Internet Journal of Society for Social Management Systems Issue 11 Vol.1 sms17-6052
ISSN: 2432-552X
ORIGINAL ARTICLE

Analysis of the Issues in Japanese Biopharmaceutical Industry by Utilizing R&D Process Modeling

Takaaki Ohara[1*], Seigo Nasu[1]

[1] School of Economics & Management, Kochi University of Technology
185 Tosayamadacho-Miyanokuchi, Kami, Kochi, 782-8502, JAPAN

[*]E-mail: gtcd01939@yahoo.co.jp

***Abstract*:** Currently, the global bio-pharmaceutical industry is leading development of cutting-edge technologies in the 21st century. However, Japan's bio-pharmaceutical industry has fallen behind those in the Western nations. Although the government has not been totally non-responsive, various attempts by the public and private sectors have not accomplished substantial results. This article explores backgrounds and factors of this situation by analyzing structures and inter-organizational relations of research and development processes.

As a result, two factors were identified. The first factor of unsuccessful bio-pharmaceutical research and development by public and private sectors of Japan is that truly important technologies for expansion of the bio-pharmaceutical industry were not within the scope and thus not addressed. The second is a 'jump' of domestic pharmaceutical research and development companies into new platform technologies developed through government-industry collaborations, resulting in failure to exploit critical technologies in depth. This jump comprised one of the barriers of bio-pharmaceutical research and development activities in Japan.

Keywords: Japanese Biopharmaceutical, R&D process modeling, Institutional & Organization set perspective

1. Introduction and Background

As the former Ministry of International Trade and Industry (MITI) succeeded in development of super LSI through a research and development (R&D) association in 1980, it set up the R&D Association on Basic Technologies for Future Industries (on three themes: recombinant DNA usage technologies [1981-1990], industrial bio-reactor [1981-1988], and mass cell culture technologies [1981-1989]), which spent dozens of billions of yens in ten years through government-industry initiatives to catch up with their competitors in the US and Europe. Participating private companies were pharmaceutical and chemicals companies[1)2)3)4)].

Subsequent bio-technologies-related national projects led by the MITI were on application technologies of functional protein complexes [1989-1998] and glycol-conjugate production technologies [1991-2000][2)4)]. A protein engineering project [1986-1995] sponsored by the Japan Key Technology Center was also launched in response to the demands of the time[2)4)].

Received: 2017.08.08 / Accepted: 2018. 02.14
Internet Journal of Society for Social Management Systems Published Date: 2017.12.20

Other bio-technology-related national projects in and around the 1980's include comprehensive researches on development of new immunity substance (interferons) by the former Science and Technology Agency (STA) and a life-science promotion project that formed usage of bio-reactors and new microorganisms[1].

Thus, a number of companies in Japan were engaged in R&D activities on new technologies such as interferons[5]. As for the landscape in Japan as of 1980, Japan's microbial fermentation and enzyme-related technologies were sophisticated[3)5)6)] and, in relation to fermentation product separation and purification processes, the antibiotics production volume of Japan were the world highest; there was no reason to think that the quantity and quality of researchers and engineers in the field were inferior to the Western nations[3)5)6)]. In fact, some recognized Japan's R&D capabilities[5)6)] and basic researches of Japanese companies in some interferons and tumor necrosis factors (TNF) were comparable with those of the Western nations[5)] while lagging behind in insulin and human growth hormone; Chugai Pharmaceutical and Kirin Brewery having strengths in fermentation technologies could even enter into patent litigation with US bio-tech companies Genentech and Amgen in discovery of erythropoietin and G-CSF[7)8)]. However, as Toyobo et al. lost patent litigation against Genentech regarding TPA[9)], Japanese companies became falling behind their Western counterparts in R&D of next-generation technologies, i.e. antibodies without side effects, and many of them withdrew from the R&D fields in the 1990's.

There were not a great number of bio-pharmaceutical products that were placed on the market by 1995, including human growth hormone, insulin, interferon-α, interferon-β, erythropoietin, t-PA, blood coagulation factor VIII, G-CSF and interleukin-2[10)].

Naturally, less reporting is available regarding companies that withdrew from bio-pharmaceutical R&D[11)12)], but the reduction of companies engaged in clinical development over time suggests that a large number of companies withdrew. One of the few records reports that three major pharmaceutical and food companies abandoned development of TNF and a leading chemical company and a middle-ranking pharmaceutical company stopped development of interferon[13)].

Currently, the global bio-pharmaceutical industry primarily led by the Western players plays the central role in development of cutting-edge technologies in the 21st century. Among all, therapeutic antibodies have drawn significant attentions from both domestic and international societies as one of the core elements of today's bio-pharmaceutical industry.

Of the 43 blockbusters, only two were developed by Japanese pharmaceutical companies - Tocilizumab (Chugai Pharmaceutical) and Nivolumab (Ono Pharmaceutical and BMS) - and this suggest Japan's significant lagging behind Western R&D[14)].

For the purpose of this study, bio-pharmaceuticals are narrowly defined as recombinant DNA derived drugs (therapeutic proteins and antibodies) and cell culture derived drugs.

2. Framework of Research

2. 1 Research Question

Japan's bio-pharmaceutical industry has fallen behind the Western nations. All-out efforts of public and private sectors resulted in substantial outcomes in the electronics industry but there have not been remarkable results from similar efforts in the bio-pharmaceutical industry. As this study aimed to identify backgrounds and possible reasons of this situation, the following research question was set:
"Why haven't the government-industry efforts in Japan generated successful outcomes?"

2.2. Previous Study Review

Tanaka of Chugai Pharmaceutical cited the following reporting in February 2014 as an opinion of the Biopharmaceutical Committee of Japan Pharmaceutical Manufacturers Association (JPMA) on the reasons of lagged bio-pharmaceutical R&D activities in Japan[15]:

- In the 1980's, Japan's bio-pharmaceutical R&D, e.g. cytokine, was comparable with Western counterparts and resulted in release of products. However, distribution of such products was limited to the domestic market due to issues in patents, etc.
- In the 1990's, drugs for lifestyle-related diseases became the global trend in pharmaceutical development and accordingly both Western and domestic major pharmaceutical companies concentrated their resources on R&D for such drugs; in other words, they chose to invest in expansion of sales channels of such drugs into overseas markets, rather than in the potential bio-pharmaceutical market, where uncertainty existed.
- Meanwhile, bio-venture companies patiently continued bio-pharmaceutical R&D and technology development and eventually commercialized therapeutic antibodies in the late 1990's, which later became the mainstream of bio-pharmaceuticals.
- In Japan, Kyowa Hakko Kirin and Chugai Pharmaceutical, which had no prevailing drugs for life-style related diseases, continued bio-pharmaceutical technology development and R&D activities and successfully developed therapeutic antibodies from Japan.
- Around 2000, major players in Europe acquired bio-technologies and seeds in an attempt to enhance their bio-pharmaceutical pipelines, but the domestic majors could not keep pace with them.

Also, Miyata of Nikkei BP noted in 1999 that Japan lost the first new bio-competition starting in 1973[16]. Three factors were identified for the defeat: (1) excessive focus on manufacturing technologies; (2) neglect of patents; and (3) R&D initiatives relying on the government. As for the factor (2), patent application processes were neglected due to lack of the concept of substance patents in Japan during the period following World War II in which R&D on antibiotics started, according to Miyata. As for the factor (3), it was mentioned that businesses did not assign their best resources to the R&D but used it as a venue for human resource development, which resulted in waste of investments. Importantly, it was also pointed out that businesses could have only chance to acquire non-exclusive licenses.

2.3. Study Objectives

Miyata's discussion[16] that businesses did not assign their best resources to the government-led projects but often used such projects as a venue for human resource training is one of the possible answers from previous studies to the research question. This is probably a reflection of businesses' reliance on national project resources. Moreover, the primary portion of national projects was led by the MITI with involvement of the STA and the former Ministry of Education, but there were no remarkable initiatives of the former Ministry of Health and Welfare (MHW) that overseas pharmaceutical affairs[1]. This is thought to be associated with Miyata's discussion of the excessive focus on manufacturing technologies[16].

Thus, this study aimed to answer the research question from perspectives other than those pointed out by the previous studies by analyzing structures and inter-organizational relations of R&D processes.

3. Research Methods and Results

3.1 Three watersheds

First of all, three important turning points were

extracted from the history of bio-pharmaceuticals in Japan. The initial turning point is the "initial entry" of over 40 companies in different industries in around 1985. The second turning point was the "sustainment & continuance" phase in the 1990's where many of the Japanese companies failed to continue the R&D activities and were forced to withdraw. The last turning point is the "course selection & considering" in the 2000's, at which Japanese companies had to choose the path toward development of unique and new drugs or the path toward development of biosimilars (equivalents of generic drugs for bio-pharmaceuticals) after the emergence of therapeutic antibodies (Fig 1).

Fig1. Three watersheds of Japanese biopharmaceutical R&D

During the phase of "initial entry," the US and Japan competed over R&D of some interferons and TPA starting in the early 1980's but the US always stayed a step ahead of Japan. However, in the late 1980's, the R&D levels of the US and Japan became evenly-matched for TNF, EPO, and G-CSF and patent disputes were intensified further[17].

In the "sustainment & continuance" phase starting in the mid 1990's, therapeutic antibodies were placed on the market in series in the Western nations, emerging at the center stage of bio-pharmaceuticals. This is because Western bio-venture companies eventually succeeded in humanization of antibodies with reduced side effects, which Japanese companies were about to abandon[18].

On the other hand, Japanese companies were engaged in antibody-related technological development, but not successfully. They were struggling in a "chasm" and many of them, especially those from other industries, withdrew from the R&D activities.

In the phase of "course selection & considering", following the successful development of new therapeutic antibodies were already in Western nations, three options were available to Japanese companies: to venture to pursue the best-in-class drugs like the therapeutic antibodies; to secure steady results by creating biosimilars of such drugs; or to do both. It was the first time for bio-pharmaceutical R&D companies in Japan to have multiple options to choose.

3.2 R&D process modeling of therapeutic antibodies

Therapeutic antibody R&D processes was then structured (Table 1). While each company employs different manufacturing processes, a generic process that could be acceptable to all companies was used for the purpose of this study. The initial and last steps of the process are almost the same as those of bio-pharmaceuticals other than therapeutic antibodies, e.g. recombinant therapeutic proteins.

Table 1. R&D process modeling of therapeutic antibodies

	No.	STEP
Manu-facture	1	Screening of target (Antigen search & setup)
	2	Construction of expression vectors (Including human antibody production)
	3	Production of antibody expressed cells (Vector transfection)
	4	Screening of antibody best expressed cells (High expression & optimized cell culture)
	5	Screening of therapeutic antibodies best used as pharmaceutical (Evaluation system)
	6	Considering of cell culture (Upstream: small scale)
	7	Considering of purification (Downstream: small scale)
	8	Considering of mass cell culture (Upstream: industrial scale)
	9	Considering of mass purification (Downstream: industrial scale)
	10	Construction of cell banks
	11	Standardization of quality for active pharmaceutical ingredient
	12	Considering of best Formulation
Development		Evaluation studies as pharmaceuticals (Including clinical trials)
Regulation		Response to the supervisory authorities

3.3. Keyword Search on Databases

Further, keyword searches were conducted on three domestic databases (Japan Medical Abstracts

Society, Nikkei Telecom 21, and Scholarly and Academic Information Navigator of National Institute of Informatics) to identify the number of search results by years between 1990 and 2016 for each keyword, which would suggest the years in which each technological term drew particular attentions in Japan (Fig 2).

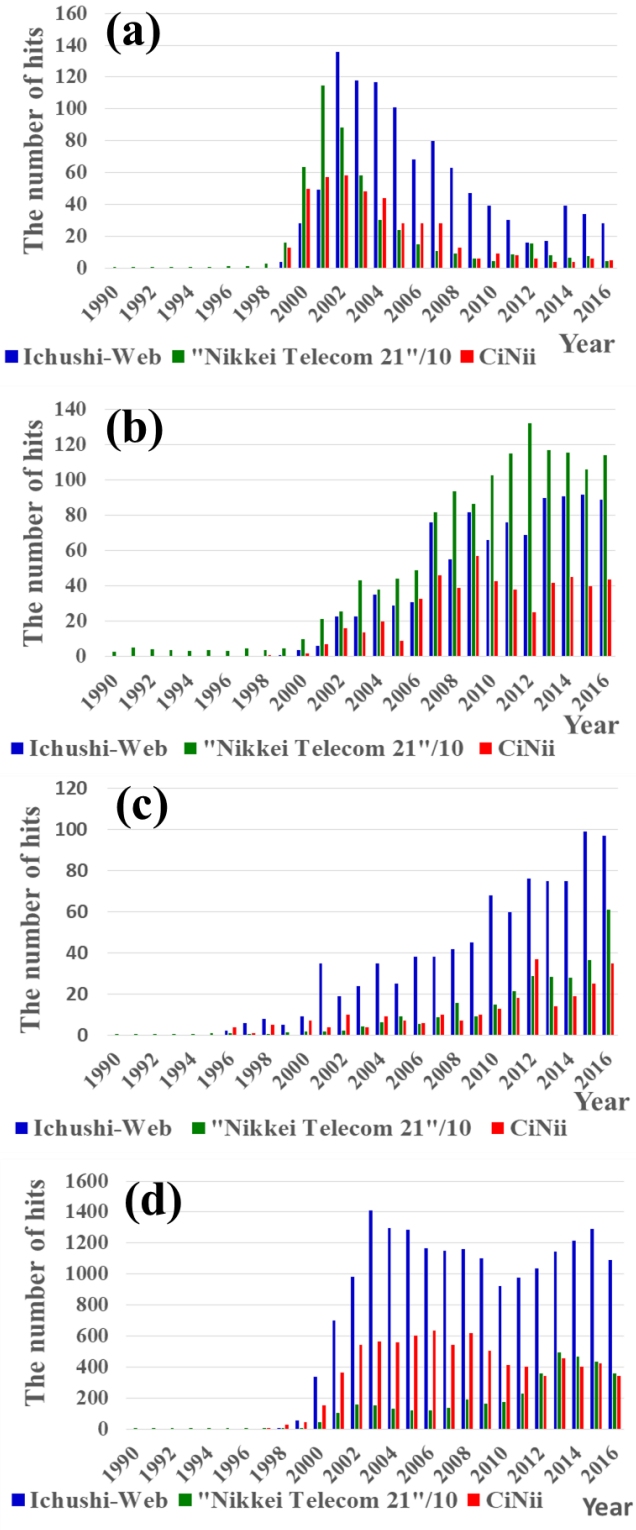


Fig 2. The number of hits per year searched by three databases

(a) Genomic drug discoveries, Peak: 2002, (b) Therapeutic antibodies, Peaks: 2009+2014, (c) Nucleic acid medicines, Peak: 2016, (d) Regenerative medicines, Peaks: 2003+2008+2015, (e) Biosimilars, Peak: 2015

Medline, the most authoritative database in the pharmaceutical and bio-technology fields, was not used because primary contents of the Medline database are English articles of Western researchers. To identify the hottest period of each technology in Japan, it is more appropriate to focus on articles written in Japanese and thus published relatively promptly (including advance academic reporting, non-academic magazine articles and newspaper articles written in Japanese).

Five search keywords used were genomic drug discoveries, therapeutic antibodies, nucleic acid medicines, regenerative medicines, and biosimilars. Although it was considered that recombinant therapeutic proteins should also be included, it was excluded because the expected period where articles relevant to this phrase were published the most was the 1980's, which was not covered by the aforementioned three databases.

3.4. Keyword Search Results

The keyword search results are shown in Figure 2 and illustrated in Figure 3 in a schematic format. For genomic drug discoveries, the results were relatively straightforward and characteristic. The number of

results was peaked between 2000 and 2004 and declined afterwards in all of the three databases, suggesting a typical pattern of a temporary boom.

For therapeutic antibodies, the figure started to rise around 2003 and formed peaks in 2009 and around 2014. The stable number of results continued until 2016. Nucleic acid medicines started to rise as early as around 2001 and it steadily continued without any significant peak until the peak in 2016.

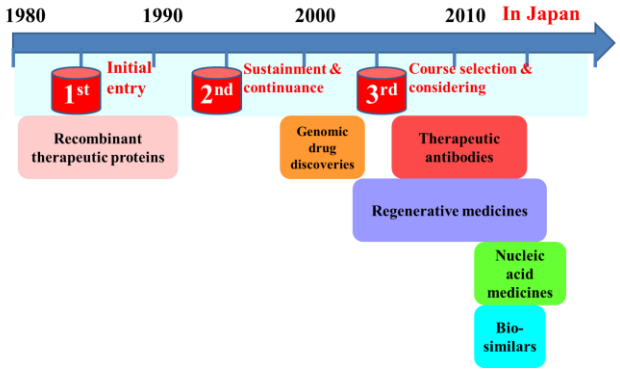


Fig 3. Quick shift of platform technologies in biopharmaceuticals

In the Nikkei Telecom 21 database, which contains more articles than the other two databases, the number of search results of therapeutic antibodies was the higher while that of nucleic acid medicines was lower, suggesting that therapeutic antibodies attracted more attentions of mass media than nucleic acid medicines.

Regenerative medicines were found to receive exceptional attentions as the number of search results of the phrase was at least ten times higher than that of any other phrases. There were also multiple peaks: in around 2003, 2008 and 2015. Recently, however, the attention to the phrase began to decline.

Biosimilars are a term defined relatively recently. Therefore, it emerged suddenly in 2009 when it was defined and was peaked around 2015. It seems to be already peaked-out.

In the schematic view of the results in Figure 3, the aforementioned three watersheds – “initial entry,” “sustainment & continuance” and “course selection & considering” - and the prime time of each platform technology are plotted. Although not subject to the database search, recombinant therapeutic proteins are also plotted in the period between 1980 and 1990, in which relevant development initiatives were the most actively conducted, along with the five keywords genomic drug discoveries, therapeutic antibodies, nucleic acid medicines, regenerative medicines, and biosimilars. As a result, it is shown that genomic drug discoveries became active after a while (a chasm) following recombinant therapeutic proteins, and then the trend of therapeutic antibodies, which still continues today, started. Therapeutic antibodies came next and finally nucleic acid medicines and biosimilars emerged in recent years. Those after therapeutic antibodies are in the "course selection & considering" phase.

3.5. Exploitation and Exploration of Bio-Pharmaceutical R&D

Extending the concept of innovation through balance of exploitation and exploration advocated by March, G. James (1991) [19], Bauer, Manuel discussed exploitation and exploration in product innovation and process innovation in the chemical industry[20]. In this study, similarly, the concept was applied to bio-pharmaceutical R&D through specific case studies.

The three watersheds of Japan's bio-pharmaceutical R&D are shown in chronological order in Figure 4. In the "initial entry" phase, the only option available was exploitation and there was no way of exploration. The representative production method was microorganisms regarding process R&D.

On the other hand, recombinant proteins were identified as the representative method for product R&D. In this phase, Japanese companies concentrated on catching up with the US companies

ahead. They introduced new technologies, but the focus was placed on in-house R&D efforts.

In the second phase "sustainment & continuance," exploitation and exploration were considered for both process R&D and product R&D of Bauer, Manuel. Specifically, the representative production method was microorganism in process R&D exploitation as in the first phase, but the animal cell-based production method was considered for exploration. Meanwhile, they worked on recombinant proteins as in the first phase for product R&D exploitation whereas they started R&D efforts on therapeutic antibodies for exploration. This means that production of therapeutic antibodies required animal cell-based production technologies. Domestic efforts for this purpose were not successful in this phase, and the barrier that hampered the efforts is hereinafter referred to as the "Wall of scientific technologies."

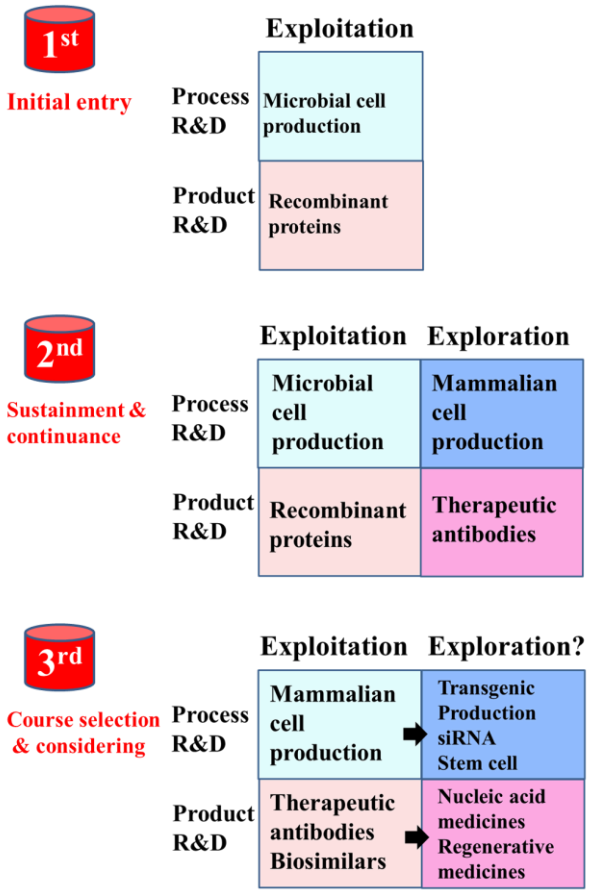


Fig 4. “Exploitation” and “Exploration”

Finally, in the third phase "course selection & considering," non-pharmaceutical companies (e.g. chemical and venture companies) started to engage in new technology development for process R&D, whereas pharmaceutical companies steadily engage in product R&D. Process R&D, the animal cell-based production technologies explored in the second phase were exploited, and therapeutic antibodies also explored in the second phase was started to be exploited for product R&D. Biosimilars also came into this category. The author assumes that items for exploration, on the other hand, should contain animal cell-based production technologies and therapeutic antibodies as they have some rooms for improvement and the market is still growing. However, there is a trend oriented toward uncertain technologies such as transgenic organism-based production, siRNA, and stem cells in the field of process R&D. Naturally, items corresponding to such technologies, including nucleic acid medicines and regenerative medicines, are listed for product R&D. At the present time, a trend of exploration and exploitation of new technologies developed by third parties through licensing-in, alliance and M&A emerges, rather than in-house exploration.

3.6. Bio-Pharmaceutical Researches and Inter-Organization Theory

Of perspectives that have been proposed in relation to analytical frameworks of the inter-organization theory, this study highlighted the institutional perspective[21)22)] and organizational set perspective[23)] as influencing perspectives in the domestic bio-pharmaceutical R&D. In this study, for the discussion of national projects in Japan, the institutional perspective was assumed to be the most relevant of all the perspectives of the inter-organization theory, and its association with the organizational set perspective was chronologically reviewed with an aim to identify factors of ineffective functioning of the national projects conducted through government-industry

collaborations.

Below are a chronological list of major institutional regulations and laws thought to be associated with the institutional perspective from sources including previous reporting[1)4)] and website data.

<Recombinant DNA-related regulations>

1979: Institution of guidelines for recombinant DNA experiment (Ministry of Education and STA)

1986: Institution of guideline for industrial application of recombinant DNA technology (MITI and MHW)

1991: Amendment of guidelines for recombinant DNA experiment (STA)

<Regenerative medicine-related regulations>

Nov. 2013: Enactment of Act on the Safety of Regenerative Medicine (Regenerative Medicine Safety Act) and Amended Pharmaceutical Affairs Act

<Biosimilar-related regulations>

Mar. 2009: Biosimilars added by MHLW (PFSB/ELD Notification No. 0304004)

Listed below are major actions of government-industry collaborations thought to be associated with the organizational set perspective in the chronological order.

<Recombinant DNA-related regulations>

1980: Bio-Technology Forum (with participation of five chemical companies)

1981: Life Science Committee (with participation of over 70 companies)

1981: Research Association for Biotechnology (R&D Association on Basic Technologies for Future Industries) (with participation of 14 companies)

<Regenerative medicine-related regulations>

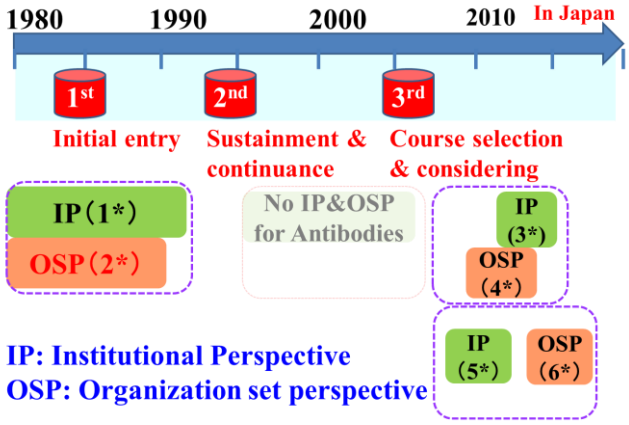
2011: Inauguration of Forum for Innovative Regenerative Medicine (FIRM) as an industry organization for regenerative medicine with 14 participant companies (currently with over 200 participant companies)

<Biosimilar-related regulations>

Apr. 2016: Inauguration of Japan Biosimilar Association (with 15 regular member companies)

Figure 5 was prepared based on the information described above, in which the aforementioned three watersheds of bio-pharmaceutical R&D in Japan are put in the chronological order with actions related to the institutional perspective and organizational set perspective plotted in a schematic format.

Important to note is that there are no actions relevant to the institutional and organizational set perspectives in the second phase. There should have national project solutions for various issues related to therapeutic antibodies in this phase, but unfortunately there were no such actions.



1* = Regulations of recombinant technologies

2* = Foundation of some bio associations

3* = Act of Regenerative Medicine

4* = Foundation of Innovation forum

5* = Revised regulation related to biosimilars

6* = Foundation of Japan Biosimilar Association

Fig 5. Two perspectives of Inter-Organizational Relations

3.7. Case Analysis

Company G was analyzed as an example of Japan's bio-venture equipped with multiple platform technologies and results are summarized in Table 2. A website and financial statements of Company G were referenced for preparation of the Table 2.

Table 2. Case: History of Bio-venture Company G focused on the platform technologies

Year	Topics	Platform
2001	Founded as a university-originated venture	
2007	Licensing-out to a Japanese pharmaceutical company: antibody	Antibody
2007	Concluded the joint development agreement with a Japanese pharmaceutical company	Biosimilar
2012	Listed on the TSE Mothers market	
2013	Launched: a biosimilar	Biosimilar
2014	Concluded the joint development agreement with a Japanese bio-venture company	Nucleic acid medicines
2016	The capital and business alliance with a Japanese bio-venture company	Regenerative medicines

Company G was enlisted on the TSE Mothers in 2012 and its sales volume for 2016 was approximately one billion JPY.

Originally the company was established as a university venture in 2001. The largest number of university bio-pharmaceutical ventures were founded in 2001. In 2007, the company licensed out a therapeutic antibody that they created to a Japanese pharmaceutical company. In the same year, the company entered into a joint biosimilar development contract. In 2013, the company placed a biosimilar on market and then entered into a joint development contract for nucleic acid medicines with a Japanese bio-venture in 2014. In 2016, the company further entered into a capital and business tie-up with a Japanese bio-venture regarding commercialization of regenerative medicines.

4. Discussions

4.1. Factor of Unsuccessful R&D 1

From findings of this research, two factors were identified as answers to the research question on reasons of the unsuccessful government-industry efforts.

As mentioned earlier, three important turning points were extracted: “initial entry,” “sustainment & continuance” and “course selection & considering.” The significant gap from Western nations originated in the continuing phase. During the phase, Western R&D successfully led to antibodies with less side effects in the mid 1990's and released therapeutic antibodies to the market. They were not stuck in a chasm but rather steadily expanded the bio-pharmaceutical industry.

On the other hand, government-industry research associations in Japan focused on cell fusion technologies, which eventually hardly contributed to bio-pharmaceutical manufacturing. Moreover, aforementioned application technologies of functional protein complexes and glycol-conjugate production technologies were said to be Japan's specific research themes[1)] and did not become mainstream of bio-pharmaceutical R&D. In other words, neither private companies nor the national government did not actually work on development of critical technologies such as reduction of antibody side effects, i.e. humanization of antibodies (Figure 5).

This was revealed by applying the institutional perspective and organizational set perspective chronologically to bio-pharmaceutical R&D. Thus, failure to engage in critical technological opportunities truly essential in expanding the bio-pharmaceutical industry is the first factor of unsuccessful bio-pharmaceutical R&D initiatives in Japan.

National initiatives were not effective in Japan, but how were governmental initiatives in the US, where the most achievements of the bio-pharmaceutical industry originate in?

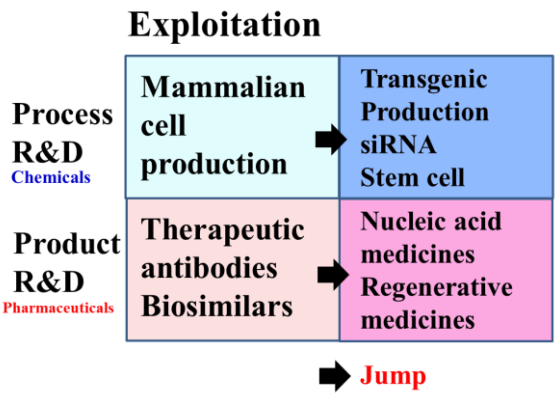
In the US, it seems that governmental support has worked effectively. However, the situation is slightly complex as follows. (1) The US government did not offer appropriate national projects. (2) The Bayh-Dole Act enacted in 1980 contributed to the substantial increase of university ventures and

TLOs[24]. These new bio-ventures eventually produced a number of bio-pharmaceuticals in the US ahead of the rest of the world. (3) NIH fund was available to US companies, especially bio-ventures[24].

4.2. Factor of Unsuccessful R&D 2

The government initiated government-industry-academia projects and, as a result, bio-pharmaceutical platform technologies emerged successively after 2000. It is probable that this in fact led to the second factor of unsuccessful R&D.

Specifically, successive booms of therapeutic antibodies, regenerative medicines, nucleic acid medicines and biosimilars took place following the genome boom in 2000 (Figure 2 and Figure 3). Meanwhile, when researchers got bogged down in R&D of one technology, they jumped in with a new technology that drew attention next. In other words, a quick shift to new technologies occurred frequently before exploiting truly important technologies such as antibodies. Then, they soon came to a dead end again with a new technology. Such a vicious cycle was repeated.



*Exploration: explored almost within the limits of conventional R&D process model

*Jump: jumped to the new R&D process model.

Fig 6. Differences of Exploration and Jump

In this paper, the act of quick shift to new technologies is expressed as a "jump." The author put an exclamation mark in "Exploration?" in the third phase of the Figure 4 because it is actually a jump, not exploration. The difference between jump and exploration is described in Figure 6 below.

At this point, there should be another question: Why did the Company G in Table 2 embark on various platform technologies? Although no mention was collected from the Company G regarding this, it is probably because the company, being enlisted, is exposed with hawk eyes of stockholders, who generally expect the company to deal with bio-technologies that receive frequent media coverage.

Here arises another question. Why does a jump into a new platform technology without exploiting critical technologies lead to unsuccessful results? There are two possible reasons:

Reason 1: R&D processes apparently differ. Steps 2 to 10 in Table 1 are totally different between therapeutic antibodies and nucleic acid medicines. At Steps 11 and 12, existing antibody know-how can be hardly used due to different presuppositions. Pre-clinical and clinical tests are also different even if subjects are of the same disease group. Experiences and knowledge on existing therapeutic antibodies may be useful in R&D of new antibodies, but hardly in R&D of nucleic acid medicines. Thus, R&D activities had to be started almost from scratch.

Reason 2: In recent years, there are increasing number of national projects to support new bio-pharmaceutical technology development. For example, efforts in regenerative medicines and biosimilars have been enriched from both the institutional perspective and organizational set perspective. Therefore, it seems that many companies just get a ride on such projects passively without in-depth strategic consideration of their own reasons to work on new platform technologies, just because other companies do the same or just because new technologies attract public attentions. It is

natural that companies acting without well-developed strategies easily jump to different new platform technologies.

A case where a Japanese company makes a jump through the course illustrated in Figure 5 is schematized in Figure 7. The company entered and started R&D in the “initial entry” phase but was unable to release bio-pharmaceuticals like many other Japanese companies in the second "sustainment & continuance" phase. In the second phase, the company wanted to embark on therapeutic antibodies, which was then under a spotlight in Western markets, but could not decide as no support from the national government was available. Later, new platform technology fields such as regenerative medicines emerged and attracted public attention and, in response, the company rushed into R&D in the field of regenerative medicines.

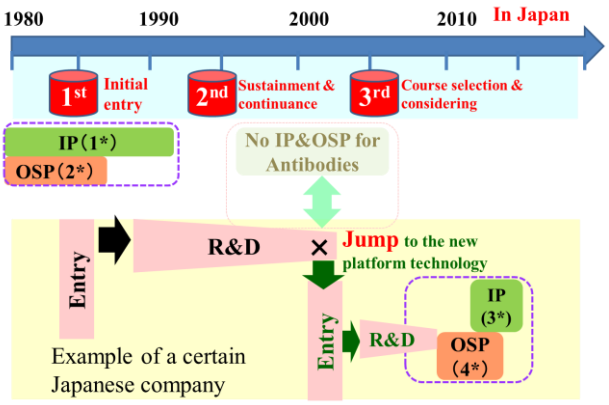


Fig 7. Jump to the new platform technology

Refer to the note of Fig 5

5. Conclusion and Future Issues

In this article, two factors of unsuccessful government-industry bio-pharmaceutical R&D activities in Japan were discussed. The first factor is failure to work on truly critical technological opportunities, and the other is pharmaceutical R&D companies' "jump" toward new platform technologies without exploitation of critical technologies.

As for the first factor, the Japanese government should have supported Japanese companies struggling in the chasm in the 1990's to enable R&D of promising therapeutic antibodies from the appropriate institutional perspective and corresponding organizational set perspective, i.e. by means of regulations (guidelines, laws and regulations, etc.) for the former and forums and research and technology associations for the latter. In fact, however, they only launched ineffective projects and failed to implement appropriate measures. The failure of Japanese government is probably due to: 1) government's inability and failure to identify which technology platform would be critical, and 2) lack of government's experiences required to provide for an appropriate and unique institutional perspective following the recombinant DNA regulations, which were instituted in the track of Western nations.

For the second factor, actions of the government could be different if they had been clearly aware of what is truly important at each point of time.

In conclusion, it is extremely important that not only pharmaceutical R&D companies in the field but also the government bodies have appropriate judging capabilities in order for future growth of Japan's bio-pharmaceutical industry. In Japan, where bio-technologies have gained popularity and often receive media exposure, it is essential to for stakeholders to stick with R&D activities that are truly important for the industry. Otherwise, it will be difficult to catch up with the Western counterparts. The principle is also applicable to countries other than the US, Europe and Japan, such as Southeast Asian countries that rely heavily on imported pharmaceutical products from the US, Europe and Japan.

There should be barriers of bio-pharmaceutical R&D in Japan other than the technological barrier and "jump" described in this article and the author will discuss these barriers in future articles.

References

1) Namiki, Toru et al., 1982. Bioinduatry: to consider its possibility, TUSHOSANGYO-CHOSAKAI, 107 -112 p.
2) Matsui, Takayuki, 1992. An Analysis on the Policies for Promoting Bioindustry, Toyama University Keizai-ronshu, 38(2):203-222.
3) Yamaguchi, Masahiro and Wakasa, Ryoichi, 1982. Bioindustry Frontline, SHIJYO-SHIMBUNSHA, 277 p.
4) Agency of industrial Science and Technology of Ministry of International Trade and Industry (Eds.),1992. Challenge to the next generation industrial technologies, Keibun Publishers, 262-265p.
5) Edwards, Christopher G., Elkington, John and Murray, Alison M., 1984. Japan taps into new biotech, Bio/technology 2: 307-321.
6) Tanaka, Masami, 1985. A Japanese view of Japan's biotechnology, Bio/technology 3: 176.
7) Kukawa, Momoko, 2002. Noble business person in the pharmaceutical world, Nikkei Business 1157:124-126.
8) Kojima, Masaru et al., 2007. Current patent issues of biopharmaceuticals, Patent 60(8): 67-80.
9) Kayano, Eiko, 2002. Biotechnological Development of Biotechnology and Patent System, BIO INDUSTRY 19(7):54-61
10) Nishijima, Masahiro and Kawasaki, Nana, 2013. From the basics of development to next-generation pharmaceutical products, KAGAKU-DOJIN, 28-29
11) Tajima, Ken et al. 2005. Why is it so difficult to enter from the other sectors? Nikkei Bio Business, 54:36-47.
12) Tomita, Minoru, 2000. Japan may hold superiority in a 25 trillion yen market, Weekly Economist, 78(13):86-87.
13) Sawai, Hitoshi, 1987. Patience and the technology to fill gaps, Nikkei Business, 469:125
14) International pharmaceutical intelligence (Eds.), 2017. Biologics Market 2016, International pharmaceutical intelligence, 1080:16-23.
15) Tanaka, Hiroshi, 2014. Expectations and remaining problems of biopharmaceuticals, Medical care and society, 24(2):159-170.
16) Miyata, mitsuru, 1999. The vision and development of bioindustry, Kansai Economics Research Center.
17) Miller, Henry I., 1989. Japanese Pharmaceutical Biotechnology: Perception vs. Reality, Bio/technology 7: 736.
18) Ohtomo, Toshihiko, 2006. The conception of biopharmaceuticals, Pharm Stage, 5(12):69-75
19) March, G. James,1991. Exploration and Exploitation in organizational learning, Organization Science, 2(2): 71-87.
20) Bauer, Manuel and Leker, Jens, 2013. Exploration and Exploitation in product and process innovation in the chemical industry, R&D Management, 43(3): 196-212.
21) Scott, W. Richard, 1987. The Adolescence of Institutional Theory, Administrative Science Quarterly, 32(4): 493-511.
22) Powell, Walter W., DiMaggio, Paul J., 1991. The New Institutionalism in Organizational Analysis, University of Chicago Press.
23) Evan, William M., 1972. An Organization-Set Model of Interorganizational Relations, Interorganizational Decision-Making, Chicago: Aldine Publishing Co., 181-200p.
24) Odagiri, Hiroyuki, 2006. Economics of Biotechnology, TOYO KEIZAI Inc.