry. TLOs are intended to have a bridging function between academia and industry to promote particularly the development of small- and medium-sized high-tech enterprises. Basically, these organizations offer support for companies, as well as public research institutions such as consulting services, hosting educational seminars and information exchange.

As of September 2001, 21 TLOs were authorized by METI. Many of these organizations have a special focus in biotechnology; for example, the Technology Licensing Offices at the University of Tsukuba, University of Tokyo, Tokyo Institute of Technology and Nagoya University.

Research and educational system at Japanese universities

At the beginning of the 1980s, the Japanese government heavily supported the building of production expertise in biotechnology [2]. The majority of research funds was therefore channeled into engineering departments rather than biology institutes. This has led to an underfunding situation for basic research at biology departments, which in turn explains the low level of basic research in modern biotechnology, an impression confirmed by looking at the number of publications in peer reviewed journals and the impact of scientific papers [12]. Although the Japanese research system emphasized applied sciences, it would be wrong to imply that Japan entirely ignored basic research. There do exist several well-known research facilities, most notably in the Life Sciences, the Institute of Physical and Chemical Research (RIKEN), which have an excellent track record in basic research.

In Japan, any active participation of professors from public universities with private companies was stifled by strict regulations. For instance, scientists in Japan were not allowed to act as consultants on a part-time basis or serve on corporate boards. Furthermore, regulations limited the amount of contract research and thus prevented the development of strong links between researchers from the public and the private sectors. Because professors, as civil servants, were not allowed to accept consulting fees, there was a lack of appropriate incentive. This system also discouraged academics supporting the creation of new ventures because it was not permitted for university professors to start their own venture and retain their position in the university. However, several of these formal barriers have been removed recently by the Japanese government, for example, the Industrial Technology Enhancement Act of 1999 (Sangyo-gijutsuryoku-kyoka-hou) allows national university professors to do consulting work and to serve on corporate boards.

However, there are still culturally induced barriers towards entrepreneurship. In Japan, the educational system mainly prepares for lifetime employment at large corporations, which offer secured jobs and provide prestige for the workers. Thus, working for a larger company until retirement is the first choice for the brightest graduates rather than taking the risk of setting up a new venture. If a new venture ultimately fails, its researchers will also have difficulty in finding new jobs. Moreover, leaving university mid-career could interrupt the researcher's social network, which is highly regarded in Japan. For these reasons, the risks involved in disrupting an academic or industrial career seem enormous so that founding one's own venture is daunting for a Japanese scientist.

Dedicated Biotechnology Firms (DBFs) in Japan

According to Bullock and Dibner [4], there was only one Japanese firm in 1988 that could be comparable to US biotechnology firms. Despite the barriers, mentioned

previously, to bio-entrepreneurship in the educational and research system in Japan, several new dedicated biotechnology companies have been established in the past few years. Following a rather broad understanding of dedicated biotechnology firms, defining biotechnology companies as private organizations, which conduct research in biotechnology (modern as well as old biotechnology) and which were established after 1980, there currently exist 247 companies dedicated to biotechnology (see Fig. 2). Given the importance of biotechnology on the discovery and development of drugs, it is notable that there are only 34 biopharmaceutical companies in Japan. Most likely, this is caused by Japan's weak research base and late entry into molecular biological sciences. As mentioned previously, molecular biology had a minor role at universities in the past so that Japan simply did not have a deep pool of researchers willing to start new businesses in the area of biopharmaceuticals.

A major portion of these dedicated biotechnology firms has been founded in the last few years (see Fig. 3) and, according to the Japan Bioindustry Association, approximately one third of these companies are established by university researchers, one third represents spin-offs of large and medium-sized enterprises and the remaining are set up by others.

By way of example, one of these spin-offs was established by Hitachi in 1999, to promote commercialization of biotechnology. Hitachi's Life Sciences Group center for genome analysis is located in Kawagoe, Saitama prefecture, and is well-equipped with analyzer and information systems. These spin-off activities are not solely limited to large companies because medium-sized enterprises are also interested in new business opportunities based on biotechnology; for instance, NIDEK Corporation, a medium-sized medical device enterprise, set up the biotechnology company J-TEC (Gamagori, Aichi prefecture) in 1997, which focuses on tissue engineering. Similarly, several other dedicated biotechnology firms have been established in the past few years (see Table 4).

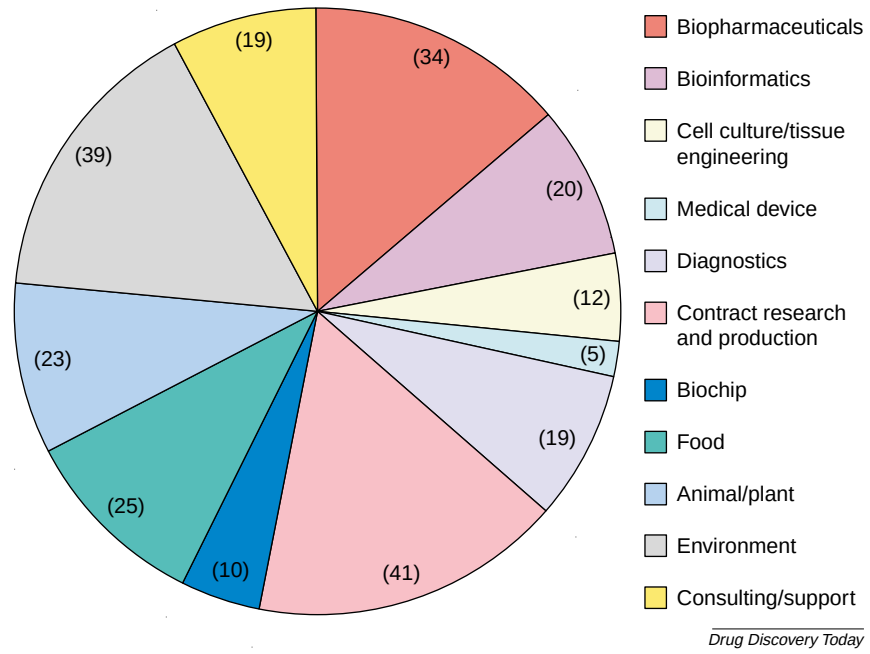

Figure 2. Focus of current Japanese dedicated biotechnology firms according to the Japan Bioindustry Association, with the number of companies in parentheses. (Data from the Japan Bioindustry Association; see http://www.jba.or.jp)

Discussion

In the preceding sections we have described separately the role of large pharmaceutical companies, the government, the research and educational

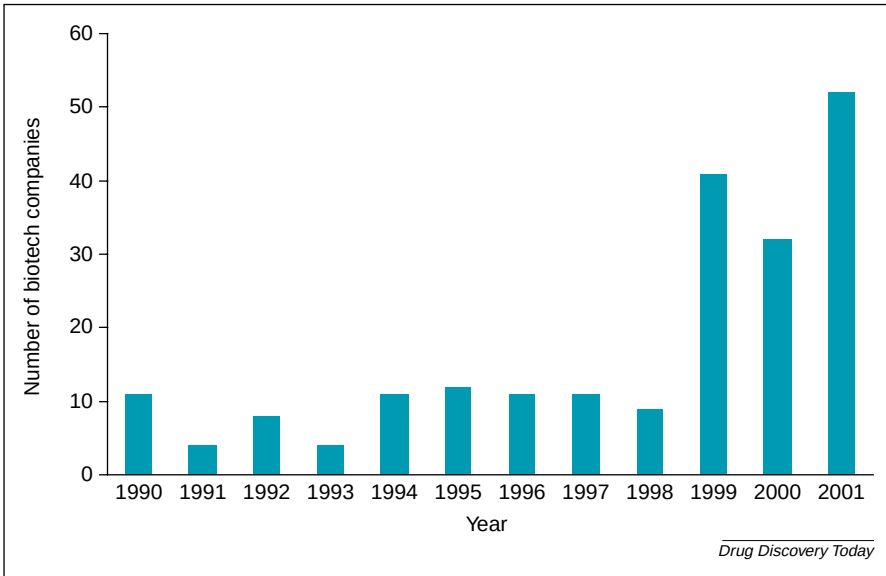

Figure 3. The number of dedicated biotechnology firms in Japan from 1990 to 2001 (as of September 2001) according to the Japan Bioindustry Association (data from the Ministry of Education, Science, Culture and Sports; see http://mext.go.jp).

Table 4. Selection of some Japanese start-up companies in biotechnology

Company	Foundation year	Business field
Pharmadesign (Tokyo)	1999	Bioinformatics
J-Tec (Gamagori)	1999	Tissue engineering
Effector Cell (Tokyo)	1999	Novel drugs for cancer and allergic diseases
GenCom (Machida)	1999	Functional gene analysis
CycLex (Nagano)	1998	Enzyme assays
TransGenic (Kumamota)	1997	Antibodies
NanoCarrier (Chiba)	1996	Drug delivery
DNAVEC Research (Ibraki)	1995	Gene therapy

system, as well as dedicated biotechnology firms on the commercialization of biotechnology in Japan. In general, the low level of basic biological research in industry, as well as in universities, and the lack of proper collaboration between universities, industry and the several ministries involved in biotechnology are regarded as some of the greatest problems. Thus, a redistribution of research funds in favor of basic research and an integrated effort to link research carried out at universities with research in private companies are needed if Japan is to be globally competitive in modern biotechnology.

Because large Japanese pharma companies have imported new technologies from abroad rather than collaborated with Japanese academic scientists, dedicated biotechnology firms might provide the missing link needed between basic research at universities and applied sciences in private companies. Often, dedicated biotechnology companies are established by researchers from academic institutions and therefore have strong connections to their former universities. This facilitates the technology transfer and has been the major stimulus for the successful development of modern biotechnology. Thus, it might be fruitful to promote entrepreneurship in Japan to strengthen the commercialization of biotechnology.

Although the Japanese government has created an environment conducive for bio-entrepreneurial activities in the past few years, there still exists a conservative attitude towards entrepreneurship. Mainly, the cultural preference for lifetime employment in universities or companies decreases the readiness to start risky endeavours, such as founding new biotechnology companies. Thus, it still requires a change in the mindset of researchers to cultivate entrepreneurship and foster the commercialization of biotechnology in Japan.

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