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Structure and Ingenuity of Ecosystem Formation in Life Science
- System Formation in Belgium and Challenges in Japan -

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Introduction

Recently, the term “ecosystem” has increasingly been used among business managers and researchers. Originally, "ecosystem" meant ‘a biological community of interacting organisms and their physical environment’, but in some respects the term is now being used to indicate that innovation is mutually complementary.

In this paper, the pharmaceutical and medical device fields are collectively referred to as ‘life science’, but the life science field is one of the fields that takes a very long time from research to actual product development. Naturally, a single organization will not be responsible for all efforts during this period. The concept of a "cluster" may apply when considering circulation within a certain region, but in reality, the process from development to market launch often spans regions and countries.

The term "ecosystem formation" presents difficulty in that it is formed in a manner that overlaps globally in industry or research & development. Of course, depending on the area, there are areas that are said to have "ecosystems", but there are also aspects that are formed as subsystems of a kind of overall system.

This paper examines how ecosystems in the life sciences have functioned in a mutually complementary manner, how they have changed, and what the challenges are in Japan, through a review of previous research and a case study.

In Chapter 1, I describe the functions of each player in the current life science ecosystem, basically in Japan, and qualitatively examine what is emphasized by each business operator.

In Chapter 2, I touch on previous research on the theory of ecosystems and confirm their definitions. After that, through various research on innovation in life science, I confirm the difficulties unique to life science and how to deal with them.

In Chapter 3, I overview the movements of the players who actually form the system over the past 30 years. In addition, I focus on the formation of an ecosystem in the "development process" and look at the movements of each player from that perspective.

In Chapter 4, based on the discussion so far, I trace the Belgian bio-industry as a case study for the formation of a life science ecosystem. Unlike the pattern in North America, I verify its characteristics while confirming from an oral history that an ecosystem unique to Belgium is being formed.

In Chapter 5, I compare the situations in Belgium and Japan based on the framework considered in Chapter 2 and, from that, reconsider the issues in Japan.

Based on these chapters, the goal of this paper is to examine the following points.

- "Mutual complementation" is important in ecosystem theory, and each player exists as an actor with complementarity. Also, life sciences as a business are characterized by long development periods and uncertainties. Specifically, as global majors (mainly in North America) expand their scale, venture capital investment increases, and as this framework solidifies, investment in academia will increase steadily and the development process will continue to grow.

- This system is globally established, and in terms of connection to the global framework, various developments have been achieved depending on the country. Belgium is developing based on investment in science and human resources. It is one country that has achieved results, and the foundation of this was the strengthening of science. This is supported by activities such as Vlaams Instituut voor Biotechnologie (VIB), which is a cross-sectoral organization in universities and carries out organizational management centered on the career development of scientists. Belgium is also currently focusing on strengthening human resources. Underlying these movements is investment in human resources.

- In Japan, the development of major pharmaceutical companies shows a certain level of growth amid globalization, but the growth and maturity of finance and academia have not kept up with this growth. In view of access to a global structure, it is necessary to 1) improve funding methods for academia in line with the career paths of scientists and 2) flexibly implement human resource development methods for VCs and entrepreneurs. I believe that there will still be room for development toward the realization of a mutually complementary ecosystem by removing bottleneck, such as 'lack of seed'. To that end, it is necessary to grasp the overall composition and discuss changes that transcend the historical background of each player.

This paper is created through revisions based on many interviews and opinions on the first draft. I would like to express my strong gratitude to those who cooperated.

Chapter 1 Life science processes and ecosystems in Japan

- In the current life science development process, roles are divided from academia to companies in a manner similar to passing the baton in a relay, with a view to bringing products to market.
- Japan is also adapting to this movement, mainly in large companies. But from the perspective of academia and venture capital, it can be said that there is still room for revitalization.

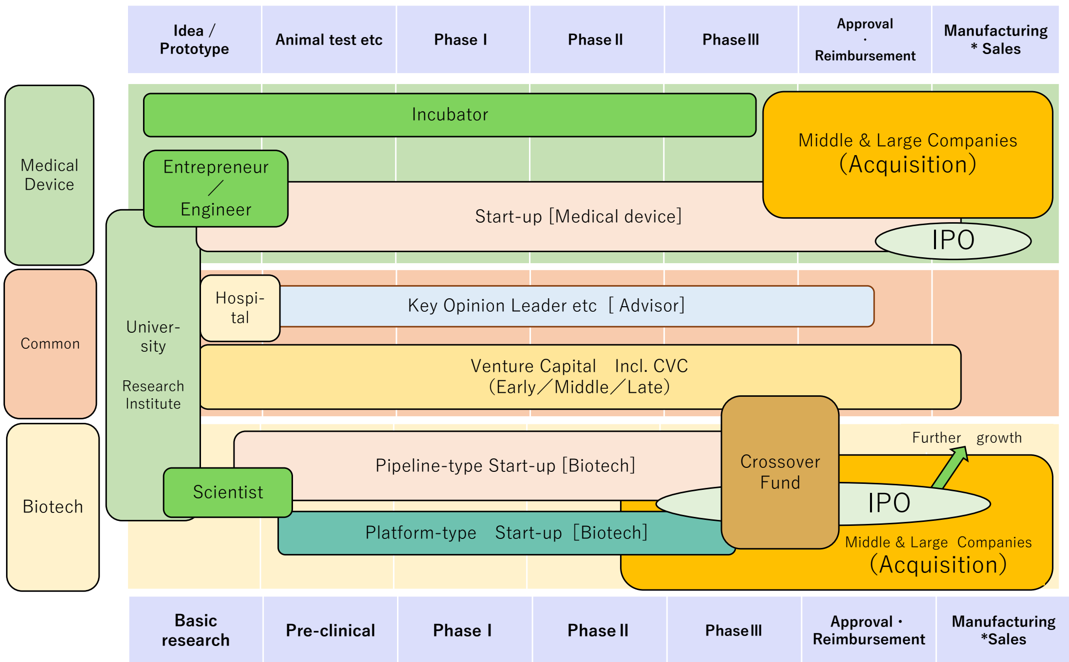
1.1 Development process in life science

First, I would like to show the movement of each player in the ecosystem underfoot. It is necessary to go through various processes in order to create pharmaceuticals and medical devices. Each product basically has processes for obtaining approvals. (There are products and services that do not require approvals, but they are excluded from the theme of this paper.)

Until the 1970s, this process was generally carried out within a single company. However, since the birth of bio-ventures in the late 1970s, venture companies and venture capital have gradually been created in the life science industry, and although there are many processes that continue to be completed within a single company, explicit division of roles increased.

Figure 1 shows the actual division of roles as of the 2020s. In this figure, the upper row is for medical devices and the lower row is for pharmaceuticals (mainly Biotech), and the timings related to the development process differ for each. Also, in pharmaceuticals, the timing of involvement of companies, universities, and research institutes differs between the development of small molecule drugs and the development of biopharmaceuticals. I would like to discuss this point without completely dividing it into cases.

Fig1 Ecosystem overview in life sciences



Created by the author

Breaking down the flow of Figure 1, there are roughly the following processes.

1. Discovery of seeds from universities and research institutes
2. Existence of venture companies and venture capital that will shape seeds, or R&D within the large company
3. Intermediation from the development stage to the commercialization stage, Support for approval processes such as clinical trials, and Commercialization development by acquiring a venture company (this is a process called business development).
4. Domestic or overseas distribution after the market launch

In the current industry of pharmaceuticals and medical devices, the flow of 1 to 4 is seamlessly established globally and, as a result, new products are born from this circulation. Of course, even now the number of companies with global sales channels is very limited. In that sense, it is not important that each region generally has global distribution channels.

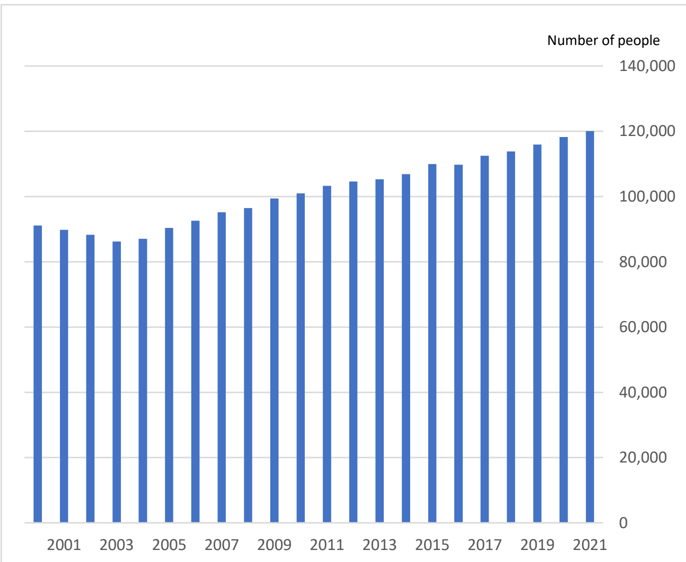
From this point on, I would like to take a look at this situation, first focusing on the current situation in Japan.

1.2 Research and development trends at universities and research institutes

The first is the process of discovering seeds. Of course, the word "excavation" itself is an expression from an industrial point of view, and research in the field of science is not carried out in order to be "excavated". However, without research and development in such places, the evolution of life sciences cannot begin.

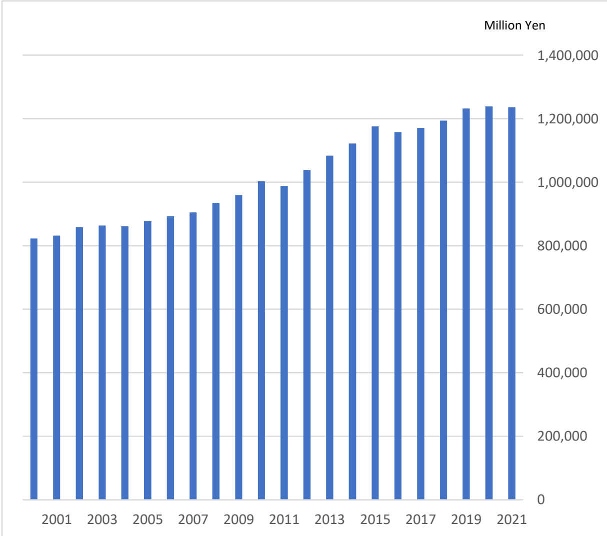
Here, I focus on universities and look at the changes in numbers of researchers in the field of natural sciences Health (medicine, pharmacy, dentistry) and their research expenditures in Figures 2 & 3.

Fig2 Trends in the number of Natural Sciences–Health researchers by organization and academic field (e.g., universities) in Japan



Source: Ministry of Internal Affairs and Communications 'Science and Technology Research Survey'

Fig3　Natural Sciences–Health research expenses for internal use (e.g., universities) in Japan



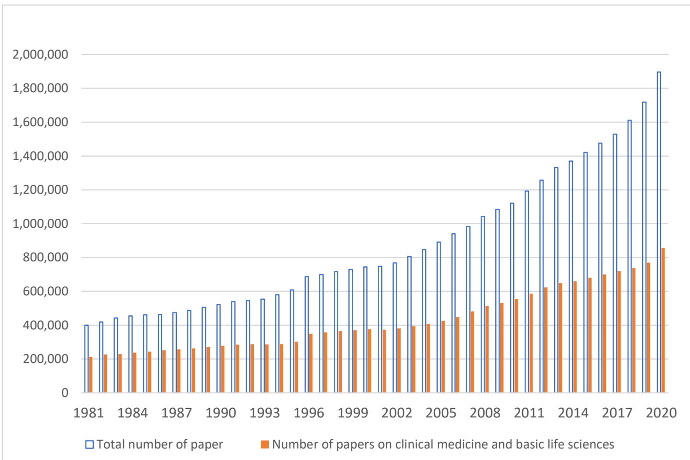
Source: Ministry of Internal Affairs and Communications 'Science and Technology Research Survey'

In terms of the number of researchers, there were 91,115 in 2000, but this will increase to 120,025 in 2021, an increase of about 1.3 times. On the other hand, the trend of research expenses is JPY 823.2 billion as of 2000, but it will be JPY 1.2364 trillion as of 2021, about 1.5 times.

This research is not being conducted in a form directly linked to pharmaceuticals and medical devices; however, it does include basic research and clinical practice for those fields, and new treatment concepts are being developed.

Next, I look at trends in the number of academic papers. Figure 4 shows trends in the number of papers worldwide. Papers in the combined fields of “clinical medicine/psychiatry/psychology” and “basic life sciences” account for 45.1% of all papers as of 2020. Over the last 40 years, these papers have increased by about 4.0 times, compared to about 4.7 times for academic papers overall, indicating that these two research fields continue to be active.

Fig4　Changes in the number of academic papers worldwide (integer count): 1981-2020

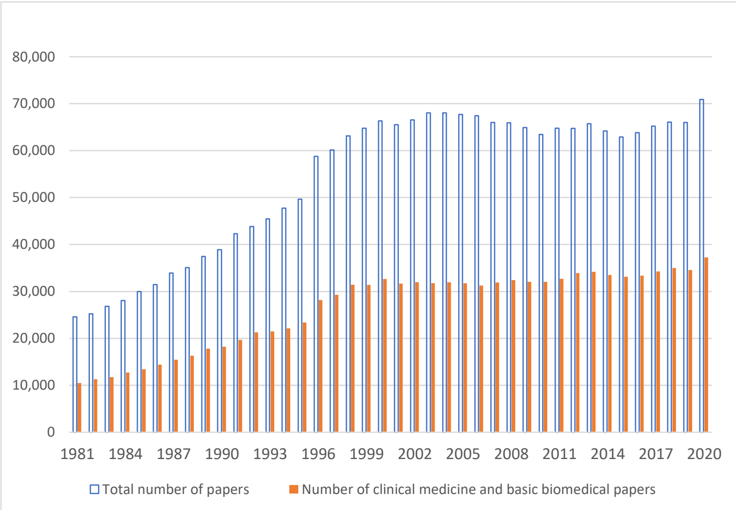


Processed and created by the author based on “Science and Technology Indicators 2022”, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and

Technology. (Data source: Web of Science XML from Clarivate)

On the other hand, Figure 5 shows the number of papers from Japan. There has been no significant change in the ratio of "clinical medicine/psychiatry/psychology" and "basic life sciences", but it can be seen that the number of papers itself has not changed significantly since around 2000. However, whereas in 2000 it accounted for 8.7% (worldwide) of the total number of papers in both fields, as of 2020, it was around 4.4%.

Fig5 Changes in the number of papers worldwide (integer count) in Japan: 1981-2020



Processed and created by the author based on “Science and Technology Indicators 2022”, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and Technology. (Data source: Web of Science XML from Clarivate)

The change in the number of cited papers will be dealt with in a later chapter.

1.3 Translational research

The next topic is translational research, which is development and research conducted with the aim of practical application of themes discovered by researchers in academia. Progress in this field has also become an issue in individual countries, and various efforts have been made by universities, research institutes, and governments.

In Japan, the secretariat materials for the "4th Industrial Structure Council Economic and Industrial Policy Innovative Subcommittee" held by the Ministry of Economy, Trade and Industry on February 16, 2020, also stated that "technological seeds in academia have not led to commercialization yet", and "Japan tends to have fewer start-ups compared to the number of patent applications".

While discussions on such issues have been going on for some time, the number of university-launched ventures has been gradually increasing in the life science field—that is, in a broader sense of the healthcare field (Figure 6).

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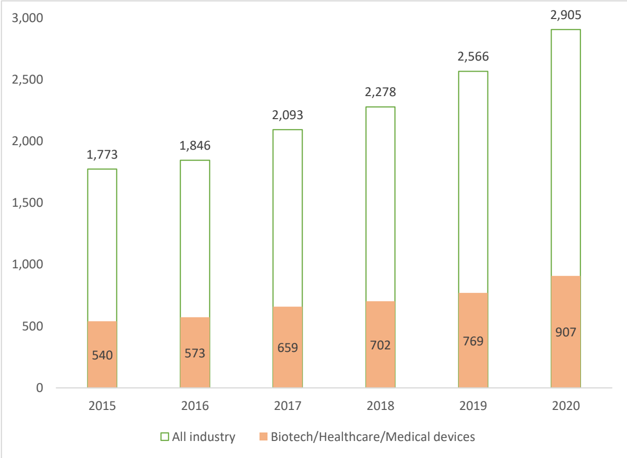
Fig6　Changes in the number of university-launched ventures in Japan



Source: Created by the author based on the website of the Ministry of Economy, Trade and Industry, "University Venture Database"

Although it is a small movement compared to trends in the number of research papers, it is clear that certain results have been achieved in terms of the technology transfer function and the involvement of researchers.

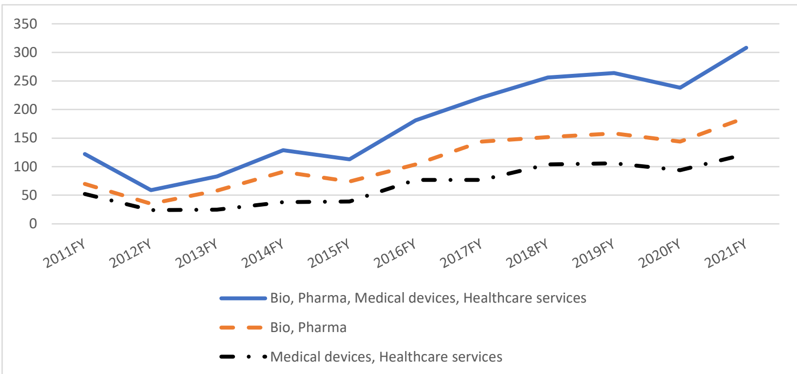
I will take the perspective of making this process more active and increasing the number of products born from that development. Specifically, it is investment activity on the venture capital side that hooks up the seeds of academia.

1.4　Functions performed by venture capital

1.4.1 Investment trends by venture capital

Japan has already experienced a bio-venture boom in the past. In 1999-2004, there was a period when biotechnology start-ups were established all at once, but this movement had calmed down in the latter half of the 2000s. On the other hand, from a global perspective in the life science field, venture capital was continuing to become a huge part of industrialization (details are described in Chapter 3), and whereas Japan had been lagging behind, its pace picked up again in the late 2010s (Figure 7).

Fig7 Number of venture capital investments (bio/medical/healthcare total) in Japan



Source: Venture Enterprise Center

It is true that this movement is linked to an increase in the number of university-launched ventures, but the important point is the probability that such development and investment will take shape.

I would like to see how venture capital has changed in recent years.

1.4.2 Activity patterns of venture capital

At what stage does venture capital become involved in development? The way it is involved changes depending both on the stage of investment—early, middle, and late—and with the times. Many articles of 10-20 years ago said that the difference between Europe/the United States and Japan was whether or not they had "hands-on" competencies. That means the VC adds various means of external support to the completed company.

However, the current role of venture capital is dependent on how far the VC can step into the company launch—that is, "company creation". Unlike the leadership of a single, strong-willed entrepreneur, the presence of VCs (or one of the actual founders) who get involved from the creation of the concept is important.

There is a wide range of items necessary for such activities, but the overall process is as follows.

1. Narrowing down of the target disease areas in comparison with current competitors
2. Teaming up of human resources necessary for the development process
3. Building of relationships with key opinion leaders who can serve as advisors
4. Based on the first three items, consultation with experts on building a clinical trial system and securing intellectual property
5. Suggestion of appropriate capital policy

Active involvement of venture capital in this process is strictly different from simple investment. Of course, the funds collected from investors should be invested in promising projects in the future. The upshot is that venture capital in the life sciences needs to create new value in the medical field while aiming to maximize returns to investors.

It should be noted that in life sciences, more and more start-up companies are choosing the "stealth" format these days. When you move to raise funds, you have to show "differentiation/ strength", but if you clear the point of "what area to attack’ and have the technology to do it, there is no need to disclose that information; so, this format trend may be inevitable.

Another aspect consists of key opinion leaders. KOLs exist not only within universities and research institutes, but also close to the site of treatment. Therefore, it is not easy for a venture company itself to handle this part alone. The function of venture capital is also important in such situations. VCs invite these KOLs into their teams as advisors for their own funds. Then the venture capital generally flows through the network for each project toward reference destinations where there is potential for new drugs and medical devices.

As its original function, a VC will evaluate the value of the venture company at the appropriate time and make follow-on investments. From the venture company side, there is also the aspect that they want to strongly assert their own value, but if the corporate value increases too early, it will be difficult to raise funds in the next round. In the worst case, the venture company will misjudge the timing of the exit. One of the roles of venture capital is to identify an appropriate investment structure.

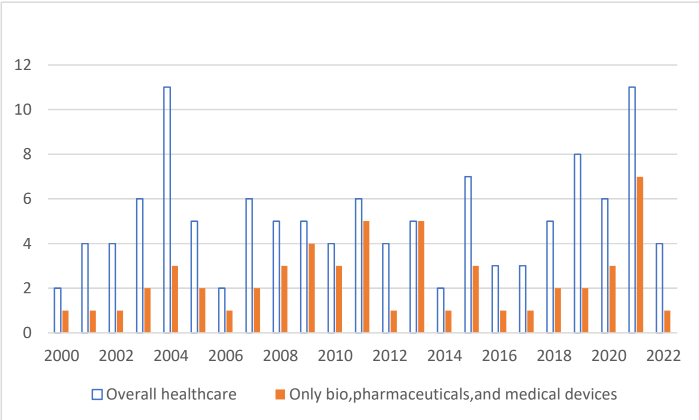
1. 5 Formation of the exit

Up to this point, I have gone through the establishment of a venture company from projects developed in academia. Next, I approach the right side of Figure 1. In life science industry, IPO is just one process, and product launch and sales constitute a major goal.

1.5.1 Approach to listing market

Figure 8 shows the timing at which companies currently listed on the Japanese pharmaceutical and biotechnology market were listed on the current market. This figure also includes large companies and service companies. Right side lines indicate only the biotechnology, pharmaceuticals, and medical equipment sectors.

Fig8 Changes in the timing of listing of healthcare companies on the current market



Created by the author

As you can see from this figure, the number of years in which there are five or more listings is limited, even for service-based healthcare providers, and it is difficult to say that the market is revitalized in Japan.

1.5.2 Exit response by large companies

In life science industry, large pharmaceutical and medical device manufacturers who market and sell their products play a major role. They acquire venture companies to add new products to their sales line-up. Another common practice is to obtain a license for rights, and this movement is active in Japan as well. These activities are collectively referred to as "business development".

There are various aspects to business development. In terms of medical equipment, acquisition targets are those that have reached the product/sales stage. In contrast, pharmaceuticals are often acquired even at the development stage. Medical devices constitute a process of adding new products to the sales channel, but pharmaceuticals are strongly influenced by the size and contents of the pipeline itself; so, the company will take over the development of products and launch them on the market.

In addition, manufacturers have a strong incentive to effectively utilize their own sales channels (for specific clinical departments), and business development personnel are watching the trend of newly developed products that match them, including overseas. Venture companies' exit strategies include approaching major companies that have channels to clinical departments where their products should be deployed.

Especially in the pharmaceutical field, such processes have become a matter of course. Comments that "Japanese companies are weak in business development" may have been heard 5 to 10 years ago, but that notion is a thing of the past. That being said, the manufacturers capable of such development are limited to companies with sales that rank among the top 10 in Japan, and overseas venture companies are the main targets (see Chapter 5).

As a result, acquisitions remain an inactive exit for Japanese venture companies.

1.5.3 Actual product launch

Table 1 shows the approval status of pharmaceuticals. More than 30 drugs containing new active ingredients are approved each year, but the majority of approvals are from large and medium-sized drug manufacturers, including foreign companies, and many of them originate from European and American ventures. Approval of Japanese venture origins is rare.

Table1 Approval Status of Drugs Containing New Active Ingredients (Japan)

Year	Numbers of Drugs Containing New Active Ingredients (Japan)		
		Biopharmaceuticals	Ratio(%)
2000	39	2	5
2001	25	7	28
2002	24	3	13
2003	16	2	13
2004	16	2	13
2005	21	4	19
2006	23	6	26
2007	35	10	29
2008	34	8	24
2009	25	8	32
2010	33	8	24
2011	38	12	32
2012	45	10	22
2013	32	10	31
2014	60	16	27
2015	38	9	24
2016	52	14	27
2017	24	8	33
2018	37	14	38
2019	39	10	26
2020	38	9	24
2021	52	24	46

(Note) Excludes in-vitro diagnostics, insecticides, and OTC drugs.
Source: “Pharmaceutical Affairs Bulletin”, Pharmaceuticals and Medical Devices Agency “List of Approved New Drugs”
From Japan Pharmaceutical Manufacturers Association DATA BOOK 2022

Many drugs are developed in-house through collaboration with Japanese universities and research institutes. However, the formation of ecosystems that include relatively clear divisions of roles has been limited—that is, in some cases some parts have been activated but a comprehensive system has not been completed.

Chapter 2 Review of existing research on ecosystems and life science business

- In ecosystem theory, “mutual complementation” is important, and each player exists as an actor with complementarity.
- Life sciences as a business are characterized by long development periods and uncertainties. It is not easy to compensate for risks related to these uncertainties, but as the commitments of companies, academia, and VCs have evolved, compensation has been strengthened step by step, and the development of the industry has been inherited.

I have written about industry trends mainly in Japan, but in this chapter I review existing research, focusing on the "ecosystem" and "science and business" perspectives.

2.1 Theory on the ecosystem

The term "ecosystem" is used in a wide variety of ways. From the side of large companies, there are many cases where it is perceived as "the amount of collaboration within the corporate strategy". It is also used when talking about the overall picture of stakeholders in the context of business development.

On the other hand, from the perspective of regional development, the relationship itself with various players in the region is called an ecosystem, and there are discussions that are close to the ‘cluster’ theory.

In that sense, it is difficult to grasp the term "ecosystem" in a unified way, but it is important in business administration that ecosystems exist as an alternative way among strategy theory and innovation theory. Among those discussions, there are by no means many examples that deal with life science itself, but the following summarizes ecosystem theory from a management perspective.

2.1.1. Ecosystem Theory by Ron Adner

Ron Adner perceives the ecosystem as a theory of corporate strategy and considers the risks inherent in the ecosystem.

He considers how to utilize responses to those risks in business development. Roughly speaking, in his paper ’Match Your Innovation Strategy to Your Innovation Ecosystem (2006)’, he envisions three types of risks:

1. initiative risk,
2. interdependence risk, and
3. integration risk.

Initiative risk involves risks inherent in the project itself. It can be said that it is the risk itself related to the development of pharmaceuticals and medical devices.

Interdependence risk is the risk related to coordinating with complementary innovators. When moving forward in the direction of development—that is, to each new step—it is essential that the complementary innovators experience success before the project itself reaches success.

From the perspective of development, ‘Research by academia’ and ‘Companies bringing their development to market’ are interdependent but very time-consuming. One example of the process is the interdependence between academia and venture capital. As mentioned in the previous chapter, the role of venture capital itself is to play the role of company creation. The VCs themselves need to be innovators because having a certain amount of success and experience in development is an important factor leading to successful development.

The third type of risk according to Adner is integration risk—that is, risk throughout the entire value chain of the introduction process of newly developed products and related to the need for consistency in the process until the product is delivered to the end user.

For pharmaceuticals, the process of "Acquisition of development rights and/or sales rights" also plays a very important role. The relationships that large and medium-sized companies foster with VCs and start-ups are critical.

In addition, Adner considers innovation ecosystems in corporate innovation strategies. He stresses the importance of aligning strategies with the system in particular in his book “Winning the right game” (2021). He states that responses to these risks will change over time: “Build as little as possible”, “Expand incrementally”, and “Inherit”. When doing so, it is necessary to transform the ecosystem for success. In other words, rather than just coordinating responses to each risk, the venture needs to take the time to make adjustments.

2.1.2 Ecosystem Theory by MG Jacobides

In his paper 'Towards a theory of ecosystems' (2018), MG Jacobides focuses on the way of "mutual complementation", which is an important element in ecosystems. In the system, modularity and cooperation are positioned as important elements. Modularity can be thought of as an element that is replaceable as a kind of part. Leveraging several categories of complementarity, the theory is not limited to the discussion of individual products, but also applies to the entire industrial structure.

In addition, an important point is that the ecosystem should not be “in the form of someone controlling the ecosystem”. Rather, the basis of ecosystem theory is that “each player exists as an actor with complementarity”.

There are aspects that are more static than Adner's arguments. On the other hand, works are being made to grasp how the products and industries are in a mutually complementary relationship as a matrix. I will also examine the matrix of the complementary relationship in life science innovation later.

An important point common to the theories of Adner and Jacobides is that while defining the existence of an ecosystem as a methodology for realizing innovation, it is also important to consider the interrelationship of the entire system.

Rather than focusing on a single business entity, they do the analysis focus on the mutual complementation of the entire system. This point will be an important guideline in the next section and later.

2.2 Life science as a business

Based on ecosystem theory as management, it is necessary to look at the life science business as a whole. However, before that, I would like to review research on the business characteristics of life sciences, especially innovation.

2.2.1 How did life science innovation spread?

Regarding ‘How did the industrial base expand from the origin of development?’, there are several examples of quantitative research in the field of biotechnology.

First, in ‘Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises’ (1998), Zucker et al. analyzed that the highest explanatory variable for the number of ventures born in each region (at the time of writing the paper) is the total number of star scientists that were active between 1976 and 1980. Then, in the follow-up 'Commercializing Knowledge' (2002), the variable "whether or not there are co-authored papers with star scientists" has a significant effect on start-ups' performance (number of patents).

Thinking about the ecosystem, these papers show that translations from academia are greatly significant to biotech industry.

On the other hand, S. Casper's 'How Do Technology Clusters Emerge and Become Sustainable?: Social Network Formulation and Inter-firm Mobility within the San Diego Biotechnology Cluster' (2007) is emphasized as a theoretical background for cluster formation. Based on insight into the behavior of senior managers in biotech companies, Eli Lilly's failed acquisition of Hybritch produced the mobility of senior managers and other talent among biotech companies in the San Diego region.

As above, in terms of network expansion, the importance of "star scientists in universities" and "influence of core companies" are key points. Biotechnology was both a new technology and a new industry in the 1970s; thus, the existence of the main scientists and the spread of human resources who have gained experience had large impacts on performance (= number of patents, etc.). This essence has important implications for the development of new modalities, which will be described later.

2.2.2 Characteristics of science business

From the perspective of taking life sciences as a business, Gary Pisano's paper "Can science become a business?: Lessons learned from biotechnology" (2006) and his book "Science Business" are still reference points.

As for characteristics of life sciences, the time from the start of research and development to actual deployment in the market is long. Pisano points out that the way the industry manages risk is inconsistent with the long R&D timetables required to create new drugs. As of 2006, he was critical of the performance of VCs.

At the same time, he said that in the biotechnology era, pharmaceutical research and development is characterized by 'Uncertainty', 'Complexity and interdisciplinary,' and 'Speed and accumulation' and will become more foreground.

In order to deal with these issues, he assumed the need for "vertical integration", against the backdrop of declining corporate profitability, and for long-term collaboration. Then he proposed strengthening funding for translational research.

If the times had progressed in the way Pisano wrote, the market for biopharmaceuticals would have contracted at some point and the scale of venture capital would have become more moderate. Instead, the pharmaceutical market expanded, mainly in the North American market.

In the fifteen years since then, various methods have been created to compensate for the long development period, such as the existence of crossover funds and "long-term collaboration". However, it can be said that he had explained most of the industrial structure itself in 2006.

2.2.3 Development process and its probability theory

Next, I would like to think about the real development process and its probability theory.

First, at universities and research institutes, development is being carried out as basic research.
Recent years have seen the flow of the "omics revolution"—that is, comprehensive research on molecules in the living body, including genomics, transcriptomics, proteomics, metabolomics and so on.

Also, from the perspective of modalities involved in actual drug discovery, in addition to existing low-molecular medicine, there is wide use of biomedicine, recombinant protein and peptide medicine, nucleic acid medicine, gene therapy and regenerative medicine. Various papers have been produced while intertwining these and other treatment methods for individual diseases.

The process of moving from basic research to actual drug discovery includes (1) treatment hypotheses for each disease and specific designation of modalities, (2) identification of drug discovery targets, (3) identification and optimization of compounds, etc.

Regarding the "uncertainty" in this process, when you take a look at the probability theory from the JPMA data for low-molecular-weight compounds, Table 2 shows a ‘1 in 22,000 chance’ of approval on a compound basis.

Table2 Number of compounds by development stage and stage transition probability (cumulative over 5 years)

Fiscal year	Number of compounds by development stage (cumulative over 5 years)				Stage transition probability (5-year cumulative)		
	Synthetic compound	Start of Preclinical study	Start of Domestic clinical trial	Approved (in-house)	～Start of Preclinical study	～Start of Domestic clinical trial	～Approved (in-house)
2000-2004	463,961	215	127	36	1:2,158	1:3,653	1:12,888
2001-2005	499,915	197	97	32	1:2,538	1:5,154	1:15,622
2002-2006	535,049	203	73	27	1:2,636	1:7,329	1:19,817
2003-2007	563,589	202	83	26	1:2,790	1:6,790	1:21,677
2004-2008	611,576	199	81	24	1:3,073	1:7,550	1:25,482
2005-2009	652,336	203	75	21	1:3,213	1:8,698	1:31,064
2006-2010	673,002	216	83	22	1:3,116	1:8,108	1:30,591
2007-2011	704,333	219	85	26	1:3,216	1:8,286	1:27,090
2008-2012	742,465	198	71	25	1:3,750	1:10,457	1:29,699
2009-2013	728,512	201	68	25	1:3,624	1:10,713	1:29,140
2010-2014	712,040	190	74	29	1:3,748	1:9,622	1:24,553
2011-2015	703,397	165	70	28	1:4,263	1:10,049	1:25,121
2012-2016	674,850	151	62	26	1:4,469	1:10885	1:25,956
2013-2017	624,482	146	65	24	1:4,277	1:9,607	1:26,020
2014-2018	582,573	150	62	26	1:3,884	1:9,396	1:22,407
2015-2019	545,967	146	53	24	1:3,740	1:10,301	1:22,749
2016-2020	505,141	173	52	23	1:2,920	1:9,714	1:21,963

Notes:

1. The number of low-molecular-weight compounds excludes chemical libraries such as combinatorial chemistry.
2. Excludes additional dosage forms and indications only for in-house products (excludes in-licensed products).
3. The step transition probability indicates the ratio of the number of compounds in each step to all compounds.

Source: Research by the Japan Pharmaceutical Manufacturers Association (total of domestic companies among R&D committee members)
From Japan Pharmaceutical Manufacturers Association DATA BOOK 2002

However, this is the story of the entire small molecule process. As for project-based probability, the numbers are different than those in the chart.

Example: MIT Laboratory for Financial Engineering 'Project Alpha' (as of 2022Q1), 68.8% (71.3% excluding cancer) from Phase 1 to Phase 2, 50.4%; (60.1%) from Phase 2 to Phase 3; 43.5% (48.4%) from Phase 3 to approval; total 10.3% (16.2%) from Phase 1 to approval

These figures are different from the roughly 1 in 22,000 figure referenced in Table 2.

Note that Project Alpha, the source of these numbers, is led by Andrew Lo, which is very important from the standpoint of looking at this development from a financial perspective.

2.2.4 The difficulty of finance from the perspective of Lo's theory

Andrew Lo's paper 'Can Financial Economics Cure Cancer?' says that the funding structure is not commensurate with the risk from the perspective of financial engineering. Pharmaceutical development is extremely costly and time consuming, and the historical probability of success is generally low. Through the omics revolution, the complexity and risks of drug development have increased, and the efficiency of the drug development process has decreased (so-called Eroom's law). The point that the "Valley of Death" is also manifesting is similar to the situation pointed out by Pisano.

Under these circumstances, only investors who seek high returns are the ones who invest in "single drug discovery", which is a high-risk asset type. Lo's theory is that in order to avoid such a situation, it is possible to appropriately raise funds by creating a portfolio of investment assets and controlling their correlation.

In the first place, early-stage biotech companies have high beta values, while pharmaceutical companies have beta values almost below 1.0. Biotech companies stand out for their high cost of capital, as they face both scientific and financial risks, with financial risks driving high betas.

Lo argues that a de-correlated portfolio of investments in these companies should free up more money for drug development.

And the expected present value of such an investment depends on three terms: the profit generated by the drug, the program's probability of success, and the cost of development. Of these, PoS (success rate) analysis is very suitable for academia; so, Lo continues to disclose the details of the project that calculates this, and this is the number of Project Alpha mentioned above.

On the other hand, based on this paper, the mystery of why development has been divided into roles can be somewhat solved. Entities that can make high-risk investments are limited to companies with a low beta value, such as large companies and giant venture companies with strong abilities to raise capital.

Therefore, it is said that it is usually difficult to invest. But on the flip side, it is possible for a group of such companies to acquire ventures that have development assets in the early stages. Also, we can see the situation that venture capital has appeared with an eye on the exit.

Of course, Lo talks about ways to overcome this situation. But it is also understandable that previously the challenges related to uncertainty were gradually covered by corporate growth.

2.2.5 Static complementary relationship

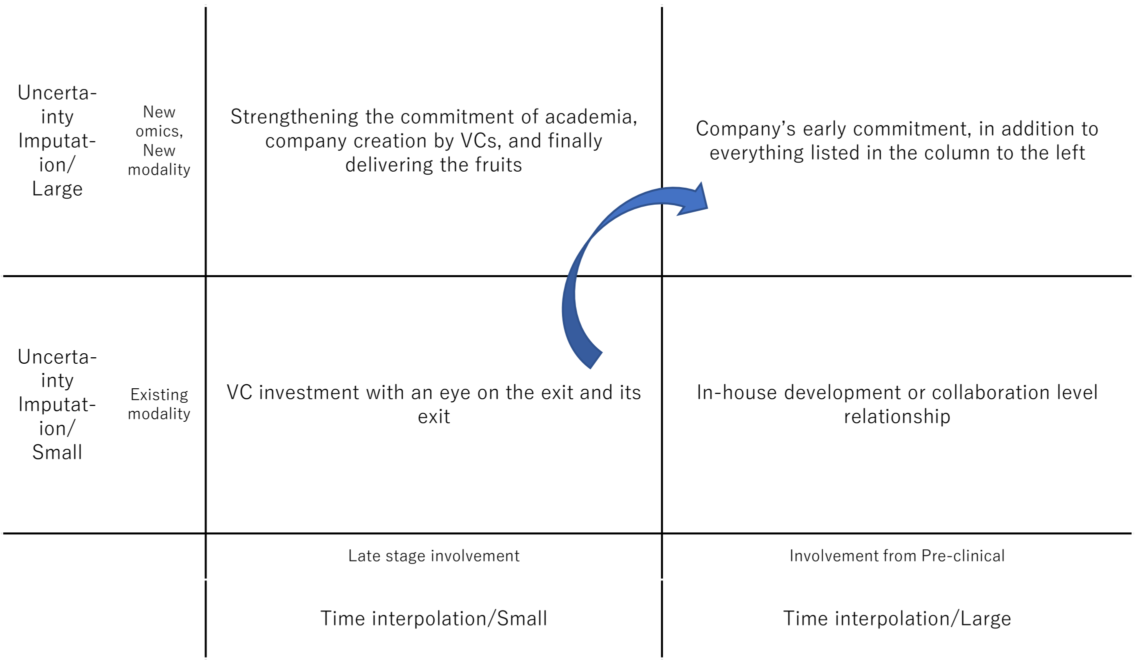
I would like to return to the discussion in 2.1—that is, Jacobides' discussion about the kind of complementary relationships being built with respect to risk in the current life science industry.

The first complementary item is that of "uncertainty" discussed by Pisano and Lo. Continuous development of existing products, development of new products, and development in new modalities all have different uncertainties. However, commercialization needs to involve laboratory, preclinical, and clinical processes. As mentioned above, Lo recommends the use of financial engineering to fill this uncertainty. However, so far, this uncertainty has been alleviated by (1) the high quality of science at the start, (2) ‘creation’ by venture capital, and (3) investors who support this process.

Another point is time compensation. In the case of life sciences, time would be (1) the number of experiments in the laboratory stage, and (2) the time (and cost) in the process from preclinical to large-scale clinical trials. From the perspective of large companies, the point is how much time should be spent on (1). Also, if you try to reduce the uncertainty risk mentioned earlier, you will have to decide whether to follow the process in (2) from scratch or to take a shortcut by introducing the product from another company.

Figure 9 was created with these points in mind. By performing such risk supplementation, it becomes possible to "present a new treatment method to the patient", which is the most important aspect.

Fig9 Matrix of complementary relationship



Created by the author

Chapter 3 Transition of Players in the Ecosystem

- The number of researchers has remained at a certain level, except in the United States, but development costs in academia have been steadily increasing.
- Venture investment has grown significantly over the past 20 years, mainly in the United States. Sales grew rapidly in Europe in the 2010s and showed growth in Japan in the latter half of the 2010s.
- Major global companies were the first to show significant growth in the ecosystem, increasing the amount of development costs and intangible fixed assets.
- Therefore, as major global companies expand their scale, venture capital investment will increase. As this framework solidifies, investment in academia will increase steadily and the development process will continue to grow.

Based on the discussion so far, this chapter focuses on the "life science ecosystem and its transition". Although a very simple method, I look at the transition of how the development cost in the life science field is invested, in absolute amount throughout the whole system.

First is investment in universities. Among them, there will be some that actually become translational start-up companies, and some that will be used for new drug discovery and medical device development at the corporate level after basic research.

From here, the story is divided into two routes, one of which is investment by venture capital. Of course, not all of this money goes to research and development expenses—it goes to all activities of the venture company, including sales—and the probability of success as a company is limited. However, much of its activity is invested in research and development itself.

The next step is research and development at the corporate level, and there is likely some overlap with university research. Also, when a venture company exits, funds are a feature of the acquisition and such payment is recorded in the form of intangible fixed assets and goodwill. After that, the company itself bears the subsequent development costs. When it comes to corporate-level figures, acquisition payments include venture capital and shareholder returns; so, figures differ from pure development investment.

In this way, the transition of capital investment in the development life cycle becomes more difficult to grasp—that is, the actual cost from the origin as it goes to the exit stage. However, by looking at how funds have been invested in each process in some countries, it will be possible to understand the evolution of the ecosystem.

3.1 Trends in figures related to individual players

3.1.1 Trends in figures related to university research

The origin of the ecosystem is universities and research institutes. As in Chapter 1, I look at the trends in the number of researchers in the life sciences.

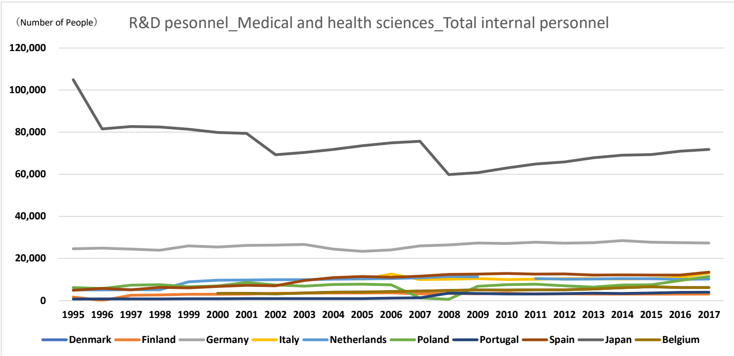
(1) Changes in the number of researchers

OECD data shows the trends in the number of researchers in each country, but countries showing disaggregated figures are limited. For example, the figures of the United States, the United Kingdom, and France do not appear in the OECD data.

Bearing in mind the above limitations, Figure 10 shows Medical and health sciences data of nine

European countries (Belgium, Denmark, Finland, Germany, Italy, the Netherlands, Poland, Portugal, Spain)[13] and Japan. The absolute number of researchers in Japan exceeds that of the nine European countries, but the overall number in Japan is declining.

Fig10 Changes in the number of R&D personnel (Medical and health sciences)

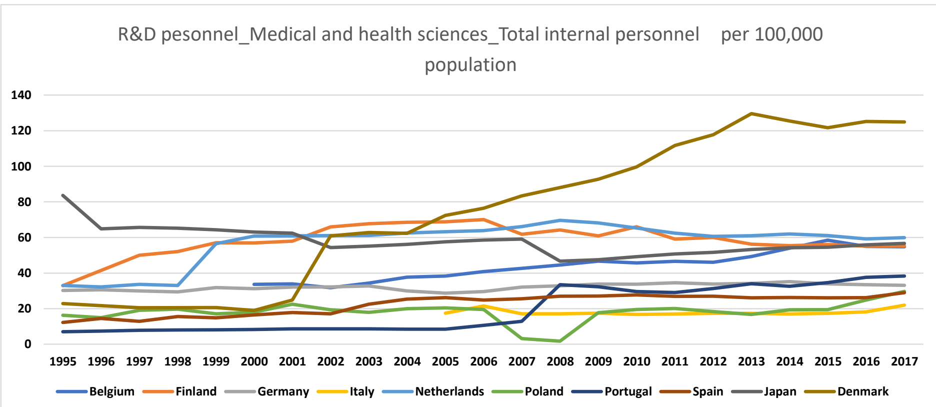


	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Belgium						3,446	3,494	3,276	3,568	3,925	4,017	4,310	4,526	4,775	5,040	4,975	5,138	5,116	5,502	6,045	6,593	6,228	6,233
Denmark	1,193		1,086		1,100	1,014	1,332	3,273	3,387	3,367	3,924	4,156	4,555		5,121	5,528	6,220	6,585	7,276	7,083	6,915	7,172	7,203
Finland	1,684	..	2,572	2,684	2,950	2,949	3,009	3,432	3,533	3,583	3,608	3,693	3,270	3,411	3,253	3,543	3,185	3,247	3,062	3,032	3,071	3,030	3,043
Germany	24,594	24,908	24,480	23,928	25,945	25,405	26,186	26,308	26,682	24,447	23,380	24,037	26,000	26,496	27,283	27,109	27,750	27,209	27,539	28,479	27,713	27,541	27,358
Italy											10,182	12,576	10,019	10,130	10,424	10,029	10,190	10,452	10,474	10,225	10,477	10,937	13,142
Netherlands	5,112	5,001	5,252	5,186	8,922	9,677	9,766	9,868	9,938	10,173	10,319	10,441	10,831	11,453	11,274		10,425	10,147	10,252	10,459	10,360	10,086	10,258
Poland	6,240	5,725	7,308	7,562	6,557	6,885	8,630	7,380	6,846	7,647	7,788	7,456	1,220	673	6,796	7,536	7,771	7,093	6,459	7,436	7,485	9,548	11,423
Portugal	700	746	792	811	825	859	893	896	899	895	891	1,121	1,351	3,532	3,414	3,135	3,076	3,291	3,565	3,385	3,588	3,885	3,950
Spain	4,859	5,781	5,165	6,282	6,020	6,691	7,245	7,090	9,518	10,853	11,438	11,048	11,591	12,399	12,566	12,883	12,551	12,640	12,156	12,200	12,106	12,174	13,493
Japan	104,920	81,566	82,668	82,466	81,386	79,908	79,361	69,299	70,358	71,754	73,555	74,903	75,658	59,817	60,740	62,935	64,827	65,839	67,800	69,073	69,343	70,958	71,864

Created by the author based on OECD 'Main Science and Technology Indicators'

Unlike Japan's decline, Belgium's growth is conspicuous. However, since the 2000s, the number of researchers in this field has increased significantly in only four of the nine European countries: Belgium, Denmark, Portugal, and Spain.

Fig11 Changes in the number of R&D personnel (Medical and health sciences) per 100,000 population



Created by the author based on OECD 'Main Science and Technology Indicators'

[13] Countries with less than 3,000 R&D personnel or countries for which data can only be obtained every other year are excluded.

On the other hand, in the United States, I look at trends in the number of newly acquired doctorates in the healthcare field. Table 3 compares these figures for Japan and the US. Relative to the population, the number of doctoral degree holders in Japan is large, but the United States has produced about 1.7 times as many doctoral degree holders on an annual basis over the past 30 years. There are no major changes in Japan. Considering population growth, the growth in the US figures is still limited, but we can see that the absolute number of researchers, which is the base, has been steadily raised.

Table3 Numbers of new doctoral degree holders in Japan and the US

-US-

	1991	1996	2001	2006	2011	2016	2021
Agricultural sciences and natural resources	1,277	1,289	1,132	1,146	1,206	1,379	1,334
Biological and biomedical sciences	4,649	5,724	5,697	6,652	8,152	8,863	8,149
Health sciences	1,041	1,324	1,540	1,905	2,177	2,297	2,331
Life sciences	6,967	8,337	8,369	9,703	11,535	12,539	11,814

-Japan-

	1991	1996	2001	2006	2011	2016	2019
Agriculture	870	1,043	1,248	1,378	1,046	933	917
Health	6,356	6,800	6,962	6,981	6,229	6,206	6,372
Total	7,226	7,843	8,210	8,359	7,275	7,139	7,289

Sources

US: National Center for Science and Engineering Statistics, Survey of Earned Doctorates

Japan: “Science and Technology Indicators 2022”, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and Technology.

(2) Trends in R&D expenses

Next is research and development expenses. The following is the change in figures in the medical field under the category of higher education in the OECD.

As was the case for previous figures and tables, the number of countries for which data can be obtained continuously up to the recent past is limited; however, since comparisons can be made up to the year 2000, including for the United States, the trends in R&D expenditures in the United States, Japan, and Germany converted per capita are shown in Figure 12.

Regarding these figures, development costs in this field were not necessarily high in the United States until the late 1990s. However, as described later, I would like to consider the United States National Institute of Health figures as reference values.

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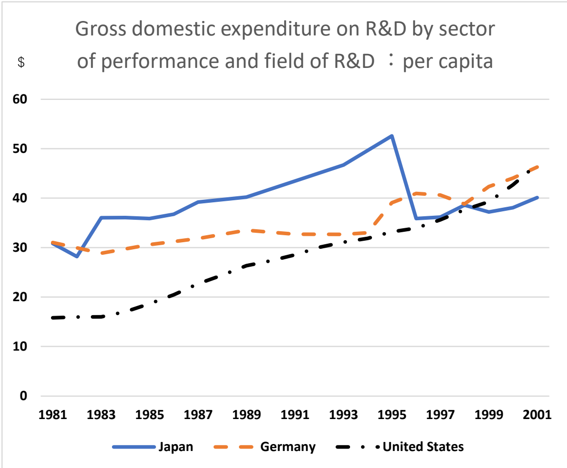
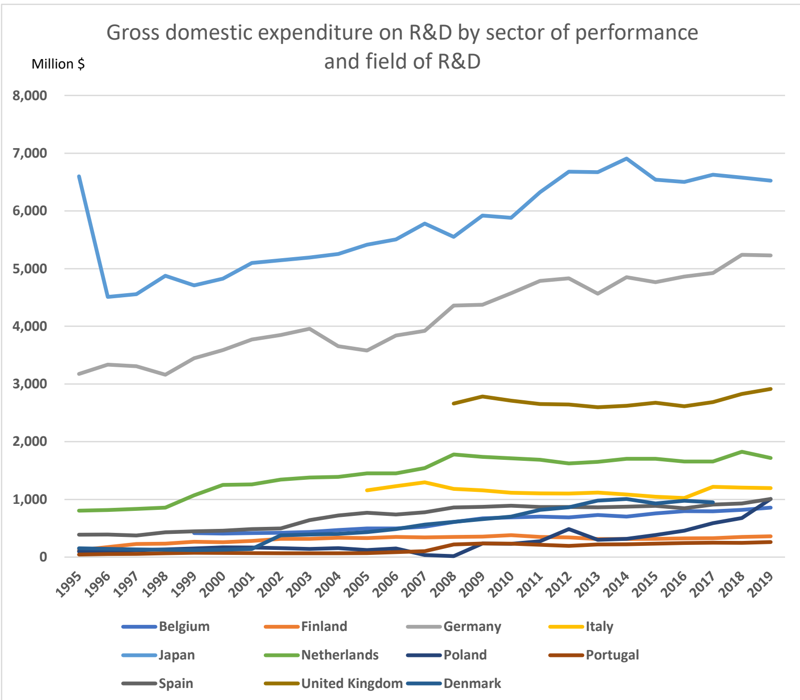
Fig12 Trends in R&D spending in the fields of medical and health sciences in higher education



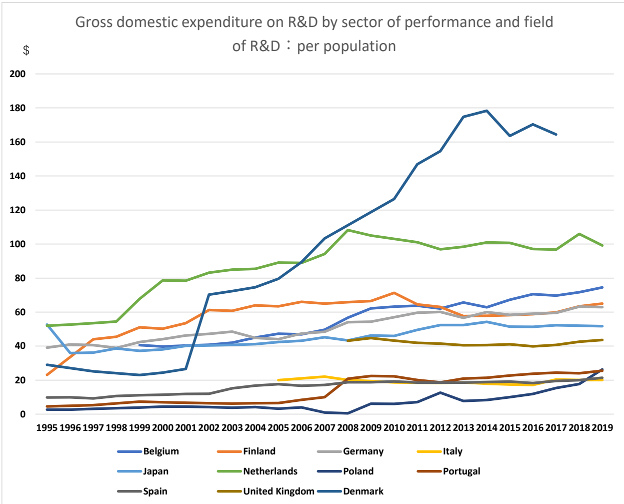
Created by the author based on OECD 'Main Science and Technology Indicators'

I can't find detailed OECD data for the United States for later years; so, for years after 1995, I look at the figures below for the previously mentioned nine European countries plus the UK. The upper part of Figure 13 shows changes in absolute numbers, and the lower part shows figures per number of people. Looking at per capita, the Netherlands, Belgium, Denmark, and Finland have grown significantly, and Germany has also shown a certain level of growth. In Japan, after a temporary decline in the latter half of the 1990s, the per capita numbers have been gradually recovering, whereas the absolute amount has returned fully to the base of the latter half of the 1990s.

Fig13 Trends in R&D spending in the fields of medical and health sciences in higher education



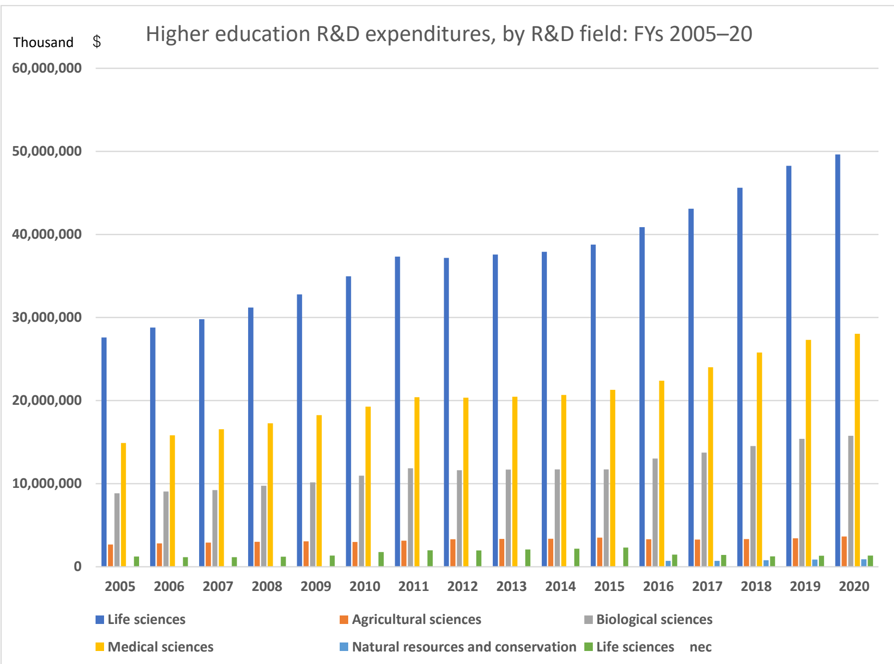
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Belgium					415	408	414	421	436	469	496	495	527	607	670	689	704	689	732	704	758	799	793	820	855
Denmark	152		133		122	130	142	378	390	403	432	486	564		656	702	818	865	981	1,007	929	976	948		
Finland	118		226	234	263	260	278	318	317	334	332	348	343	350	355	382	348	341	313	315	319	323	329	350	358
Germany	3,176	3,337	3,310	3,161	3,447	3,589	3,772	3,850	3,957	3,655	3,580	3,841	3,924	4,360	4,373	4,574	4,787	4,833	4,566	4,851	4,767	4,860	4,922	5,238	5,229
Italy											1,158	1,229	1,294	1,183	1,157	1,115	1,105	1,102	1,121	1,084	1,047	1,025	1,219	1,205	1,197
Japan	6,597	4,511	4,557	4,875	4,712	4,826	5,099	5,143	5,195	5,251	5,414	5,506	5,781	5,549	5,919	5,879	6,326	6,678	6,671	6,907	6,542	6,504	6,626	6,576	6,526
Netherlands	804	816	834	856	1,071	1,251	1,259	1,342	1,378	1,390	1,452	1,453	1,543	1,780	1,735		1,686	1,623	1,653	1,703	1,705	1,654	1,657	1,826	1,719
Poland	98	102	119	133	148	169	168	155	143	157	122	151	36	15	236	231	274	485	300	317	386	456	588	679	1,008
Portugal	46	50	53	64	75	72	70	67	65	67	69	87	105	219	237	235	211	196	218	222	235	244	250	247	263
Spain	386	392	372	431	448	459	484	495	640	720	769	739	777	861	870	892	866	866	862	875	888	848	909	931	1,006
United Kingdom														2,662	2,784	2,709	2,653	2,642	2,597	2,623	2,673	2,614	2,685	2,829	2,912

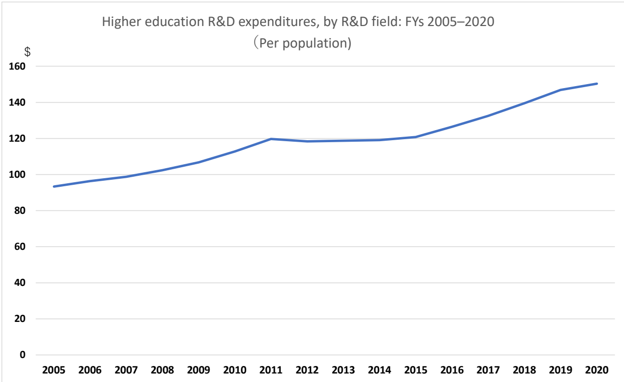


Created by the author based on OECD 'Main Science and Technology Indicators'

I also look at US data for the same period, but it is based on R&D expenditure in US universities in this field (see Figure 14).

Fig14　Trends in R&D spending in the life sciences field in higher education in the United States



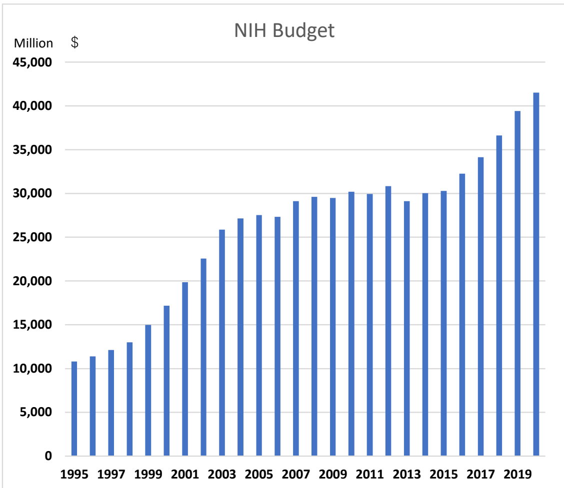


Sources: National Science Foundation/National Center for Science and Engineering Statistics, Higher Education Research and Development Survey

Looking at the transition here, the movement of the numbers is different from the situation up to around 2000 seen in Figure 12. Compared to Germany and Japan, which have grown about 1.2-1.4 times since 2005, the growth rate in the United States is 1.6 times, even per the population.

Supplementing this data, I show the budget growth at the National Institutes of Health in Figure 15 below.

Fig15 Changes in the NIH budget



Source: NIH Data Book

(3) Changes in the number of papers

On the other hand, here I look at the transition in the number of papers as one of the achievements of academia. Table4 shows trends in the number of papers published in basic life sciences and clinical medicine over the past 30 years, as well as the number of corrected Top 10% papers and the number of corrected Top 1% papers. In Chapter 4, I would like to see more detailed trends in each European country.

In terms of the number of Top 10%-cited and Top 1%-cited papers, Japan most recently has not been among the top 10 countries in either category (ranked 12th in both).

Note that the obviously large growth in China's production of papers is not discussed in this article, partly because the movement is rapid.

Table4　Changes in the number of papers published by country/region

-Basic life science-

	FY1997-1999(average)		FY2007-2009(average)		FY2017-2019(average)	
Number of papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	77,327	U.S.	94,506	U.S.	112,508
2	Japan	19,888	U.K.	22,737	China	83,780
3	U.K.	19,349	Germany	22,103	U.K.	30,021
4	Germany	17,479	Japan	21,692	Germany	29,262
5	France	13,786	China	18,505	Japan	21,768
6	Canada	10,892	France	15,514	Brazil	20,542
7	Italy	8,335	Canada	14,693	Italy	19,513
8	Australia	6,780	Italy	13,230	France	19,050
9	Spain	6,543	Brazil	11,647	Canada	18,757
10	Netherlands	5,768	Spain	11,363	India	16,971
Number of Top 10% cited papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	11,263	U.S.	13,833	U.S.	15,981
2	U.K.	2,659	U.K.	3,725	China	9,203
3	Germany	1,860	Germany	2,925	U.K.	5,147
4	France	1,360	France	2,011	Germany	4,415
5	Japan	1,353	Canada	1,850	Italy	2,810
6	Canada	1,302	Japan	1,606	France	2,747
7	Netherlands	759	China	1,586	Australia	2,660
8	Australia	715	Italy	1,367	Canada	2,535
9	Switzerland	651	Australia	1,335	Spain	2,216
10	Italy	638	Spain	1,250	Netherlands	2,013
Number of Top 1% cited papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	1,307	U.S.	1,608	U.S.	2,042
2	U.K.	287	U.K.	444	China	848
3	Germany	180	Germany	323	U.K.	699
4	France	135	France	219	Germany	573
5	Canada	123	Canada	207	France	366
6	Japan	117	Australia	162	Australia	360
7	Netherlands	82	Japan	162	Canada	342
8	Switzerland	76	Netherlands	142	Italy	328
9	Australia	67	Italy	132	Netherlands	316
10	Sweden	60	China	123	Spain	274

-Clinical medicine-

	FY1997-1999(average)		FY2007-2009(average)		FY2017-2019(average)	
Number of papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	55,236	U.S.	73,522	U.S.	104,356
2	U.K.	15,460	U.K.	20,056	China	46,698
3	Germany	13,499	Germany	17,782	U.K.	29,061
4	Japan	13,497	Japan	14,857	Germany	23,034
5	France	8,979	Italy	11,545	Japan	19,808
6	Italy	6,964	France	11,136	Italy	18,030
7	Canada	6,318	Canada	10,650	Canada	17,660
8	Netherlands	4,654	China	8,677	Australia	16,326
9	Australia	3,989	Australia	8,016	France	14,466
10	Sweden	3,742	Netherlands	7,794	Netherlands	12,777
Number of Top 10% cited papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	8,187	U.S.	11,507	U.S.	15,763
2	U.K.	1,917	U.K.	3,014	U.K.	5,568
3	Germany	1,151	Germany	2,110	China	4,636
4	Canada	944	Canada	1,720	Germany	3,734
5	Japan	886	Italy	1,586	Italy	3,385
6	France	820	Netherlands	1,428	Canada	3,153
7	Italy	763	France	1,385	France	2,640
8	Netherlands	714	Australia	1,103	Netherlands	2,617
9	Sweden	506	Japan	1,078	Australia	2,600
10	Australia	476	Switzerland	802	Spain	1,983
Number of Top 1% cited papers						
	Country	Papers	Country	Papers	Country	Papers
1	U.S.	969	U.S.	1,369	U.S.	2,106
2	U.K.	220	U.K.	419	U.K.	931
3	Canada	132	Germany	267	Germany	615
4	Germany	102	Canada	246	Canada	562
5	France	102	Italy	214	France	510
6	Italy	89	France	210	Italy	507
7	Netherlands	89	Netherlands	195	Australia	453
8	Japan	54	Australia	144	Netherlands	428
9	Sweden	54	Switzerland	122	China	396
10	Australia	53	Spain	112	Spain	370

Processed and created by the author based on “Science and Technology Indicators 2022”, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and Technology (Data source: Web of Science XML from Clarivate)

(4) Brief Summary

Here's a quick summary of what I can learn from these numbers.

- In Japan, although the number of researchers themselves is on the decline, R&D expenditures have returned to the mid-1990s level, and R&D expenditures per capita are increasing slightly. However, the number of Top 10%-cited and Top 1%-cited papers dropped out of the top ranks.

- In Europe, data is available only for a limited number of countries, but within the scope of nine countries, Germany's movement is standard, and around that, Belgium, the Netherlands, and Finland are moving actively. Looking at Germany, the number of researchers has increased only slightly since the mid-1990s, but the cost of investment in research and development has reached 1.6 times, showing a steady increase. However, like in Japan, there are some countries where R&D spending is sluggish.
- In the United States, R&D expenditure levels have accelerated since around the year 2000, and not only personnel but also development costs are at 1.8 times their 2005 levels.

The financial input to science at the university level differs from country to country, but with the exception of the United States, there are not many Western countries where an extreme increase can be seen, and there are some countries where, similar to Japan, it is somewhat flat.

3.1.2 Changes in investment amount of venture capital

Next, I would like to look at the status of capital investment in ventures. Since it is difficult to obtain continuous and consistent numbers in this field as well, I look at the overall picture while checking it with the data that can be obtained. Please forgive the lack of consistency in that sense, as there are considerable differences in the fields covered by the figures, such as those for biotechnology and life sciences in general.

First of all, if I look at the start-up of "venture capital investment in the biotechnology industry" rather than in life science as a whole, the cumulative investment amount exceeded USD 5 billion from 1978 to 1994. In 1998, cumulative investment exceeded USD 10 billion, and thereafter continued to increase by USD 3 to 5 billion annually until 2004. The first half of the 2000s was a period of full-fledged takeoff in the biotechnology field.

On that premise, I would like to consider the following transitions as involving deals in the life sciences as a whole.

[USA]

Data from NVCA (National Venture Capital Association) shows that investment in this field progressed at a pace of about USD 4 billion annually in the 2000s overall. Since 2013, the figure has exceeded USD 10 billion annually, and this figure is increasing at a rapid pace.

In addition, the scale of fundraising became extremely large in the latter half of the 2010s.

Since the life science field has also included digital aspects, the increase factor is not necessarily directed to pure drug discovery and development of therapeutic medical devices, but compared to the latter half of the 1990s, the situation in the United States is that the amount of annual investment has grown tenfold in just 20 years.

[Europe]

On the other hand, regarding the trend of figures in Europe, the investment amount of the entire venture capital remained at the level of EUR 2 to 3 billion from 2007 to 2016, but since 2017 it has grown very strongly.

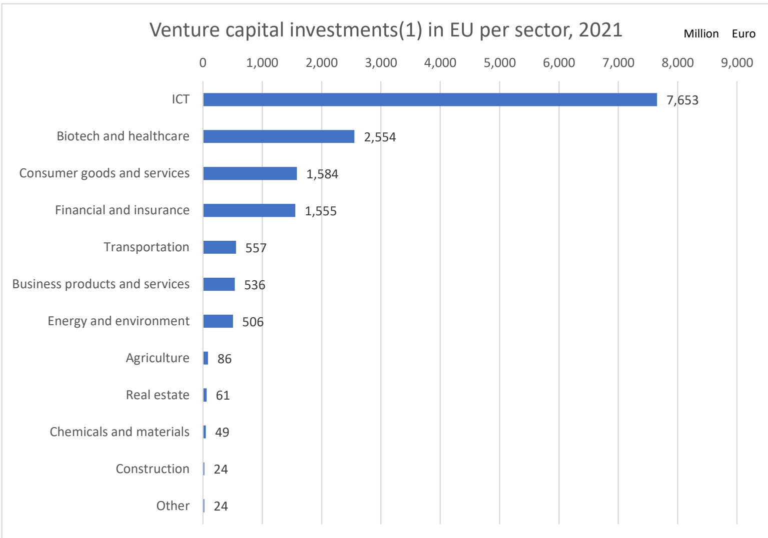
Table5 Venture capital Investments in the EU

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Capital Invested（EUR billion）	3.6	3.8	2.4	2.5	2.7	2.2	2.7	2.7	3.3	3.8	4.7	6	7.5	8.2	15.2

Source: Invest Europe, 2022
Note: (1) Data are measured following the market statistics approach, an aggregation of the figures according to the country in which the investee company is based, regardless of the location of the PE fund. At the European level, this relates to investments in European companies regardless of the location of the PE firm.
From Science, Research and Innovation Performance of the EU 2022

And in terms of life sciences, as of 2021 the figure for biotech and healthcare is 15% of the total, or about EUR 2.5 billion. Looking at biotech and healthcare as a whole, in the first half of the 2010s it was around EUR 1 billion, and in the latter half of the 2010s it held steady at the level of EUR 3 to 4 billion. Due to the growth in recent years, the situation is approaching the level of the United States in the 2000s.

Fig16 Venture capital investment by sector in the EU



Source: Invest Europe, 2022
Note (1): Data are measured following the market statistics approach, an aggregation of the figures according to the country in which the investee company is based, regardless of the location of the private equity fund. At the EU level, this relates to investments in EU companies regardless of the location of the private equity firm.
From Science, Research and Innovation Performance of the EU 2022

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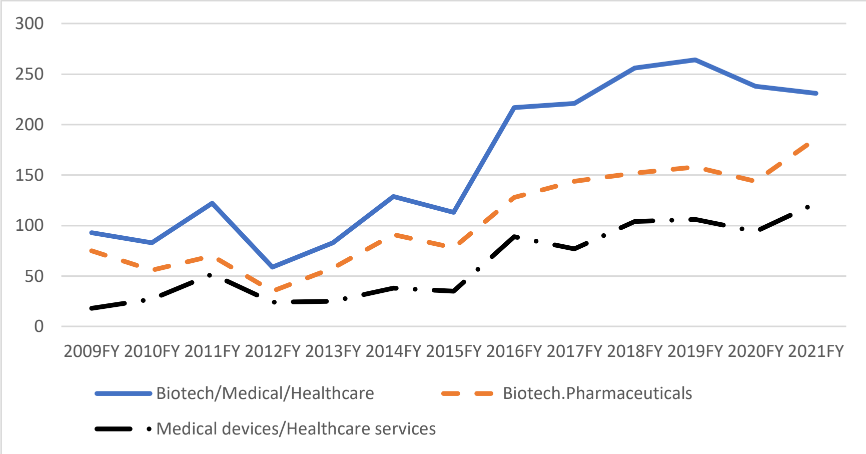
[Japan]

In Japan, the amount of investment in this field is showing a certain increase.

Fig17 Changes in the number of venture investments



Source: Venture Enterprise Center

It is reasonable to think that the level exceeded JPY 50 billion in FY2021, and that it has been trending at about one-tenth of the total in Europe.

In terms of population, in 2010 the EU had 441.02 million and Japan had 128.04 million, and in 2020 the EU had 448.31 million and Japan had 125.71 million. The fact that Japan's venture capital investment in healthcare is about one-tenth of EU is a major feature.

The point is at what pace this level increased. A steady increase occurred in the United States in the early 2000s. After the Lehman Brothers collapse, from the 2010s onwards, companies shifted gears again, and the annual investment amount has increased by about 10 times in about 25 years. There was some movement in Europe as well, but full-scale growth started in the latter half of the 2010s. As mentioned above, at this point Europe for the first time reached the size of investment seen in the United States in the first half of the 2000s. In Japan, the number of investments and the amount of investment increased at the same time as in Europe, but the scale was smaller. Considering that there is no big difference in R&D spending per capita at universities, one characteristic is that there is a limit to translational movements in Japan.

3.1.3 Changes on the company side

Section 3.1.2 showed the weakness of Japanese venture capital, but when it comes to corporate-based deployment, this trend changes slightly. A conclusion is that Japanese companies are moving closer to global standards, while simultaneously it is becoming meaningless to "determine the nationality of a company based on the location of its headquarters."

Based on that, I look at changes in corporate activities in relation to the ecosystem. In this section, rather than capturing the total value of the industry, I add up the figures for major companies. Table 6 shows the sales, R&D expenses, and intangible fixed assets of top global companies. Table 7, on the other hand, looks at the movements of Japanese companies.

Table6 Changes in financial statements of major pharmaceutical companies*[1] (average value)

(Million $)

	2000	2005	2010	2015	2020
	Average of 9	Average of 10	Average of 11	Average of 11	Average of 11
Amount of sales	20,827	32,775	43,461	40,719	46,278
R&D expense	2,591	4,577	6,867	6,852	9,287
Total assets	27,370	56,950	86,406	92,867	113,075
Current assets	14,130	22,108	28,991	27,797	31,924
Property, plant and equipment	6,903	9,945	12,731	12,430	13,312
Intangible assets and goodwill	3,361	18,882	36,587	40,556	54,940

*1 Johnson & Johnson, Pfizer Inc, Roche Holding AG, Novartis AG, Bayer AG, Merck & Co. Inc, GSK PLC, Bristol-Myers Squibb Co, Sanofi SA, AstraZeneca PLC, Eli Lilly and Co.

Note: Figures for fiscal 2000 are for nine companies, excluding Merck and AstraZeneca, and figures for fiscal 2005 are for 10 companies, excluding AstraZeneca.

Created by the author based on each company's financial statements

Table7 Changes in financial statements of major Japanese pharmaceutical companies*[1] (average value)

(JYP Million)

	2000	2005	2010	2015	2020	
	Average of 11	Average of 9	Average of 10	Average of 10	Average of 10	Average of 9 (Excluding Takeda)
Amount of sales	383,968	543,353	679,019	789,630	970,634	723,169
R&D expense	45,381	82,427	127,085	141,407	169,429	137,607
Total assets	635,169	1,015,121	1,097,909	1,442,241	2,607,966	1,463,041
Current assets	370,985	536,634	602,069	687,425	891,704	689,349
Property, plant and equipment	211,233	132,960	167,764	198,520	325,493	200,112
Intangible assets and goodwill	10,190	23,370	180,561	371,577	1,107,726	348,248

(USD Million)

	2000	2005	2010	2015	2020	
	Average of 11	Average of 9	Average of 10	Average of 10	Average of 10	Average of 9 (Excluding Takeda)
Amount of sales	3,811	4,930	7,735	6,523	9,090	6,773
R&D expense	450	748	1,448	1,168	1,587	1,289
Total assets	6,303	9,210	12,508	11,915	24,425	13,702
Current assets	3,682	4,869	6,859	5,679	8,351	6,456
Property, plant and equipment	2,096	1,206	1,911	1,640	3,048	1,874
Intangible assets and goodwill	101	212	2,057	3,070	10,374	3,262

*1 Takeda Pharmaceutical, Otsuka Holdings, Astellas Pharma (in FY2000 Yamanouchi and Fujisawa separately), Daiichi Sankyo (in FY2000 Daiichi and Sankyo separately), Chugai Pharmaceutical, Eisai, Sumitomo Pharma, Ono Pharmaceutical, Kyowa Kirin, Shionogi Pharmaceutical

Note: Figures for fiscal 2000 and 2005 are 11 and 9 companies, respectively, excluding Otsuka Holdings.

Created by the author based on each company's financial statements

Looking at the figures taken up here, what stands out is the increase in intangible fixed assets and research and development expenses. I would like to touch upon this point a little further below.

[Trends in intangible fixed assets]

The level of intangible fixed assets has increased significantly since 2005 for major global companies, and since around 2010 for Japanese companies. Initially, this movement was conspicuous in the process of integration and acquisition between large companies, but with the introduction of International Financial Reporting Standards, the depreciation policy changed, and with the maturation of the ecosystem, there were large-scale acquisitions of venture companies. In 2020, the ratio of intangible fixed assets to total assets was expected to be 47% for major global companies and 43% for Japanese companies.

Unlike R&D expenses, which are paid out as a flow every fiscal year, intangible fixed assets are not something that accumulates at a fixed percentage every fiscal year, because they are recorded in the form of goodwill when acquiring a company. However, over the long term, the trends in the numbers clearly show when company activity stepped up a gear.

[Trends in research and development expenses within companies]

Even as complementarity proceeds, companies are still required to invest in research and development on their own. There continues to be company-specific development, as well as post-integration development such as acquisitions and licensing, and the pace of R&D is not slowing.

Looking only at trends since 2000, I can see an average tripling of development costs for global companies, whereas the overall figure for Japanese companies has been a bit more moderate, roughly doubling (Table 8).

Table8 R&D spending in the pharmaceutical industry (Japan)

Fiscal Year	R&D expenses (expenditure amount)	Year-on-year change		% of sales
	(JPY billion)	(JPY billion)	Growth rate(%)	(%)
1980	1,898	129	7.3	5.45
1985	3,419	466	15.8	7.04
1990	5,161	601	13.2	8.02
1994	6,328	36	0.6	7.79
1995	6,422	94	1.5	8.03
1996	6,671	249	3.9	8.11
1997	6,433	−238	−3.6	8.06
1998	6,811	378	5.9	8.07
1999	6,894	83	1.2	8.07
2000	7,462	568	8.2	8.60
2001	8,109	647	8.7	8.52
2002	9,657	1,548	19.1	8.91
2003	8,837	−820	−8.5	8.43
2004	9,067	230	2.6	8.64
2005	10,477	1,410	15.5	10.01
2006	11,735	1,258	12	10.95
2007	12,537	802	6.8	12.11
2008	12,956	419	3.3	11.74
2009	11,937	−1,019	−7.9	11.66
2010	12,760	823	0.9	12.02
2011	12,299	−461	−3.6	11.96
2012	13,061	762	6.2	11.81
2013	14,371	1,310	10.0	11.70
2014	14,953	582	4.1	12.21
2015	14,577	−376	−2.5	11.93
2016	13,516	−1,061	−7.3	10.04
2017	14,653	1,137	8.4	11.10
2018	14,047	−606	−4.1	11.05
2019	13,392	−655	−4.7	10.08
2020	13,216	−176	−1.3	9.68

(Note) The research and development expenses described here are internal research expenses defined in the Ministry of Internal Affairs and Communications' "Science and Technology Research Survey". External research expenses (those outside the company), such as commissioned research and joint research, are not included.

(Source) Ministry of Internal Affairs and Communications, “Science and Technology Research Survey”
From Japan Pharmaceutical Manufacturers Association DATA BOOK 2022

As can be seen in Table 9, the proportion of non-clinical trials in R&D expenses for US companies has declined significantly over the past 20 years, and the composition ratio of phase 2 trials has increased significantly. This point is symbolic in the sense of a change in the way companies are involved in development.

Table9 Composition ratio of pharmaceutical company R&D expenses by stage (US)

	Year	Pre-clinical study	Phase1	Phase2	Phase3	Approval application	Phase4	Subtotal	Uncategorized R&D expenses	Total
R&D expenses (Million $)	2001	9,647.4	1,659.2	3,151.2	4,502.2	2,307.9	3,286.9	24,554.8	5,167.9	29,722.7
	2002	10,481.6	1,490.2	2,968.1	6,268.4	2,455.0	3,855.2	27,518.5	3,493.7	31,012.2
	2003	10,983.3	2,333.6	3,809.6	8,038.1	4,145.4	3,698.1	33,008.1	1,445.2	34,453.3
	2004	9,585.7	2,473.3	3,770.4	9,682.1	3,415.3	4,902.9	33,829.7	3,188.4	37,018.1
	2005	10,258.1	2,318.9	4,670.9	10,176.4	2,750.0	5,284.2	35,458.5	4,399.4	39,857.9
	2006	11,816.1	2,902.7	5,687.4	12,187.3	2,649.3	5,584.6	40,827.4	2,611.6	43,439.0
	2007	13,087.4	3,547.7	6,251.0	13,664.7	2,413.8	6,439.9	45,404.5	2,498.6	47,903.1
	2008	12,795.6	3,889.6	6,089.7	15,407.4	2,225.8	6,835.8	47,244.0	139.1	47,383.1
	2009	11,717.4	3,752.9	7,123.7	16,300.1	2,046.9	5,302.7	46,243.8	197.8	46,441.6
	2010	12,578.2	4,130.3	6,483.3	18,598.1	3,108.3	4,839.0	49,737.2	972.6	50,709.8
	2011	10,466.3	4,211.0	6,096.4	17,392.9	4,033.4	4,760.9	46,961.0	1,684.0	48,645.0
	2012	11,816.3	3,823.3	5,756.2	15,926.8	3,834.6	6,776.5	47,933.8	1,653.8	49,587.6
	2013	10,717.8	3,666.9	5,351.3	15,239.2	5,395.4	7,574.2	47,944.8	3,668.7	51,613.5
	2014	11,272.7	4,722.0	5,697.8	15,264.4	2,717.7	8,827.0	48,501.6	4,751.5	53,253.1
	2015	–	–	–	–	–	–	–	–	–
	2016	11,292.6	6,054.8	7,426.1	18,327.3	2,413.8	7,466.1	52,980.7	12,557.6	65,538.3
	2017	11,168.7	6,201.0	8,277.4	21,377.0	2,788.7	8,152.9	57,965.7	13,433.8	71,399.4
	2018	13,069.0	7,749.4	8,436.0	23,033.2	2,647.6	9,230.2	64,165.4	15,437.4	79,602.8
	2019	13,034.3	7,260.8	8,045.7	23,979.8	3,538.8	9,321.1	65,180.5	17,775.7	82,956.3
	2020	13,604.0	6,968.3	8,429.4	24,773.1	3,932.5	10,512.4	68,219.7	22,906.6	91,126.3
Composition ratio	2001	39.3%	6.8%	12.8%	18.3%	9.4%	13.4%	100.0%		
	2002	38.1%	5.4%	10.8%	22.8%	8.9%	14.0%	100.0%		
	2003	33.3%	7.1%	11.5%	24.4%	12.6%	11.2%	100.0%		
	2004	28.3%	7.3%	11.1%	28.6%	10.1%	14.5%	100.0%		
	2005	28.9%	6.5%	13.2%	28.7%	7.8%	14.9%	100.0%		
	2006	28.9%	7.1%	13.9%	29.9%	6.5%	13.7%	100.0%		
	2007	28.8%	7.8%	13.8%	30.1%	5.3%	14.2%	100.0%		
	2008	27.1%	8.2%	12.9%	32.6%	4.7%	14.5%	100.0%		
	2009	25.3%	8.1%	15.4%	35.2%	4.4%	11.5%	100.0%		
	2010	25.3%	8.3%	13.0%	37.4%	6.2%	9.7%	100.0%		
	2011	22.3%	9.0%	13.0%	37.0%	8.6%	10.1%	100.0%		
	2012	24.7%	8.0%	12.0%	33.2%	8.0%	14.1%	100.0%		
	2013	22.4%	7.6%	11.2%	31.8%	11.3%	15.8%	100.0%		
	2014	23.2%	9.7%	11.7%	31.5%	5.6%	18.2%	100.0%		
	2015	–	–	–	–	–	–	–		
	2016	21.3%	11.4%	14.0%	34.6%	4.6%	14.1%	100.0%		
	2017	19.3%	10.7%	14.3%	36.9%	4.8%	14.1%	100.0%		
	2018	20.4%	12.1%	13.1%	35.9%	4.1%	14.4%	100.0%		
	2019	20.0%	11.1%	12.3%	36.8%	5.4%	14.3%	100.0%		
	2020	19.9%	10.2%	12.4%	36.3%	5.8%	15.4%	100.0%		
composition ratio (including uncategorized)	2001	32.5%	5.6%	10.6%	15.1%	7.8%	11.1%	82.6%	17.4%	100.0%
	2002	33.8%	4.8%	9.6%	20.2%	7.9%	12.4%	88.7%	11.3%	100.0%
	2003	31.9%	6.8%	11.1%	23.3%	12.0%	10.7%	95.8%	4.2%	100.0%
	2004	25.9%	6.7%	10.2%	26.2%	9.2%	13.2%	91.4%	8.6%	100.0%
	2005	25.7%	5.8%	11.7%	25.5%	6.9%	13.3%	89.0%	11.0%	100.0%
	2006	27.2%	6.7%	13.1%	28.1%	6.1%	12.9%	94.0%	6.0%	100.0%
	2007	27.3%	7.4%	13.0%	28.5%	5.0%	13.4%	94.8%	5.2%	100.0%
	2008	27.0%	8.2%	12.9%	32.5%	4.7%	14.4%	99.7%	0.3%	100.0%
	2009	25.2%	8.1%	15.3%	35.1%	4.4%	11.4%	99.6%	0.4%	100.0%
	2010	24.8%	8.1%	12.8%	36.7%	6.1%	9.5%	98.1%	1.9%	100.0%
	2011	21.5%	8.7%	12.5%	35.8%	8.3%	9.8%	96.5%	3.5%	100.0%
	2012	23.8%	7.7%	11.6%	32.1%	7.7%	13.7%	96.7%	3.3%	100.0%
	2013	20.8%	7.1%	10.4%	29.5%	10.5%	14.7%	92.9%	7.1%	100.0%
	2014	21.2%	8.9%	10.7%	28.7%	5.1%	16.6%	91.1%	8.9%	100.0%
	2015	–	–	–	–	–	–	–	–	–
	2016	17.2%	9.2%	11.3%	28.0%	3.7%	11.4%	80.8%	19.2%	100.0%
	2017	15.6%	8.7%	11.6%	29.9%	3.9%	11.4%	81.2%	18.8%	100.0%
	2018	16.4%	9.7%	10.6%	28.9%	3.3%	11.6%	80.6%	19.4%	100.0%
	2019	15.7%	8.8%	9.7%	28.9%	4.3%	11.2%	78.6%	21.4%	100.0%
	2020	14.9%	7.6%	9.3%	27.2%	4.3%	11.5%	74.9%	25.1%	100.0%

(Note) Data for 2015 are not published.
(Source) PhRMA: Industry Profile 2001-2012, PhRMA Annual Membership Survey since 2013
From Japan Pharmaceutical Manufacturers Association DATA BOOK 2022

[Regarding sales and employment levels]

Sales on a major company basis have approximately doubled over the past 20 years despite continued mergers and other factors. Japanese companies, in particular, are in a situation where growth in the existing domestic market is limited to a certain extent, considering financial constraints.

In terms of sales, besides the major companies whose figures can be continuously obtained, there are other companies such as Chinese companies and bio-venture companies that have rapidly increased their sales over the past 5 to 10 years. Therefore, the sales growth by major companies is somewhat limited.

However, even if such factors are excluded, the level is somewhat moderate compared to the increase in venture capital investment and the increase in R&D expenses / intangible fixed assets on the corporate side.

Employment by the companies is even more extreme, with major global companies on the decline, and a cessation of growth even in Japan. However, it must be noted that the fact of the intermediate stage of development occurring outside the company may have led to an increase in employment at peripheral companies and venture companies.

3.2 Ecosystem transitions

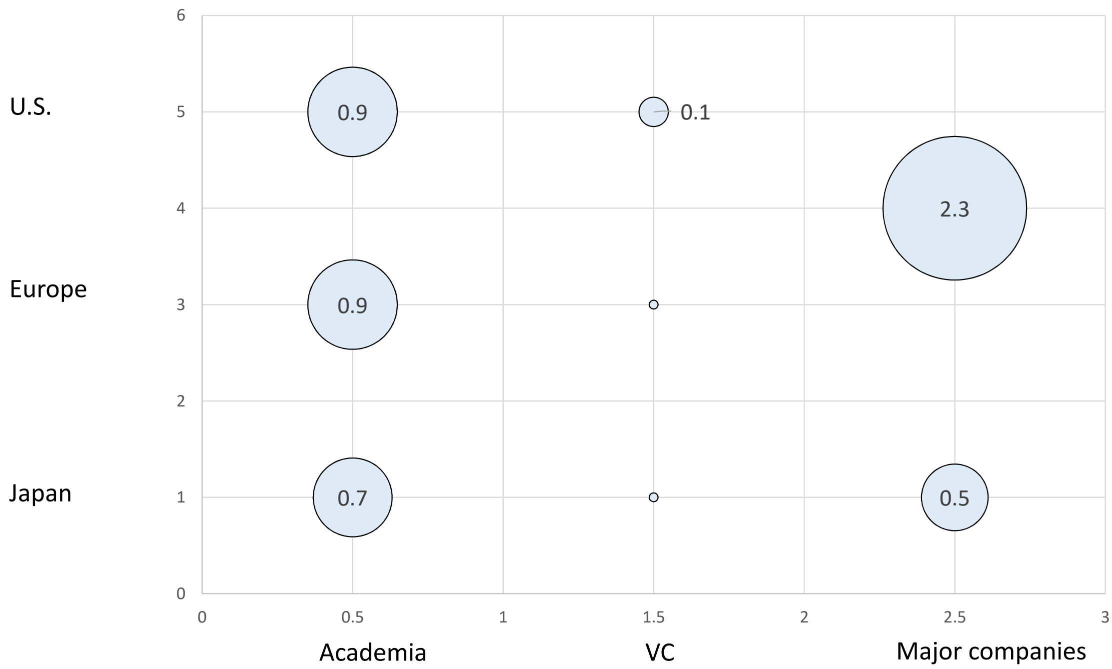
I would like to organize the changes in research and development up to this point in a somewhat schematic way, chronologically.

3.2.1 1980s-1990s: Dawn

Looking at the changes in numbers from the 1980s to the 1990s, it can be inferred that the evolution of science and the growth of companies basically moved moderately.

The following chart plots the development of each process based on an image of the amount (see page 34). It is created to give an overview of how the balance has changed over time.

Fig18 Image of each player in the 1990s



From academia's point of view, although there are translational R&D projects that are being put to practical use, in the era of small molecule drugs, the function of corporate research laboratories was also important, and it is surmised that academia played a strong role in basic science.

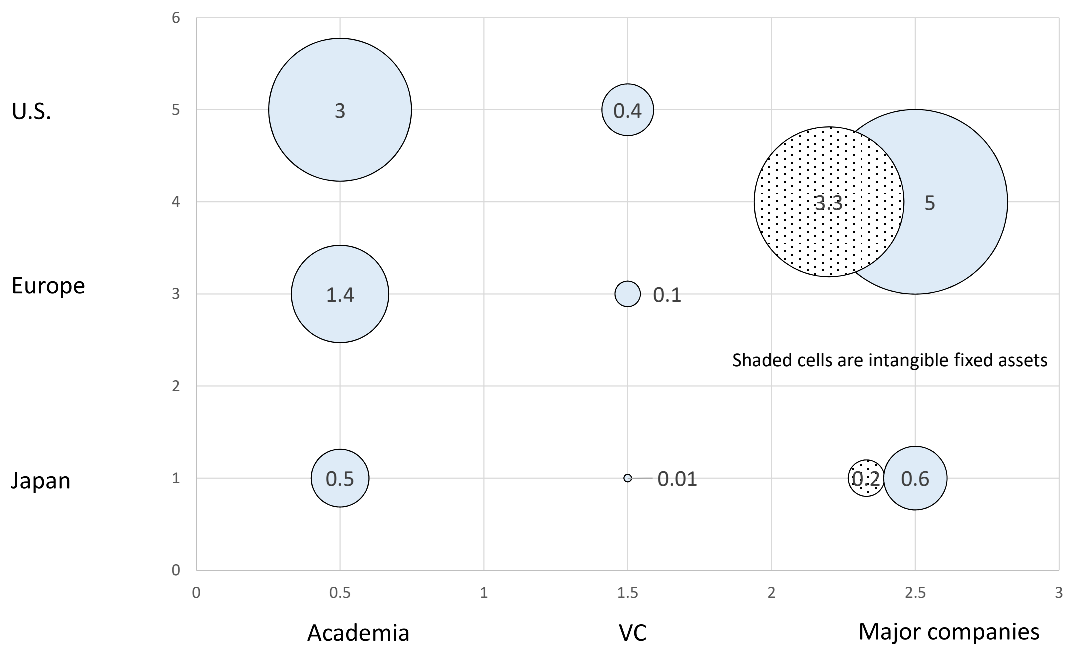
For example, in the case of San Diego (see 2.2.1), the hub of the ecosystem is the venture company Hybritech, and in this era the ecosystem was born in the form of decentralized venture companies.

In this era, "business risk" itself was embodied in independent venture companies; and in terms of "interdependence risk", venture capital funds themselves were limited in terms of the size of the market as a whole and could not be used to supplement this risk. On the other hand, regarding "integration risk", although the number of acquisitions was gradually increasing, it was still small, and intangible fixed assets were small compared to the total assets of major companies.

3.2.2 2000s: Beginning of a clear division of roles

In the first decade of the 2000s, changes occurred in the business scale of each player.

Fig19 Image of each player in the first decade of the 2000s



As for the business risk itself, it can be imagined that the risk increased in the early stages as the modalities began to gradually shift away from the focus on small molecule drugs.

On the other hand, there are only a limited number of countries where research and development increased significantly at universities. The United States is an exception among them, with an increase of about three times over a decade beginning in the mid-1990s. The NIH budget has also increased by 2.5 times, immediately accelerating spending on life sciences.

The appearance of vertically integrated large companies contributed to a large movement in which R&D expenses of major companies increased by about 2.5 times. By the way, the increase in intangible fixed assets is not necessarily invested in research and development. It also is used as a strong reward for the development of venture companies; thus the shading in Figure 19.

Also, venture capital investment has increased, and as mentioned above, in the United States, the number of pre-clinical developments by large companies has decreased, and development costs have begun to slide from Phase II onwards.

From the company's point of view, this is an act to fill in the "uncertainty" risk. On the other hand, with the industrialization of venture capital and the intensive and time-consuming development of venture companies, the risk related to "time" has been somewhat buried.

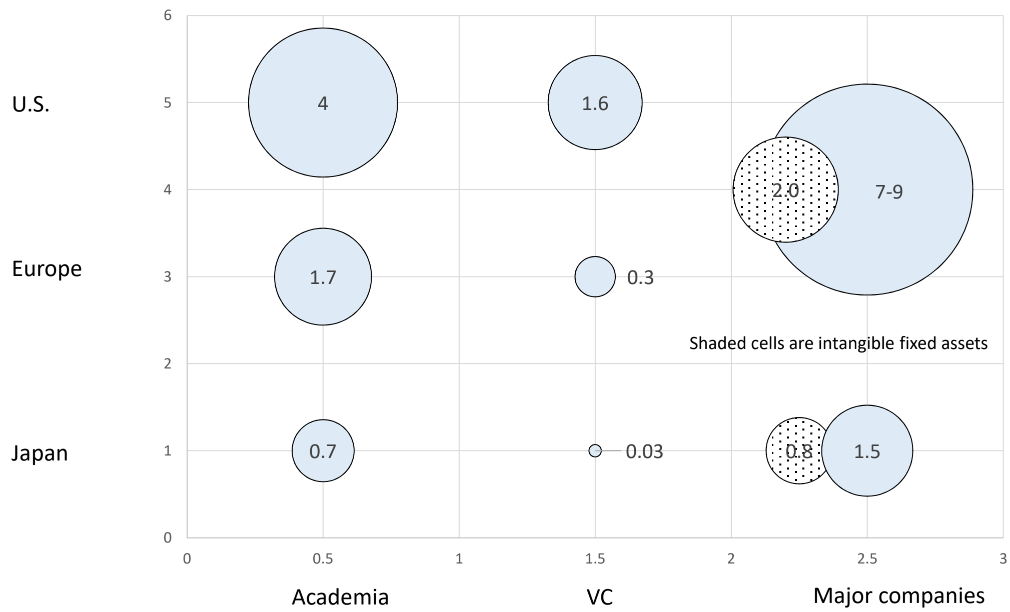
As a result, even in new development, a complementary relationship between venture capital and venture companies was created, and the response to "integration risk" has progressed.

But with the exception of the United States, research and development in academia has not moved much in terms of money. Since the investment environment for venture capital has not yet been established in such places, it cannot be said that the development is interdependent from a global perspective.

3.2.3 2010s: Dynamic ecosystem

In the 2010s, research and development by companies, investment by venture capital, and increases in research and development expenses at universities began to occur in parallel, and the signs were seen not only in the United States but also in Europe.

Fig 20 Image of each player in the 2010s



As business risks continue to rise, responses to the above-mentioned interdependence risks are changing further. In the United States, the investment amount of venture capital increased to a level that cannot be ignored compared to the research and development expenses of companies and universities, and the relationship between science and venture capital deepened.

As research by academia becomes more translational, it can be said that the logic of budgeting development costs has been established; and at the same time, it has become easier to collect external funds. Therefore, research and development spending at universities also continues to rise in the United States and some European countries.

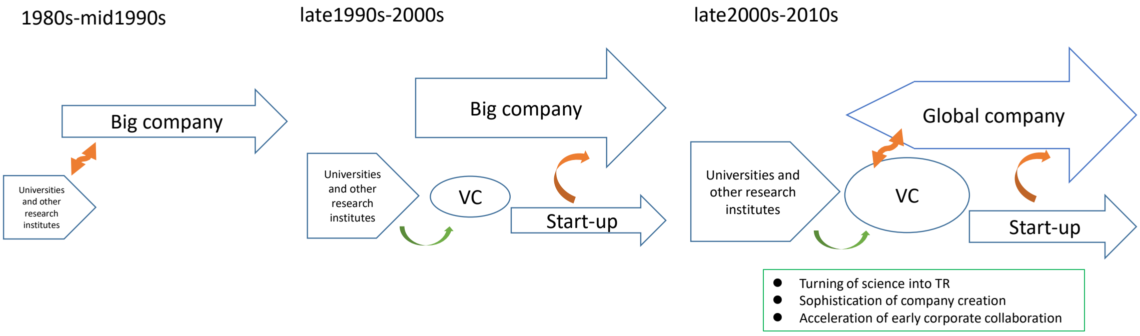
In venture capital, the participants gained experience as the number of projects accumulated, thus expanding the range of practical responses to ‘company creation’, which increased the trust of universities and research institutes.

Under these circumstances, venture companies have found expanded opportunities around the globe for their exits. International barriers to business development are also considerably lower.

Above all, company commitment to development began happening at an earlier stage. This is partly linked to the improvement of corporate strength and companies proceeding in the direction of building their own portfolios.

The following diagram shows this flow. The important point is 'order': after the corporate strength was strengthened, the venture capital market was strengthened and, as a result, funds flowed into science again. This hypothesis is based on the transition so far.

Fig21 Ecosystem transition



3.2.4 Summary

In this chapter, I discussed how the life science ecosystem creates its complementary relationship. I presented an overview of what has been achieved in tracing the changes in the industrial structure. It is not that one player has pulled it in one direction in a visionary way: companies, venture capitalists, and academia have moved in their own directions with an eye on the next step.

This chapter has only looked at trends in R&D expenditures, but it can be seen that the mechanism for "commercialization of science" is gradually changing: product launches with new modalities are progressing more than before.

And within this overall composition, there are countries that have developed their own ecosystems by exercising originality and ingenuity. It is impossible for a single country to create a framework identical to the global one, but it is beneficial for Japan to see the process of forming its own ecosystem while connecting its own flow to the global framework.

Chapter 4 looks at the history of biotech ecosystem formation in Belgium as an example.

Explanation of conceptual illustrations (unit numbers: USD 10 billion)

Academia:

United States

- Figure 12 1995 (90s), Figure 14 around 2005-09 (00s), Figure 14 around 2015 (10s) *Not shown for NIH

Europe

- It is assumed that the countries in Figure 13 account for about 80% of the total expenditure in Europe. For Italy and the UK, in 1995, 3.5 million was added (1990s); in 2005, 2.5 million was added (00s). Both numbers are multiplied by 1/0.8.

Japan

- Figure 13 figures for 1995 (90s), 2005 (00s), and 2015 (10s)

VCs:

United States - 1995 (90s), 2005 (00s), 2015 (10s) based on NVCA published data
Europe - see the text below Table 5(00s and 10s)
Japan - see Figure 17, 2015 (10s)
Note: European 90s and Japanese 90s and 00s are kept to a minimum.

Major companies _Research Expense (in Europe, America and Japan)**:**

1990s ⇒ Total value of Tables 6 and 7 as of 2000
2000s ⇒ Total value of Tables 6 and 7 as of 2005
2010s ⇒ Total values of Tables 6 and 7 as of 2020 (because the figures for 2015 are irregular)
Note: Intangible fixed assets are set at one-tenth of net increase (total value) for each age group.

Chapter 4 History of Belgian bio-ecosystem formation

- Belgium has created a robust bio-industry in terms of science, R&D and production.
- One of the roots of this was the strengthening of science. A symbolic example is the establishment of VIB. It has worked side by side with universities and has produced results by implementing organizational management while incorporating peer reviews, centering on the career development of scientists.
- After the fact, this trend spread to the Wallonia region. Then, the financing to support it was also formed in each area. As a result, human resources from academia are steadily being supplied to industry.
- Now, the focus is on strengthening human resources, such as the Advanced Master School and the EU Biotech Campus. This is the latest form of development in the country, given the importance of 'investing in human resources'.

4.1 Assumptions of Belgium's life science ecosystem

As an example of ecosystem formation, this chapter discusses the formation of an ecosystem related to biotechnology in Belgium. The reason why I chose Belgium as the subject of our analysis is that it is characterized by the process of growing the base of science, bringing about the development of the industry, and obtaining employment and evaluation from the market.

4.1.1 Geographical features of Belgium

Belgium's regional administrations are divided into the Flanders region (hereafter Flanders), the Walloon region (hereafter Wallonia) and the Brussels metropolitan area. Basically, Flanders in the north is the Dutch-speaking region, and Wallonia in the south is the French-speaking region. There is also a German-speaking community: Deutschsprachige Gemeinschaft in the east.

Fig22 Belgium map

Source：Wikimedia Commons

The total population is about 11 million, which is about one-tenth of Japan’s, and population trends are as follows.

Table10　　Population trends in Belgium and its regions (thousands)

		1981	1991	2001	2011	2021
Belgium		9,855	10,022	10,310	11,036	11,584
	Flemish	5,642	5,795	5,973	6,351	6,699
	Wallonia	3,218	3,276	3,358	3,546	3,663
	Brussels	994	951	979	1,139	1,222

Source: NBB.stat

4.1.2 Universities

First, major universities in Belgium are listed in Table 11 (listed in order of establishment). Vlaams Instituut voor Biotechnologie (VIB), which will be described later, is an organization that connects these universities (especially in Flanders).

It is said that the reason for the existence of two separate universities in 1970 is that the University of Leuven and the Free University of Brussels were split between the French-speaking and Dutch-speaking countries after student disputes in the late 1960s.

Table11　List of major Belgium universities

University	Establishment	City	Region	The number of students
Catholic University of Leuven(KUL)	1425	Leuven	Flanders	65,186
Ghent University	1817	Ghent	Flandes	49,216
University of Liege	1817	Liege	Wallonia	28,064
Free University of Brussels(ULB)	1833	Brussels	Brussels metro area	30,880
University of Antwerp	1852	Antwerp	Flanders	21,428
Catholic University of Louvain(UCL)	1970(split)	Louvain-la-Neuve	Wallonia	34,318
Free University of Brussels (VUB)	1970(split)	Brussels	Brussels metro area	19,156

Created by the author based on various materials

In this list, the University of Leuven ranks in the top 100 in biological sciences according to the Times Higher Education World University Rankings 2023, followed by the University of Ghent (within Japan, the University of Tokyo and Kyoto University are also in the top 100).

Among the major national universities in Japan, the University of Tokyo has the largest number of students (over 26,000—not limited to life science students). The comparable number in other major national universities is around 20,000. Per-capita matriculation is larger at major Belgian universities than at Japanese national and public universities.

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4.1.3 Major pharmaceutical companies

Table 12 below lists major pharmaceutical companies in Belgium.

Table12 Major pharmaceutical companies located in Belgium

Company	Location	Overview
Janssen Pharmaceutica	Beerse	A large base where more than 5,000 people work at the Janssen campus. Establishment of a new CAR-T therapy center in Zwijnaarde.
GSK	Wavre, Rixensart	GSK's research and production base for vaccines
UCB	Braine L'alleud	Transitioned from a chemical manufacturer to a biotech company. Currently focusing on gene therapy.
Pfizer	Puurs	Manufactures over 400 million doses of injectable vaccines and medicines in a variety of formats. Production of COVID-19 vaccine is also underway.
Sanofi	Geel	Production of therapeutic proteins from cell cultures for the purpose of producing biological drugs. In 2016, it evolved into a multi-product facility with monoclonal antibody production.
Takeda	Lessines	Purification and packaging centers for immunology and hematology products covering over 80 countries worldwide. Recently opened a plasma production line.

Created by the author based on materials published by each company

Here, I need to explain three Belgian-origin companies (including those currently under the umbrella of a major global pharmaceutical company). The three companies are Janssen Pharmaceutica (Janssen), GSK, and UCB.

Janssen is currently a leading company in Flanders. Since Dr. Paul Janssen established the research institute in 1953, it has created many new compounds, including the pain medicine fentanyl and the antipsychotic drugs haloperidol and risperidone. In 1961, it joined the Johnson & Johnson Group (hereafter, J&J) and still occupies a central position in the company's pharmaceutical business division (like J&J, currently headquartered in New Jersey, USA). Beerse is an innovative pharmaceutical research base and a main production base (employing over 5,000 people). Recently, the establishment of a hub for CAR-T treatment in Zwjinaarde was announced.

GSK is a global company headquartered in London, formed in 2000 by the merger of SmithKline Beecham and Glaxo Wellcome. Belgium is home to the company's global headquarters for vaccines (three major vaccine sites: Wavre, Rixensart, Gambloux), whose origins lie in the company RIT (Recherche et Industrie Therapeutique) founded by Pieter Desomer (who was also the Rector of KUL) together with Christian de Duve. GSK currently has 1,800 scientists conducting research and over 9,000 people working in Belgium.

UCB was established as a chemicals company in 1928. In 2004 it acquired the UK-based biotech company Celltech (transitioning to a biopharmaceutical company after having entered the pharmaceutical market) and developed drugs such as the blockbuster 'Cizmzia'. Currently, the company has entered the gene therapy field, aiming to have 25% of its pharmaceuticals based on gene therapy by 2030. In September 2022, it announced an investment of EUR 1 billion over the next 10 years in this field.

4.1.4 Characteristics of the Belgian life science field

As seen in 4.1.3, it is clear that Belgium already has a certain industrial concentration related to pharmaceuticals, but again I would like to look at the relationship between academia and industry.

(1) Resource investment and performance in academia in Belgium

As mentioned in Chapter 3, among the countries for which OECD data can be obtained continuously, R&D investment trends at Belgium universities have been growing steadily (Figures 11 and 13-2).

Fig 11 Changes in the number of R&D personnel (medical and health sciences) per 100,000 population

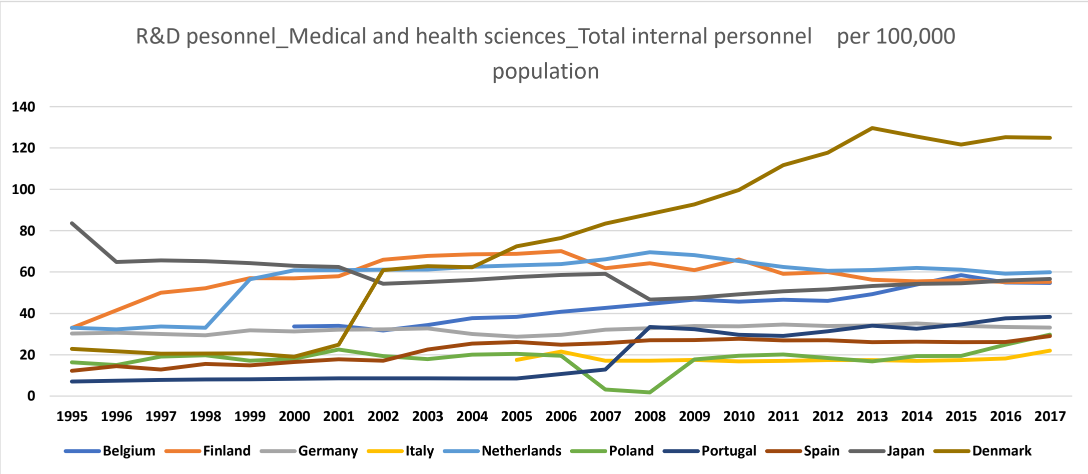
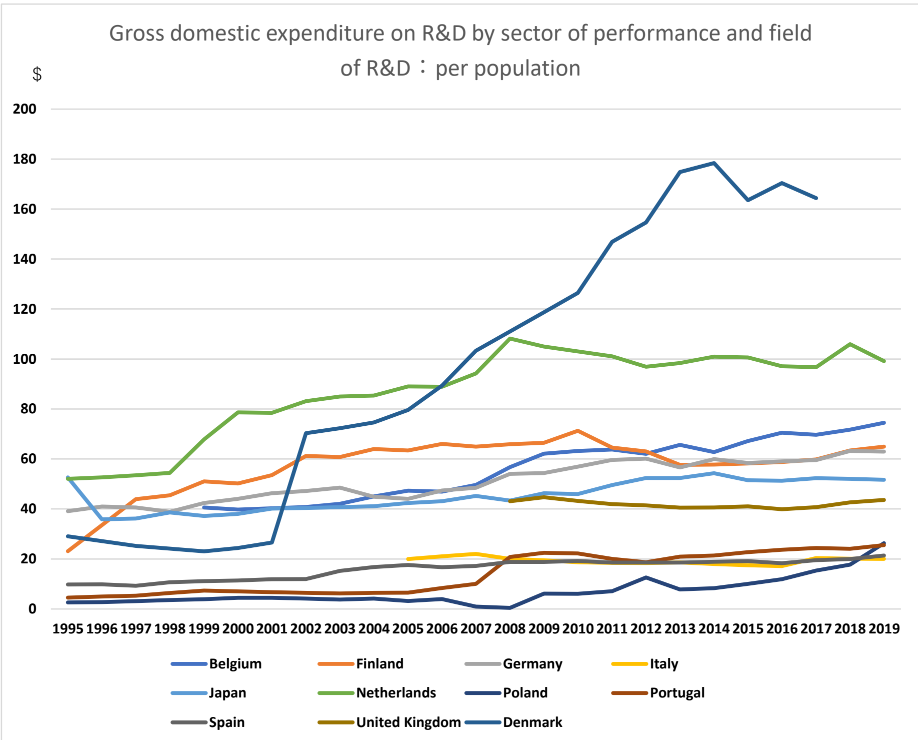


Fig 13-2 Trends in R&D spending in the fields of medical and health sciences in higher education (per population)



The number of papers per capita in Europe is also shown below. Although this level is inferior to Switzerland, Denmark, and Sweden, it maintains a high level on par with the Netherlands.

Table13 Number of papers per million population (Basic Life Science_FY2017-19(average))

Number of papers	Papers	Per 1million population
Switzerland	9,174	1,067.8
Denmark	6,082	1,053.7
Sweden	7,582	755.5
Australia	16,855	668.8
Netherland	11,103	649.4
Belgium	6,588	570.9
Austria	4,661	520.5
Canada	18,757	501.4
U.K.	30,021	444.6
Germany	29,262	350.4
Spain	16,325	349.3
U.S.	112,508	341.9
Italy	19,513	322.3
France	19,050	292.5
Korea	13,024	254.2
Poland	7,664	202.3
Taiwan	4,557	193.1
Japan	21,768	171.6
Iran	8,636	104.2
Brazil	20,542	97.3
Turkey	6,270	75.2
China	83,780	59.3
Mexico	5,874	46.0
Russia	5,983	41.0
India	16,971	12.0

Top 10% corrected number of papers	Papers	Per 1million population
Switzerland	1,689	196.6
Denmark	1,016	176.0
Sweden	1,294	128.9
Netherland	2,013	117.7
Norway	572	106.3
Australia	2,660	105.5
Finland	533	96.3
Belgium	1,093	94.7
Austria	757	84.5
U.K.	5,147	76.2
Canada	2,535	67.8
Israel	552	64.8
Portgul	599	58.6
Germany	4,415	52.9
U.S.	15,981	48.6
Spain	2,216	47.4
Italy	2,810	46.4
France	2,747	42.2
Korea	1,081	21.1
Poland	647	17.1
Japan	1,623	12.8
Iran	866	10.4
China	9,203	6.5
Brazil	1,307	6.2
India	1,295	0.9

Top 1% corrected number of papers	Papers	Per 1million population
Switzerland	250	29.1
Denmark	145	25.1
Sweden	192	19.1
Netherland	316	18.5
Ireland	87	17.8
Norway	91	16.9
Australia	360	14.3
Finland	79	14.3
Belgium	161	14.0
Austria	112	12.5
U.K.	699	10.4
Israel	85	10.0
Canada	342	9.1
Germany	573	6.9
U.S.	2,042	6.2
Spain	274	5.9
France	366	5.6
Italy	328	5.4
Korea	131	2.6
Poland	80	2.1
Japan	193	1.5
Iran	103	1.2
Brazil	143	0.7
China	848	0.6
India	158	0.1

Processed and created by the author based on “Science and Technology Indicators 2022”, National Institute of Science and Technology Policy, Ministry of Education, Culture, Sports, Science and Technology. Data source: Web of Science XML from Clarivate

(2) Investment in development funds in industry

Regarding R&D in the industrial sector, a comparison within Europe reveals that R&D expenditures are at a very high level when converted to per capita amounts.

Table14 Pharmaceutical Industry Research and Development in Europe

	Amount (€ Million)	Per 1million population		Amount (€ Million)	Per 1million population
Switzerland	6,383	743.0	Italy	1,600	26.4
Belgium	3,846	333.3	Spain	1,212	25.9
Denmark	1,543	267.3	Hungary	242	25.0
Sweeden	1,104	110.0	Norway	126	23.4
Germany	8,466	101.4	Bulgaria	91	13.0
Slovenia	180	86.6	Portugal	117	11.4
U.K.	5,437	80.5	Croatia	40	9.7
Cyprus	85	70.9	Poland	339	8.9
France	4,451	68.3	Czech Rep,	62	5.8
Ireland	305	62.5	Russia	727	5.0
Netherlands	642	37.6	Greece	51	4.9
Austria	311	34.7	Romania	75	3.9
Finland	182	32.9	Turkey	137	1.6

Created by the author based on EFPIA (European Federation of Pharmaceutical Industries and Associations) 2019 data

As can be seen in Table 14, Switzerland ranks among the highest in this area, but this is inevitable given the country’s concentration of head offices of global pharmaceutical companies.

At the same time, neighboring Denmark reflects the active research and development situation in the area connected to Sweden in the form of the so-called "Medicon Valley."

Since the figures in Table 15 are per capita, the figures for Germany, France, and the United Kingdom are larger on an actual value basis, but Belgium ranks fifth after France.

Next, in Table 15, I would like to look at employment and pharmaceutical production.

Table15 Employment and production in the pharmaceutical industry in Europe

Employment	Units	Per 1million population
Ireland	37,000	7,578
Switzerland	46,652	5,430
Slovenia	11,213	5,394
Denmark	24,821	4,300
Belgium	38,489	3,335
Greece	25,700	2,454
Hungary	23,300	2,406
Malta	1,033	2,346
Bulgaria	15,000	2,143
Romania	35,000	1,807
Austria	16,094	1,797
Czech Rep.	18,000	1,684
France	98,780	1,517
Iceland	500	1,475
Cyprus	1,755	1,464
Germany	119,994	1,437
Croatia	5,763	1,395
Latvia	2,232	1,171
Netherlands	20,000	1,170
Sweeden	11,012	1,097
Italy	65,800	1,087
U.K.	72,000	1,066
Finland	5,672	1,025
Spain	47,449	1,015
Portugal	9,000	880
Norway	4,000	744
Poland	24,736	653
Turkey	39,000	467
Lithuania	1,220	442
Slovakia	2,287	419
Estonia	380	287

Production	Amount (EUR million)	Per 1million population
Switzerland	54,305	6,321
Ireland	19,305	3,954
Denmark	14,391	2,493
Belgium	17,547	1,521
Sweeden	9,840	980
Slovenia	1,659	798
Italy	34,000	562
France	35,848	550
Hungary	3,859	398
Germany	33,158	397
Netherlands	6,180	361
U.K.	23,039	341
Finland	1,877	339
Spain	15,832	339
Austria	3,024	338
Iceland	89	263
Cyprus	253	211
Norway	1,072	199
Portugal	1,737	170
Croatia	664	161
Latvia	255	134
Greece	1,376	131
Czech Rep.	858	80
Poland	2,550	67
Slovakia	356	65
Turkey	3482	42
Russia	5,881	40
Romania	655	34
Bulgaria	121	17

Created by the author based on EFPIA (European Federation of Pharmaceutical Industries and Associations) 2019 data

Even in these two fields, Belgium maintains its position next to Germany, France, the United Kingdom, and Switzerland on an actual value basis. Given the fact that it is among the top three in various indicators per capita, it can be seen that not only biotech but also the pharmaceutical industry as a whole has established a stable position in Europe.

(3) Overall balance

Currently, Belgium is in an environment where relatively large amounts of development costs can be invested in the life science field, both in academia and industry. In the midst of this trend, new biotech companies have been born, and their market capitalization has remained stable in the top three in Europe for the past ten years.

Not all of this process has been completed within Belgium, but it is characteristic that, despite being positioned as a hub in Europe, the country is developing by appropriately cultivating human resources. An ecosystem different from that of the United States, which has a different scale, has been formed.

Based on the situation, I would like to focus on the aspect of biotechnology and use it as a case study in ecosystem formation.

4.2 Formation of an ecosystem in biotechnology

4.2.1 Movements up to the 1990s

I would like to start with the prehistory of biotechnology's establishment in Belgium after the global rise of biotechnology. Initially, it was mainly deployed in Flanders.

(1) Pioneering biotechnology

In the 1980s, in addition to the companies shown in 3.1.3 having a strong presence in the world of small molecule drugs and vaccines, the biotechnology industry was born in Belgium. Its origins date back to 1982 with the establishment of Planet Genetic Systems (PGS), a spin-off of the Institute of Plant Genetics at the University of Ghent. Dr. Marc Van Montague and Dr. Jozef Schell founded the company after developing genetic engineering methods for plants. The company was not involved in pharmaceuticals, but focused on the production of genetically engineered plants, known today as genetically modified organisms (later sold to AgrEvo GMBH in 1996).

In 1982 Prof. Van Montagu came to the just-incorporated GIMV (public Flanders investment company) with the first evidence of stabilized genetic change in plants. After discussion about the protection of the IP and identifying a suitable CEO bringing private investment along, GIMV decided to invest in PGS. (The first investment of a very long series of pioneering LS/VC-investments by GIMV)

The first biotechnology company in life sciences was InnoGenetics, founded in 1986. This company is also a spin-off company, in this case of the Institute of Molecular Biology at the University of Ghent, and its founder is the eminent scientist Dr. Walter Fiers (1931-2019). Dr. Fiers was also one of the co-founders of Biogen in 1978, at that time in the suburbs of Geneva. InnoGenetics is a company with two business segments: diagnostic drugs (CNS and infectious diseases) and therapeutic drugs (vaccine against type C infectious virus [HCV]), and GIMV is also a shareholder.

The company was the first Belgian biotechnology company to list on EASDAQ, in November 1996, and its market capitalization exceeded USD 1 billion in May 1998, just two years after the listing. Later, in September 2008, it was acquired by the Belgian chemical company Solvay and delisted. In 2010 it was sold to the Japanese company Fujirebio, and three years later the company name was changed to Fujirebio Europe NV.

Although it is not a research institute directly related to life science, I would like to cite the establishment of IMEC (Interuniversity Micro Electronics Center) as one of the important events of that era. In the history of research institutes in Flanders, IMEC (1984), VITO (1991), VIB (1996), and VIB Make (2003) have created organizations that cross the boundaries of universities, and IMEC was the first to do so. It is an institution in which six Flemish universities collaborate, jointly promoting the research functions of each university, and is one of the world's leading microelectronics research institutes.

(2) Walloon district at that time

In Wallonia at that time, EuroGentec was established (in Liège in 1986). The company was founded by Joseph Martial and Andre Renard from the molecular biology laboratory at the University of Liège. EuroGentec's main business is the sale of research tools, and they have units for producing oligonucleotides for genome sequencing and biologics (recombinant antigens for producing recombinant vaccines) using bacteria. The company was acquired by Kaneka, a Japanese company, in 2010.

In 1994, EuroScreen, the creation of three professors at the Free University of Brussels Medical School, was spun off, after which the company was renamed Ogeda and developed drugs to treat menopause-related vasomotor symptoms. The company was eventually acquired by Astellas Pharma.

These were independent movements by the companies, and the related development of Wallonia as a whole had just begun.

4.2.2 Trends in the 1990s

(1) Trends in private venture capital

Several venture companies were born in this way, but in the 1980s the only one in terms of financing for ventures was GIMV. But GIMV targeted biotech companies based in Flanders, not Wallonia. Fundraising was not easy at first, and for InnoGenetics, the first bio-venture company, there was no exception. The flow was to collect funds from a small number of entrepreneurs, followed by procurement from GIMV.

In 1995, the investment company PMV (100% owned by the Flemish government) was established as a spin-out from GIMV and became independent in 1997. In addition to PMV, around 1996, Life Science Partners (Netherlands), Forbion (Netherlands), Gilde Healthcare (Netherlands), Sofinnova (France), Apax Partners (France), Abingworth Management Ltd (UK) and others appeared as first-generation life sciences venture capital. Some commercial banks have also set up their own biotechnology private equity funds.

Then, in addition to EASDAQ, Germany's Neuermarkt and London Stock Exchange's Alternext were established as markets for start-ups, expanding the possibilities of IPOs for biotechnology companies. However, after InnoGenetics went public, there were no IPOs of biotechnology companies born in Belgium until 2006.

(2) Existence of a research institute called VIB

In terms of the success of bio-ventures, there were no major movements at that time, but in terms of science, a new movement was born in Belgium in the 1990s. It was the establishment of VIB (Dutch: Het Vlaams Instituut voor Biotechnologie / English: Flanders Institute for Biotechnology) from the Flanders government. VIB is an important institute; thus, I would like to introduce the concept and set-up in detail.

This content is based on an interview held at their Ghent office in August 2022 with Dr. Jo Bury who today is Director emeritus of the VIB

Twenty-six years ago, he was instrumental in setting-up the VIB and in writing its charter, and, along with a co-managing director, has led its development for all these years.

I. Overview

VIB is an organization founded in 1996 by the Flemish government. It was established with the goal of not only creating a university-like organization that produces excellent research, but also creating an organization that has a global impact and can lead science.

The Flemish government visited areas such as Boston, San Francisco, and Stanford, and was surprised by the industrial development based on research and development of universities, and this project was launched.

The basic concept is to integrate all biotechnology-related research activities at all five Flemish universities and operate the resulting organization (called the VIB) like a single research organization. The project itself is operated under a management agreement with the Flemish government, and evaluations are carried out every five years (currently in the sixth cycle).

The annual government grant as of 1996 was EUR 22 million, which remained unchanged for the first five years, but then increased as the organization's evaluation improved. At present, it is EUR 80 million per year.

Its governance is non-profit, and its identity is that of a research institute. As a result of expanding from time to time, VIB has strong partnerships with five universities and is structured as nine research centers, all based on the campus of one of the partner universities.

The important point is that it is established as a double affiliation (qualified by both the relevant university and VIB). All IP that is generated by VIB-projects is jointly owned.

VIB currently has more than 1,700 co-workers of 78 nationalities.

VIB's focus area is "discovering molecular differences in cells", and it is broken down into separate areas: cancer, immune system, nerve system, and plant biology. The approach and targets are constantly being renewed, but the concept itself has not changed since its establishment.

II. VIB as a research center

As a research institute, VIB aims to create a "big difference", and has continued to improve the environment to create top-level science. Only top 5% level research is advanced for each adopted research project, and others are not allowed to continue within VIB.

Such a system puts a strong selection pressure on researchers. If each field is likened to a kind of 'league', it is important to be the champion, and the papers and IP that result from that are the cornerstones of achievements.

In order to promote these movements, VIB makes various investments on its own and adds new initiatives each year to improve the research environment of VIB. In terms of investment, core facilities are important, and they have continued to invest in them. Currently, VIB has 10 core facilities, serving the scientific community of VIB and beyond with state-of-the-art and emerging technologies, supporting expertise and advanced equipment.

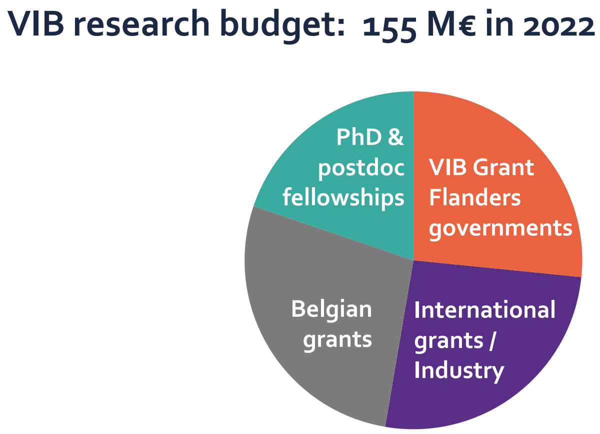
In terms of human resources, the group leader (hereafter, GL) will hire 10-15 staff members to run the lab; so, the GL needs to improve the environment. Each team consists of young PhD-students, postdocs in their 30s, lab technicians and GLs. The average age is around 34 years old. And they go to a new step every five years. In that sense, it is also an investment in the career development of the constituent members.

The annual research budget of VIB as a whole is now about EUR 150 million a year, of which about a quarter is granted by the Flemish government, and the rest is domestic grants, PhD and postdoctoral fellowships, and international grants. Direct funding from the Flemish government is only one-fourth, and the leverage is effective.

This balance results in half being funded by the universities and half by the VIB.

This double affiliation structure constitutes a mirror, providing for VIB and each university to share the returns with each other.

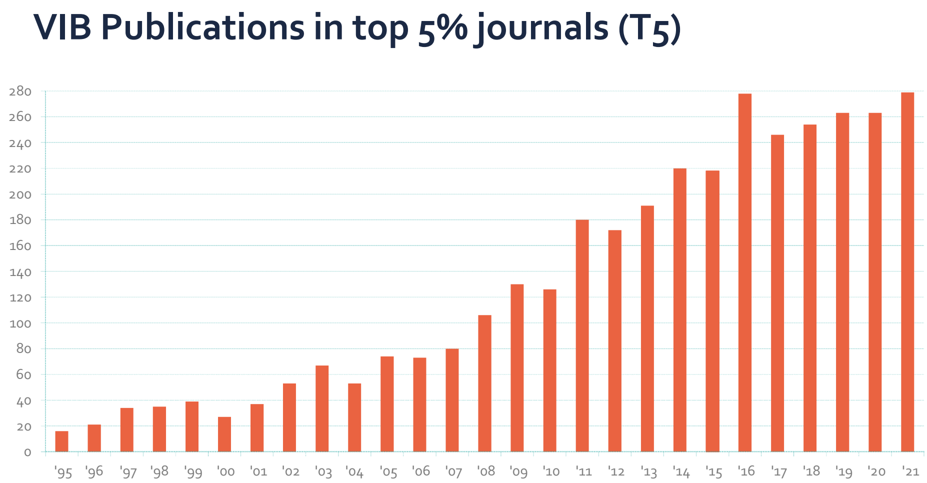
Fig23 Sources of VIB's research budget



Source: VIB materials

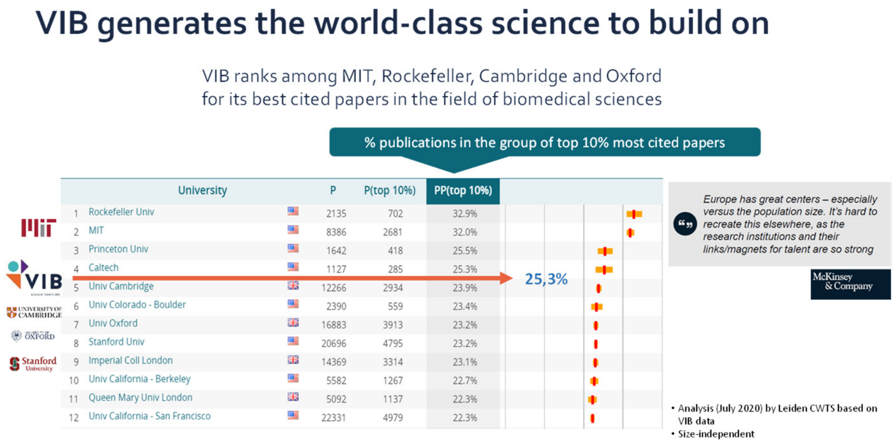
An important point for VIB is "impact", and while the more than 800 peer-reviewed articles are important, the more important thing is the existence of more than 270 breakthrough articles a year. The number of papers published by journals in the 5% Tier is increasing year by year, and the percentage of most cited papers worldwide is ranked next to MIT and Rockefeller, and exceeds those of Oxford and Cambridge universities.

Fig24 Changes in the number of VIB papers published in top 5% journals)



Source: VIB materials

Fig25　Comparison of highly cited papers by VIB



Source: VIB materials

In parallel with these scientific results, many VIB group leaders (>1/3) have a running ERC (European Research Council) grant.

III. Translational research

The next important part is translation. Here is an excerpt from an interview with Dr. Bury[14].

--How did you develop the research department into the industrial world?

Dr. Jo Bury (hereinafter referred to as J): It is necessary to convert knowledge into value, but I first came up with a basic framework for translation while observing the efforts of MIT and various research institutes. Prepare members who observe science on a daily basis, and grasp what is happening.

On top of that, one important theme is collaboration with existing companies such as out-licensing, and the other is fostering start-ups. To date, 34 start-ups have been born as a result, and these start-ups have been able to attract about EUR 3.4 billion equity investment.

--Where do you find it difficult?

J: To begin with, most scientists are basically not interested in filing for IPs or collaborating with industry.

On the other hand, it is also important that VIB itself is non-profit and has a goal to bring value "for patients and consumers". We approached the scientists in various ways. We tried to see how their research could be applied to the business world and provided them with a team of tech transfer professionals that turn their science into IP and translational actions.

In addition to direct employment of scientists, a large number of jobs are being created from newly created companies. This is an important part of local government efforts.

There are cases where start-ups receive funds from overseas venture capital, and this is also proof

[14] VIB's former managing director/current director-emeritus. Dr.Bury has a master's degree in Pharmacy and a PhD in Pharmaceutical Sciences (University of Ghent). He obtained an MBA degree at the Vlerick School for Management in Ghent. After performing scientific research in the field of atherosclerosis for several years, he has made a career in science policy.

that "funding basic research creates ripple effects in terms of economic expansion".

Of course, the evolution of VIB itself is also important. For example, most recently, it was involved in establishing an international school for children of scientists from all over the world. This enables VIB researchers to easily find a local international school for the education of their children.

IV. Scientist career path

-I think it's also a difficult issue to decide when to receive evaluations for these efforts. Life sciences require time for research and development, but do you think it would be better if, for example, they could be evaluated every six years instead of every five years?

J: Yes, of course. We have evaluated the pros and cons of a 5-year cycle versus as 6-year cycle. The major disadvantage of a 5-year cycle is that it is short. In fact, in the fourth year, VIB starts preparing for the evaluation of all VIB research groups and spends a considerable amount of time on this. In the fifth year, the institute (VIB) is evaluated by the government, involving peer review, consultants and bibliometric analysis. That means that in a 5-year cycle, two years are spent on evaluation and only three years are available to develop the institute to the next level. If we extend it to six years, the period of developing the institute would be four years, which provides a better balance between development and review. In fact, we proposed a 6-year cycle to the government, and it was almost accepted. However, in the end the government administration responded, "In that case, let's do an interim evaluation after three years". I believe that if the assessment had been made at an intermediate time point, the outcome would have been much worse. So, we decided to stick to the 5-year cycle.

Scientists are generally promoted in a 5-to-7-year cycle, especially at the top level. We've talked a lot about postdocs. What kind of cycle is good for postdocs? We expect that some of our most promising postdocs choose an academic career. The next step for them is to become an independent group leader and to apply for funding. A major – high standard – funding resource in Europe is the ERC. However, to apply for an ERC starting grant, scientists are only eligible in the time window 2-7 years after attaining their PhD. As a postdoc in life sciences normally takes 5-7 years, only limited options are available to these scientists to apply for such a position.

Instead, if we create an environment where they can do it well for 5-6 years, the scientist will be able to continuously ride the cycle and produce more results.

V. Back to 1995

J: Now I want to go back to 1995. Lucky for us is that we "stand on the shoulders of giants". In Flanders, Belgium, we had a number of extraordinary scientists with world-class reputations in life sciences. They were the starting point of VIB, and it was through them that we were able to attract international researchers.

In 1995, there were only five biotech companies in Flanders (Plant Genetic Systems, InnoGenetics, Eurogenetics, Tibotec, and Corvas.). On the other hand, during the Pre-VIB era, an initiative called Flemish Action Program Biotech (1990-1996) was running, and its vision was to realize a "knowledge economy".

Among them, VIB advocated molecular biology and genetics. But the problem was ‘How?’. The original running Flemish Action Program Biotech, like many other projects, invested in 'projects'. But it didn't do much, and it didn't have the impact of reaching critical mass. So, we thought we needed to pick ‘people’ and invest in them, not projects.

It took time to obtain the cooperation of each university. We kept trying until we got the understanding that the efforts were mutually complementary. For example, on a trivial note, it took a considerable amount of time to ask for the VIB logo to be included in their papers. Of course, we set the rules, but the scientists (still embedded in the universities) did not understand it well; so, we contacted them each time and asked them to make a presentation with the VIB affiliation. Of course, we don't have that trouble now.

In any case, nine university departments were selected for the opening in 1996, 650 scientists were nominated, and multiple sites were started.

--It is said that they are mutually complementary, but where was the incentive for the university to commit to this story?

J: That's right, the university side felt that, "Scientists don't want to create such a center. I understand the part that actually creates critical mass, but I doubt if this will actually work".

Naturally, there were opinions of whether it would be better to directly fund the university. However, seven years after its establishment, during a meeting to review the program in 2002, the then-serving rector of the University of Leuven said "Had these funds been put into the university for the same amount of time, they wouldn't have achieved as much. Stopping this project now is not good”. The story called a response in various places and the evaluation went up.

Regarding the discussion of critical mass, it is difficult for each university to gather good human resources with only one PI. As the project progressed, each university realized that something like VIB can be created by gathering a certain number of excellent PIs: creating a critical mass of excellence.

Peer reviews were also important. In the first peer review five years later, it was still halfway to the point for evaluating the science, but scientists from all over the world joined the reviewers and evaluated the contents on-site over several days. As a result, we were evaluated to the effect of, "This is very good content; it would be a waste to stop it halfway". It was significant that the reviewers were international rather than domestic.

Anyway, ‘time and trust’ are important. We gained credibility by spawning two new companies in the first five years (devGen and CropDesign), both in agro-biotech. Both also attracted early VC-funding, another necessary component of the ecosystem. After that, spin-out companies were formed relatively smoothly (Ablynx, etc.). Then, this trend gradually became a trigger to attract the support of global companies.

VI. Subsequent VIBs

- Did things go smoothly after that?

J: VIB has indeed created an ecosystem (see Figure 26), and it has been strengthened especially since the beginning of the 2010s. The ecosystem has started to work, and various initiatives have taken the form of being able to do it here.

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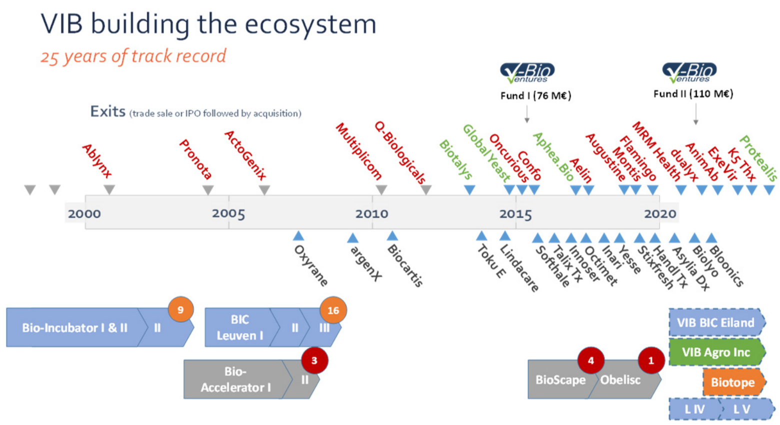
Fig26 Ecosystem built by VIB



Source: VIB materials

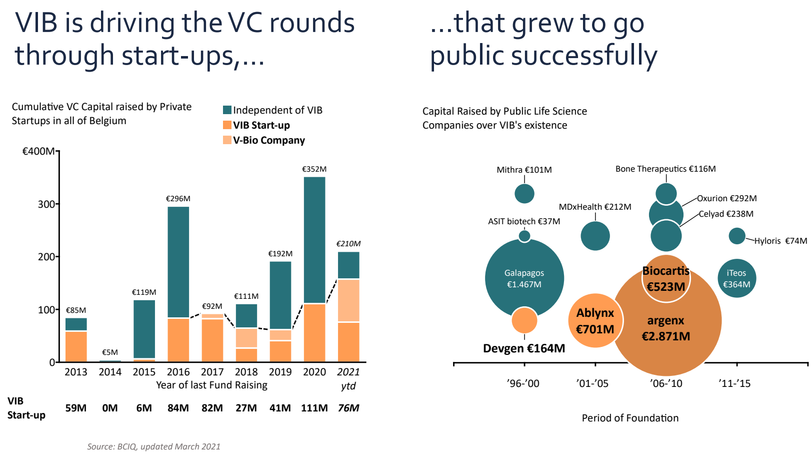
And not only for VIB: among the initiatives one called Bio-Incubator and Bio-Accelerator was created.

-Is there a big master plan for these efforts?

J: It's true that there was no big master plan, but the process has been completed in a gradual manner. I've seen other cases of people investing in projects and failing. After a few years, when the project stops, nothing remains, and it doesn't lead to the formation of an ecosystem.

We have invested in people and created venture companies. As a result, as shown in Figure 27, VIB-originated start-ups are the main investment destinations of venture capital, and occupy the current mainstream. This can be said to be a good impact of creating an ecosystem.

Fig27 Venture investment environment created by VIB



Source: VIB materials

-Is it important to know 'what kind of discipline to follow'?

J: That's right, and it's quite possible that the amount of science being translated is limited despite the huge amount of research expenditure. There are parts where the university side has to change its stance. The system inside is necessary.

It is difficult for each university's TTO to cover everything. I think it is necessary to create the best organization from the viewpoint of how far we can actually cover.

[Supplement 1] Flanders.bio

Flanders.bio was founded in February 2004 with VIB being one of the founding partners.

The idea to create a biotechnology cluster organization had matured a few years before its creation, to a large extend from discussions held within the VIB board of directors, from a growing awareness about the need to provide specific support to start-ups and spin-off companies in their earliest stage of development, and from the realization that such kind of support was difficult or impossible to organize from within the existing organizations in the ecosystem.

Basically they share roles in seminars, conferences, technology transfers, education, etc. outside of VIB's core business. The number of member companies was initially extremely limited, but now it is 340 or more. Biotech and pharmaceutical companies account for only about one-third of the number, and many business operators in areas such as professional services and consulting and other support have joined. In terms of area, 70% are from Flanders, but there are also those from Brussels and Walloon, as well as companies from outside Belgium.

They are also focusing on SMEs because the number of SMEs has increased along with the growth of the biotech industry. They regard SMEs as key catalysts for the growth of the ecosystem and support them.

In Flanders, a system has been put in place to create a system centered on science in this way and to continue to disseminate it to its base.

[Supplement 2] QBIC

As a further supplement, I would like to take up another organization that has been influenced by VIB's movement. QBIC is a private fund in Flanders. It is explained below by Danny Gonnissen, a partner in QBIC I.

Danny (hereafter, D): There is no horizontal connection between Technology Transfer Offices (TTOs) of universities in Flanders for funding university spin-offs in the Flemish region. Learning from the interuniversity approach introduced by VIB in life sciences, TTOs from the universities of Ghent, Brussels and Antwerp (the University of Leuven decided to continue working with its own seed fund) joined forces and created an interuniversity fund: QBIC. QBIC is a seed and early-stage venture capital fund that provides entrepreneurial support and funding to spin-offs of these universities. Its activities are not limited to life sciences.

The people managing QBIC are independent from the universities but know very well how the TTOs work and can count on external expertise that is present in the universities to analyze the spin-off projects.

Before QBIC, each university had its own, small seed fund. This allowed it to encourage entrepreneurship, but it was difficult to sufficiently fund a project after it was incorporated as a company. QBIC solved this.

-Why does this kind of culture exist in Flanders?

D: This is largely due to the fact that research institutes such as VIB in life sciences, but also IMEC in micro-electronics, have collaboration programs across each university and have achieved very good results in translating scientific knowledge into business.

QBIC was established in 2012 with the three aforementioned universities. Later other universities, such as the University of Liège in Wallonia, and research institutes such as VITO (multidisciplinary research institute in Flanders) also joined this framework.

As you can see from the portfolio in which QBIC has invested, the origin of the companies is nicely spread over the different universities and knowledge centers, showing a good variety of project sources. Favorable project exits are steadily appearing.

4.2.3 Flow of the first decade of the 2000s

In Belgium in the early 2000s, with core research institutes such as VIB, biotech companies were growing conspicuously and, at the same time, their expansion into Wallonia was also conspicuous.

(1) IPO market trends since 2000

The second wave of IPOs of biotechnology companies in Belgium came in the latter half of the first decade of the 2000s.

2006 ThromboGenic, 2007 Ablynx, Tigenix

2013 Cardio3 Biosciences

2014 Galapagos Genomics, ArGen-X

Among them, Galapagos, Celyad (formerly Cardio3 Biosciences), and ArGen-X have also succeeded in dual listing on Euronext/NASDAQ. In particular, ArGen-X raised USD 114.7 million on NASDAQ in 2017. The company, which was born from Ghent University's technology, was founded in the Netherlands, but later moved to Belgium.

(2) New developments in public finance

In 2006, SFPIM (Societe Federale de Participations et d'Investissement), an investment company owned by the Belgian government, was established.

SFPIM has played a role as a government investment institution, including investments in funds such as Vesalius and participation in privatized public works such as Brussels Airport and Brussels Airlines.

As of 2020, the investment balance was EUR 1,956 million, approximately JPY 270 billion, and the investment ratio of portfolio companies was 10-25%.

SFPIM itself has a matching fund-like function, and has the aspect of matching investment with external capital, and has achieved a traditional priming effect.

Also, the life sciences sector also accounts for 8.5% of their current portfolio.

(3) Deployment in Wallonia

Wallonia currently has support organizations for life sciences called WELBIO and Biowin, which were established in 2009 and 2006, respectively. WELBIO is a support organization for fundamental research, and Biowin is a support organization when spin-out companies are established from universities.

I interviewed Vinciane Gaussin (Managing Director) for WEL Research Institute (the name of the institute has recently changed from WELBIO to that name) and Marc Dechamps (International Affairs) for BioWin.

[WELBIO (WEL Research Institute)]

WELBIO has the role of cross-cutting basic research between universities located in Wallonia and was created within the framework of the Marshall Plan II. It was established to support basic research and translate scientific discoveries into biomedical applications.

As for the program for researchers, WELBIO calls for applications every two years, has them submit applications for a four-year program (research grant), and has them screened by an international scientific evaluation commission (11-12 people in total).

During the research period, they have regular meetings with WELBIO members to develop an intellectual property search and valuation plan. At that time, Biowin, SPW, and people from the industrial world also participate in the discussion, and WELBIO provides support to create a spin-off.

As a result, the project has progressed for six terms so far, and 630 papers have been produced in 88 projects. Scientists have also been able to get 12 grants from the ERC.

In terms of translation, WELBIO projects have implemented 33 intellectual property applications. Also, Chromacure, Generon, NeuVasq, and Santero have spawned four spin-offs, and Ncardia, OncoDNA, and Eurogentec (Kaneka) have collaborated with industry.

Governance members are well-balanced (academia, industry, government, and the outside world), and WELBIO itself has fewer occasions of exclusive control, and is built into the existing system.

Research programs are submitted by Principal Investigators in universities of the Wallonia-Brussels Federation. Funded Principal Investigators are automatically affiliated with WELBIO (WEL Research Institute). The composition of the evaluation committee in the international lineup, the period, the evaluation method, etc. are influenced by VIB.

In terms of relationships with industry, the pool of corporate human resources in Walloon is large. But in addition to the number of human resources, the fact that representatives of the main Walloon life science industries are part of the Governing Board is a great asset.

[Biowin]

As I wrote in the section above, Biowin was born as an organization that connects the bio-industry within the framework of the Walloon government's Marshall Plan II.

The two priorities for 2020-2023 have been defined as (1) accelerating the production of vaccines and biomanufacturing, and (2) making Wallonia a champion in the field of healthcare innovation.

Specifically, Biowin has provided support in terms of promotion of collaborative research projects related to innovation, scale-up of companies, international expansion support, human resource development, and communication including conferences.

With strong leadership by local governments and the provision of funds by public institutions such as SRIW(an investment fund in Wallonia / current ‘Wallonie Entreprendre Life Science’), Wallonia is currently seeing a rapid increase in funding for companies. Wallonia, which used to have a strong color as a manufacturing division centered on GSK, is now turning to innovation.

Mr. Alain Parthoens of Newton Biocapital, who was also present, said, "Previously, we were in a situation where we would rush around to create various elements for a start-up, but now we can consult with Biowin first, which is a big difference".

[Ventures in Wallonia]

And at this time, in parallel with the above movement, a movement of bio-ventures in Wallonia also have become active. Companies such as Promethera BioSciences, Iteos Therapeutics, Bone Therapeutics, Novadip, MasTherCells, Univercells, Epics Therapeutics, Neuvasq Technologies, etc. have been born.

In particular, the Walloon local government has been promoting the development of cell therapies (adult stem cells, CAR-T cells, iPSCs) as the core, characterizing the current development of Walloon's life sciences.

4.2.4 Situation in the 2010s

With the growth of biotech companies and their expansion into Wallonia conspicuous, since the 2010s, the growth of these emerging companies and the core companies have once again crossed paths.

I asked Marc Dechamps, who was mentioned earlier, and Frēdēric Druck, Director of Essenscia, an industry association in the pharmaceutical industry, about the current Belgium situation.

(1) Current Belgian industry

- What do you think of the current strengths of the Belgian life sciences industry?

Mr. Dechamps (De): Belgium is currently established with the following stakeholder balance.

Fig28 Stakeholders in the Belgian ecosystem

Source: Biowin & Flanders.bio material

I think the strength in innovation has been discussed separately, but apart from that, the large number of clinical trials is one of the characteristics. Belgium accounts for 2.6% of the EU population, but the number of clinical trials is 16%.

At the same time, it is also characteristic of 'roles of a production base and a supplier'. In the current Covid19 situation, one billion doses of vaccines are being deployed worldwide, mainly by Pfizer. EU Chairman von der Leyen also mentioned the contribution of Belgium to production technology in dealing with this Covid19 era.

At the same time, thanks to the geographical advantage of being in the center of Europe, capital investment by major pharmaceutical manufacturers is progressing smoothly. In relation to the pandemic, the role of the EU-led Health Emergency Preparedness and Response Authority (HERA) is also significant.

Amidst these movements, strong employment has been created, with more than 120,000 people, including over 40,000 in direct employment.

- What are the current challenges?

De: The biggest part is human resources. Aptaskil in Wallonia and ViTalent in Flanders are running human resource development programs, and in 2025 a center called the EU Biotech Campus will be established in Wallonia.

The purpose of these human resource development movements is not only for start-ups, but also to develop people who work in this industry, including in production, and to support conversion from other industries.

Such initiatives are already being undertaken in Ireland, Paris, and Barcelona, but are new to

Belgium.

Note: Mr. Dechamps is heavily involved in human resource development for innovation at Solvay Brussels School (SBS), which will be discussed later.

(2) EU Biotech Campus Initiatives and Collaboration with Companies

The EU Biotech Campus will open in 2025, and I asked Mr. Druck, who is also involved in the project, about the current situation.

--It seems that human resource development in Belgium is now becoming buzzword-like. What is the background?

Mr. Druck (Dr): Of course, the aspect of developing entrepreneurs, which SBS is currently doing, is important, but the aspect of vocational training related to production is also strong. It is an element of dealing with the recruitment and training of large amounts of jobseekers, the upskilling of industry workforce as well as the reskilling of employees from other industries. Aptaskil started in 2010, but has recently changed its framework. ViTalent officially kicked-off in late 2022. Since the EU Biotech Campus is added to this, you can think that these efforts are being made at the same time. The EU Biotech Campus itself is not a master program, but on the other hand, one of the features is that soft skills needed in pharmaceutical companies are addressed in the course. The main purpose of the EU Biotech Campus is nonetheless to address the need for training in advanced biomanufacturing processes and in digitalization/data management applied to biotech innovation and manufacturing processes.

--I think that collaboration between large companies and start-ups is always an issue worldwide, but what about Belgium?

Dr: That's right, but the system has changed recently. Fifteen years ago, collaboration with small companies became a must in order to obtain subsidies and other funds from local governments. As you can see in these stories, agility is a strength these days. Even during Covid19, the production lines were flexibly reassigned, and cooperation was implemented.

(3) Dialogue with venture company: Epics Therapeutics

So far, I have discussed the recent expansion of the industry. Next, I also interviewed a key manager of a venture company that embodies the innovation that is the core of the Belgian ecosystem: Mr. Graeme Fraser, CSO of Epics Therapeutics, who grew up in the environment. The company is an epigenetics company, and its key members are the former members of a company called Ogeda that was acquired by Astellas in 2017 for EUR 800 million with a greater than 20x return to Ogeda shareholders.

- What do you think are the characteristics of the Belgian ecosystem?

Mr. Fraser (F): Belgian universities are certainly a foundation for producing good start-ups. The companies EuroScreen, Ogeda and Epics, for example, were born out of ULB, and KUL is also very strong. Ghent University is also extremely strong in the field of antibodies. Each has its own specialty and is learning from its successes. I'm from Canada and came to Belgium; so, I think it's possible to make a comparison with other areas, and Belgian universities are modest about enforcing rights of the university to limit the business ventures of its researchers to some extent, which is positive for allowing companies to start. Then the universities actively try to create spin-outs, add entrepreneurs, and create various team compositions. In that respect, Belgian universities deal with those aspects very well.

As for whether talents gather in Belgium, it is easy to attract young talents because of its strength in science. Wallonia also has a strong scientific culture, with a large number of knowledgeable scientists. And because Wallonia is French-speaking, there is also a tendency to attract qualified people to move here from France. Also, tax rates on surplus income are entrepreneur-friendly, which helps in the recruitment and retention of top managers.

In comparison with North America, 'valuation' for start-ups is also a good balance between entrepreneurship and science. Investors also tend to take moderate risks while waiting for opportunities, including long-term holdings. However, in terms of finance, the greater amounts of finance required to move to the next phase in clinical trials is still weak. There are not too many big, deep-pocketed financial investors in Belgian; so, finding finance at this stage of company maturation is difficult to do in Belgium. So, this is probably where the Belgian ecosystem can still change.

- Could you explain about the transition process from Ogeda to Epics (Epics was already established as a spin-out from ULB, and the members joined Epics after Ogeda's deal)?

F: While Ogeda was being sold, the acquirer (Astellas) was looking for compounds and did not need human resources. The team at the old Ogeda are all very close and have all moved on to the new company. In Belgium, the members have a relatively close relationship, and they know each other well. That transfer was a natural process.

--When Epics succeeds, wouldn't the influence of these members on the ecosystem also be great in terms of producing human resources?

F: Ogeda's team members were originally all very young. The young members have come this far while learning how to realize drug discovery; so, the experience is really great. Of course, I do not know how this team will develop in the future, but it is certain that it is a very strong asset.

I think that "learning at university" and "pursuing drug discovery on a business basis" are really different. The process of teaching students how to do something different from what they have learned at university will become important in the future.

SBS is creating a new master school this time, and I think this is a very good initiative. In order to think about how to develop a business company on a business basis, it is necessary to consider various elements in the development process. Many people in the field participate as faculty members in this new program. This is a feature not found in other programs, and these kinds of things are 'teachable', I think.

4.2.5 Coming Up Next: Solvay Brussels School

The need for national concerns in developing human resources is discussed above. Lastly, I spoke with Academic Directors Marc Dechamps and Philip Vergauwen about the human resource development program for the life sciences that started in October 2022.

This course is a master course opened by Solvay Brussels School belonging to ULB, and is called Advanced Master in Biotech & Medtech ventures. The problem lies in making up for the shortage of entrepreneurs in the biotech and medtech industries. Another feature is that it is a course that incorporates plenty of practical experience.

The course itself consists of the five modules listed below and an intensive program of 1,800 hours in one year, with over 20 coordinators for each course. In addition, about 40 guest lecturers are scheduled to be on stage in connection with these lectures.

[5 modules]
1. Basic Knowledge of the Start
2. Starting Up the Development – Company Seed Stage Funding
3. Initiating the Clinical Development – Series A Funding Preparation
4. Consolidating the Company and the Governance – Preparing Series B Funding
5. Finalizing the Clinical Development – Preparing for Market Access

For biotech, medtech and digital health, students will learn a continuum of processes for ideation and product development, clinical trials and approval processes, finance, launch and market development. The details and concepts are as follows, according to the interviews of the directors.

- ✓ This course is divided into five modules, and the first module is designed to provide a bird's-eye view of the whole. In the end, it will return to the content touched on in module 1 many times.
- ✓ We anticipate that there are about 25 students per grade, and we would like to have a diverse range of backgrounds and nationalities. Since the selection of students also considers learning as a "team", it is always in my mind to distribute roles well.
- ✓ The current membership consists mainly of young people with corporate experience and a scientific background like a PhD in sciences—for example, bioengineer, pharmacist.
- ✓ We are thinking having the research center adopt a style of analyzing industry and making policy recommendations instead of writing a thesis at university. Large-scale research cannot be conducted without proper team composition, and even in the real world, working in a team does not necessarily go well. It is necessary to find each role in it.
- ✓ This is an attempt by both biotech and medtech, and this is the first time that such an advanced master course has been created.
- ✓ I think there are three major challenges for this program: (1) gathering the best talent, (2) organizing appropriate programs and a lineup of industry professionals, (3) fostering trust and promoting networking. We are assembling a course thinking about how to address these challenges concretely.
- ✓ In that sense, rather than “teaching”, we think that the proposition is how to stimulate the entrepreneurial candidates who are already there.

4.3 As a summary of the Belgium part

Notable scholars in bio, initiatives such as VIB based on their works (and IMEC's initiatives before that), efforts of individual venture companies, regional horizontal development of measures, and construction of ecosystems including large companies: the SBS Master Course is an extension of all that.

Considering the intimacy and flexibility that flow through the core of this course, I felt it was a very emblematic program.

This case study does not touch on finance, but in the process of forming the ecosystem in Belgium, the existence of various public funds and private venture capital, starting with GIMV, has supported this movement.

These interviews were held in Brussels, Ghent, Wavre and other cities in late August 2022. With the help of members of Newton Biocapital (NBC), which is one of such venture capital firms and is investing in both Europe and Japan, I was able to do the interviews. I would like to express my gratitude to those members at the end of the book.

In addition to the interviewees listed here, I heard many stories during the above interviews, but not all of them are listed in this chapter. However, the essence is reflected in each item.

Lastly, the history of individual Belgian venture companies was based on information provided by NBC's Louis De Thanhoffer. Without that information, this chapter would not have been possible. I want to thank him deeply.

Chapter 5 Comparison of Belgium and Japan as Ecosystems — As a methodology for strengthening human capital

- As depicted in Chapter 4, individual players in Belgium's ecosystem grew in line with the growth of major global pharmaceutical companies, achieving their own development based on investment in science and human resources in a form that can be connected to this environment.
- In Japan, major pharmaceutical companies are showing some growth in the midst of globalization, but the growth and maturity of finance and academia are not sufficient.
- However, by (1) improving funding methods for academia and (2) flexibly implementing human resource development methods for VCs and entrepreneurs, the shortage of seeds will be resolved. Then, if it is possible to encourage the early commitment of the companies, there is a possibility of realizing a mutually complementary ecosystem.

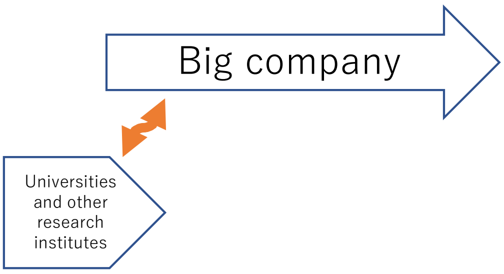
In this chapter, while referring to the ecosystem theory mentioned in Chapter 2, I compare the development processes of the ecosystems in Belgium and Japan and find out the implications.

5.1 Formation of Belgium's bio-related ecosystem

5.1.1 Changes in ecosystem formation

As with any country's life sciences ecosystem, from today's point of view, the 1990s was a period of foundation building. In Belgium, an organization like VIB was created based on successful cases such as IMEC, and R&D was cross-linked. At the same time, companies were investing in R&D and improving employment.

Fig29 Image of the 1980s - mid 1990s in the Belgium ecosystem



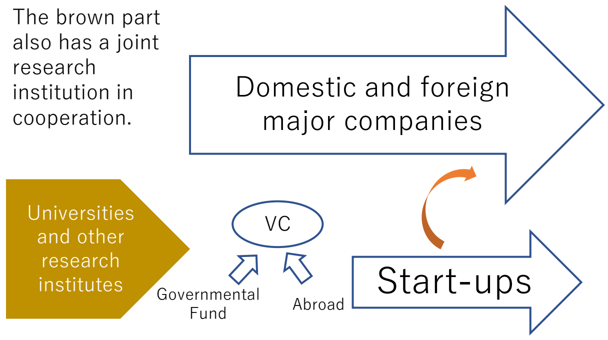
Figures 29 – 32 were created by the author.

Since the beginning of the 2000s, support for science has steadily been strengthened, and this movement itself has likewise been strengthened, including horizontal expansion to Wallonia.

What was important during this period was that science-based start-ups were born and their value blossomed.

In the process, along with the government's support, venture capital was active, but it would be appropriate to think that various European funds were also active in Belgium. In addition to the venture companies' focus on development, their exits targeted global companies rather than being confined within Belgium.

Figure 30 Image of the mid 1990s - 00s in Belgium's ecosystem



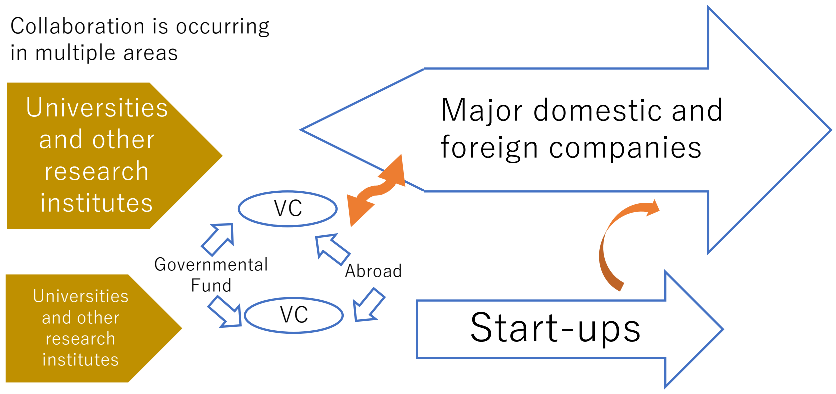
The major point since 2010 is that these movements have been integrated and diversified at the same time (this aspect can also be seen in the recent trend of VIB).

The way large companies interact with each other, including cooperation in terms of human resources, is changing in a complementary way.

Belgium's strength in science attracts human resources. And after a venture company exits to a global company, the human resources are circulated domestically. At the same time, as large companies collaborate with research institutes and venture companies, human resources from large companies will also circulate in the labor market, including venture companies. Therefore, the various organizations strengthen their human resource development programs, which effectively raises the level of the human resources that exist there.

In this way, a unique ecosystem has been formed in present-day Belgium.

Fig31 Image of the late 00s - 2010s in the Belgium ecosystem



5.1.2 What kind of complementarity was observed?

I would like to examine how the concepts of "mutual complementarity" and "integrated complementarity" have worked in relation to these changes.

✓ **Mutual Complementarity**

Scientists in Belgium, based on the perspectives and evaluations they naturally face, improve their quality and develop their research results in a translational form, creating a situation where it is easy to build relationships with venture capital.

- ✓ **Integrated complementarity**

In order to contribute to the creation of added value generated from the ecosystem, large companies and venture companies create a situation in which human resources are exchanged with each other, raising the overall industry level.

In addition, the transition itself takes the following process: "building with the minimum elements", "expanding step by step", and then "succeeding".

Below I list the actions that seem to have worked particularly well in realizing the system, picked up from Chapter 4.

- ✓ Local government support, including financial support. Support for collaboration between large and small companies.
- ✓ Collaboration between research institutes and universities, the idea of "people, not projects", and awareness of one’s positiion in one’s field.
- ✓ Providing programs that align with the career plans of scientists, and management, by incorporating international peer reviews.
- ✓ Awareness of issues in each layer related to human resource development and responses to them.
- ✓ Actual circulation of human resources, including among large companies (see Appendix 5-1)

Behind these activities lie trust and respect for scientists, epitomizing the notion of "standing on the shoulders of giants".

Appendix 5-1. Example of ‘Knowledge-transfer’

Returning to the case of VIB, I would like to present an image of how human resources spread within the industry. The following excerpts from an interview with Jo Bury by Jean Claude Deschamps (NBC) are reproduced with permission.

- It is important to know how the renewal of staff happens inside VIB. The academic world in general encourages the staff to move on to the general employment market. Of the 1,800 in total currently employed (including supporting staff) the breakdown is as follows.
  - PhD students total around 600. On average they will be in the VIB for 4 or 5 years and leave.
  - PostDocs are around 550. They have a 3 – 6 year span of presence in VIB, and then leave.
  - Once a person moves up to the level of staff scientist, VIB provides them with a long-term employment contract. Together with the lab technicians, they form the backbone of the institute.
- In total throughout the five universities, there are 90 VIB research-teams, each with a Team-leader. VIB might want to retain Team-leaders “for life”, though still under “rolling tenure”, requiring excellence demonstrated in the peer reviews, which come up every five years. Those failing these reviews move on—that is, they leave.

  In total the 5-year rhythm-of-evaluation results in about 17%~20% of the staff leaving each year. This rate of turnover requires VIB to hire on average at least one new member every day.
- Where do the leavers proceed to? What kind of employment is their next one, after leaving VIB?
  - Half of those who leave find a job in academia—a majority of them outside Belgium.

* Another 37% find their next employment in industry—over four out of every five in the local biotech industry in Flanders.
* Roughly 10% find their way into education, hospitals, government.

5.2 Current status of the ecosystem in Japan

As seen in Chapter 1, a life science ecosystem has already been established to some extent in Japan. However, depending on the scope, it has been ten years since the level of permeation has been relatively in line with global trends. As seen in Chapter 3, there are unbalanced elements when considering the transition of each player.

5.2.1 Overview of large companies

First, I would like to take a look at large Japanese companies that are globalizing. Chapter 3 shows changes in Japanese companies over the past 30 years.

For the past decade, Japanese companies have realized the main part of their business development through overseas sales growth. At the same time, the business development capabilities of Japanese companies have certainly improved over the past decade.

In fact, as can be seen from Table 16, some companies are proceeding with the acquisition of venture companies and the introduction of technology from venture companies.

Table16 Recent acquisitions of overseas companies by Japanese companies

	Acquisition company	Acquired company	Acquired company location
2016	Astellas	Ganymed Pharmaceuticals	Germany
	Dainihon-Sumitomo	Tolero Pharmaceuticals	U.S.
	Dainihon-Sumitomo	Cynapsus Therapeutics	Canada
2017	Tanabe-Mitsubishi	NeuroDerm	Israel
	Takeda	ARIAD Pharmaceuticals	U.S.
	Astellas	Ogeda	Belgium
	Otsuka	Neurovance	U.S.
2018	Takeda	Shire	Ireland
	Takeda	TiGenix	Belgium
	Otsuka	Visterra	U.S.
	Astellas	Mitobridge	U.S.
	Astellas	Protenza Therapeutics	U.S.
	Astellas	Quethera	U.K.
	Astellas	Universal Cells	U.S.
2019	Dainihon-Sumitomo	Roivant Sciences	U.K.
2020	Astellas	Nanna Therapeutics	U.K.
	Takeda	PvP Biologics Inc.	U.S.
2021	Takeda	Maverick Therapeutics	U.S.
	Takeda	GammaDelta Therapeutics	U.K.

Created by the author based on various materials

In tandem with this trend, the amount of R&D investment as a company has remained steady over the past 30 years (see Chapter 3), and it is important that core companies exist at a certain level. This is an important feature when considering ecosystem formation in Japan. However, since there is a limit to the growth of the domestic market, maintaining and strengthening each company’s stability is also an urgent issue.

5.2.2 Positioning of venture capital

As can be seen from Table 16, many of the acquisitions are overseas. The number of acquisitions in Japan is limited, and the scale of many of them is small.

In Japan, there are companies that have expanded their ventures, achieved IPOs, and continued to grow their value while maintaining their independence. In the US and Europe as well, being acquired by a company is not the only exit story. In that sense, Japan is not incongruent with other countries, but the reality is that there are extremely few exits to companies.

As seen in Andrew Lo's thesis in Chapter 2, considering the high risk, it is unavoidable in this field that some countries have underdeveloped venture capital markets due to differences in the degree of risk selection. On the other hand, the United States, as a result of its investment activities, has created a kind of 'baton relay' market and has adapted to development risks and development periods.

At the same time, large companies increased their financial strength through mergers and other means.

It can be said that it is rational not to force the venture capital market to expand in Japan where such a situation is not ready. But considering the situation where Japanese companies are able to carry out business development activities, a change is necessary.

In fact, Japanese venture capital firms with global experience and networks are also growing, a situation linked to the movement of certified venture capital by AMED. The direction of improvement can be seen.

5.2.3 Research and development environment in academia

Next, regarding science, research budgets are in a trend cycle of decreasing and then increasing again. But fixed management, rather than the degree of global growth, is the aspect that is conspicuous. In addition, not only are the numbers of researchers and the budgets important, but also the quality of the journals.

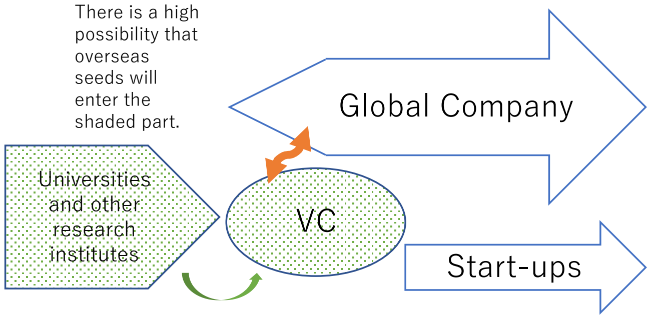
The increase in university-launched venture companies is conspicuous, but there is a possibility that the purpose of establishment has become a KPI separate from quality. It will be necessary to pay attention to whether high-quality venture companies will be born from such movements.

Financial factors are also a major factor behind the stagnation of research and development trends at universities in Japan. Another factor is the prevalence of the "selection and concentration" strategy, which, as has been pointed out, presents problems such as "research themes that are easy to adopt are selected on the premise that narrowing down are carried out, and basic research capabilities may decline".

5.2.4 Overview of Japan as an ecosystem

The situation in Japan is as shown in Figure 32. While continuing to retain a large portion of in-house development, it incorporates innovation from overseas. Therefore, the venture capital market and translation from academia are still weak, and the mutual connection between the two seems to be lacking.

Fig32 Current ecosystem image in Japan



However, this is not such a strange story. From the view of a company, it is not important where the "mutually complementary functions" are located. Corporate efforts exist in challenging themselves to apply new technology, no matter which country produces it.

On the other hand, it is difficult for academia to move geographically. Of course, it is normal for star scientists to move between countries, but it is impossible for the university itself to leave the area. Considering the budget levels of individual universities, it is easy to imagine how difficult it would have been to expand beyond the status quo. This is because the university itself does not exist to form an ecosystem.

It seems that the phenomenon is occurring in various parts of the world where the domestic environment does not shift to a complementary structure, doing so while being connected to the global ecosystem that has been completed.

How should we approach that challenge?

5.3 Necessity of mutually complementary functions: Formation of an ecosystem that only progresses in a complex manner

As we saw in Chapter 3, there is a structure in which academia expands after or at the same time as the company grows, and venture capital also grows along with this growth.

One way to expand academia is through a kind of political investment, like in North America. An alternative is a strategy of strengthening academic capabilities through connecting existing research institutes, like in the case of VIB. In any case, the structure does not expand naturally.

Whether venture capital is in the form of a giant industry (USA) or in a form that strongly stimulates the movement from science to translation (Belgium), the entire system moves in a complementary manner, and the flow from academia to industry moves dynamically.

Japan's problem is that it has not been able to form an ecosystem in a mutually complementary relationship, even though the level of science and R&D expenditure are not necessarily low. In what direction should each part move?

There are two major problems facing academia. First, since scientists are doing research for the sake of science, translation is essentially secondary. There are TTOs to solve that problem, but how do you deal with the situation where universities are dispersed and exists independently?

The second, more fundamental, problem is that while development funding does not rise, it's difficult make careers as scientists attractive.

It is essential to find a way to develop good scientists in this environment. VIB-like methodology may be one way to address the issue.

Next, venture capital players must first create a situation in which they can commit to company creation regardless of region. However, there is an absolute lack of human resources on both the VC side and the entrepreneur side, and there is also a lack of funds in the background. Development risk in the life sciences is a big factor behind the lack of funds. However, it could be the case that early exit measures on the part of large companies could reduce this risk. In that sense, it is necessary to improve the communication between VCs and venture companies and, thus, “human resource development” is important in the sense of creating an environment conducive to such communication.

Behavior of large companies is such that if there is a level of translational output that can be expanded globally from universities and ventures, they will acquire it. Of course, it would be better if companies would improve their strength and be able to commit to projects at an earlier stage. But "ecosystem formation" is not a driving corporate concern for them, and I don’t anticipate that point changing significantly in the future. However, there is a possibility for earlier commitment timing and a more-active ecosystem.

Each player needs to improve little by little and compromise. Ultimately, however, what is needed is a methodology to strengthen science. In order to create a local environment for that purpose, it will be necessary to set rules and invest in people.

5.3.1 Cooperation of multiple universities and research institutes and improvement of organizational/academia environment

What should be paid attention to in Belgium's movement away from "competing alone" in science. When it is difficult to show overwhelming strength in science, it is important to maintain a competitive ecosystem level by collecting multiple pies and choosing the best from them.

First of all, it is important for universities and research institutes to seriously think about how they impact the global structure. The reality is that each organization's history and existing personnel tend to narrow the scope of this thinking, but what is needed is an appropriate set of scale, autonomy, and duration.

First, regarding scale, Flanders has a population of 7 million, and the Wallonia district, which has newly followed this system, has a population of 4 million. If the movement had been attempted at 10-20 times that scale, I highly doubt it would have worked. To some extent, specifying the area and scale is key to the need.

Next is autonomy, or governance. For example, in the case of Belgium, it is under the auspices of the Flemish government, which has delegated a significant amount of authority to VIB. In order to ensure that autonomy, they are gathering human resources who can judge the progress and direction of research on a global basis. It would be difficult for the local members to pull this debate together and pick the best (peer review feature).

On top of that, it will be necessary to give universities and research institutes the function of making their own investment decisions.

And for this to work, we need a certain "duration" as the selection period. Of course, it is necessary to consider the compatibility the duration with the career path afterward; so, it is necessary to make use of the existing university functions.

Now, let's say that we could divide Japan into 5 to 10 areas (such as Hokkaido/Tohoku, Kanto, Hokuriku, Tokai, etc.), conduct the project jointly among multiple universities, and create an "independent institution" on one side. Would there be incentive for universities to cooperate with and provide business to this scheme?

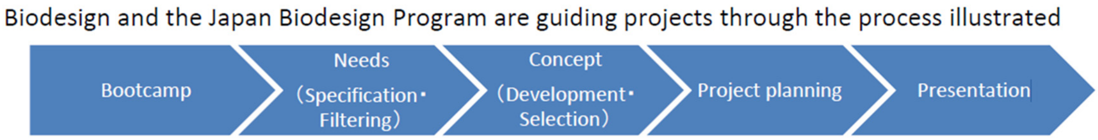
In order to do that, it would be necessary to instill trust that such a team and system would produce results. A step-by-step method, such as starting with cross-collaboration among TTOs and then strengthening the selection of research and development, may also help.

5.3.2 Education of professional human resources

Strengthening human resources who can create impact in academia is essential, and it is not hard to imagine that it will take time. The first thing we can do is strengthen human resources involved in translational research. These human resources include many support personnel from universities and research institutes, entrepreneurial personnel, and venture capitalists.

A good example would be the "Biodesign" program in the medical device sector. "Biodesign" was started in 2001 by Dr. Paul Yock of Stanford University as a human resource development program to lead medical device innovation based on design thinking. It is characterized by an approach that realizes innovation. In collaboration with Stanford University in October 2015, Osaka University, Tohoku University, and the University of Tokyo announced the launch of the "Japan Biodesign Program", which has been developing in Japan ever since.

Fig33 Processes of the Biodesign Program



Source: "Method of Innovation for Japanese Med-Tech Industry – Essence of Silicon Valley Style and How Japan Can Tap IT" (Development Bank of Japan)

New efforts are being made in Belgium, as we have seen at SBS, and are other countries have their own human resource development programs. Development of entrepreneurial human resources and investors who will complement each other is considered urgent, either by introducing a new such system or by partnering with a university that already has such a system.

And when taking such actions, it is important to have a sense of the distance between the research sites and the project site and of how to create hooks in the system. Industry's commitment is essential—that is, a university's new "initiative" is not enough.

5.4 Summary of this chapter: How should we exercise ingenuity?

Japan's problem in life sciences is that although the level of science and R&D expenditure are not necessarily low, the ecosystem has not been fully formed in a mutually complementary relationship. My point is not to simply create a framework like the VIB or SBS master schools but to supply the parts that are missing from the flow that has already been completed (including finance, of course).

A global ecosystem has been created through various transitions in the process from research and development to product launch. Japan has strengths within the ecosystem. Among them is the fact that major Japanese pharmaceutical companies continue to maintain a certain position in the global market. Another strength is that, even though its global ranking is dropping, Japan still publishes solid papers in science, in and out of the top 10.

Japan needs a framework in which individual players compete with each other and human resource development is fostered, focusing on the following measures.

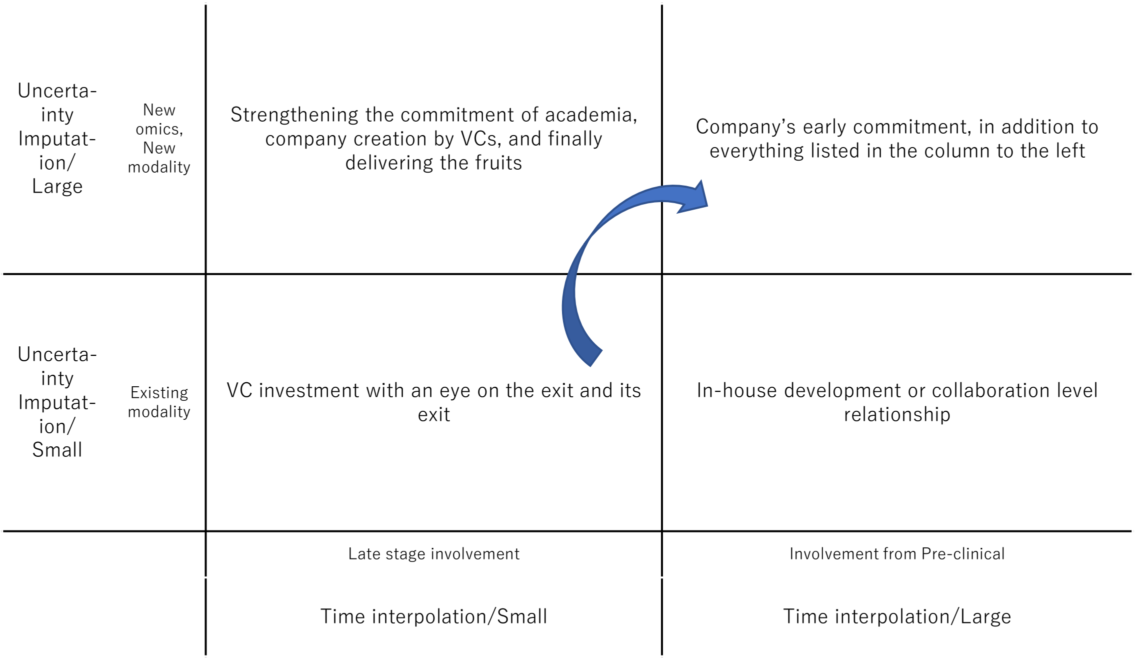
1) provision of a high-level R&D support framework in academia (including a VIB-like format) that

matches the global career paths of scientists,
2) development of human resources who support venture human resources on both the management side and the investment side, and
3) commitment of major companies to the domestic ecosystem, including the circulation of human resources.

Providing a high-level R&D support framework is particularly critical, as investment in academia, not just companies, is increasing not only in the United States but also in Europe. It is not easy to significantly increase the amount of money, but it is important to consider how to efficiently produce results that are commensurate with the investment.

Japanese academia and VCs also exist in the overall composition shown in Figures 18-20. It will be necessary to consider this in order to have a discussion that transcends individual historical backgrounds. I believe that by creating such changes, it is possible to realize the mutually complementary ecosystem shown in Figure 9. I would like for us to make an effort to do so.

Fig9 Matrix of complementary relationship



Created by the author

Conclusion

Although this paper is written on the life science industry and management, it is not based on the quantitative analysis that can be found in recent papers on business administration. As such, it is an attempt to look back on Belgium's efforts over the past 30 years and compare them with those of Japan.

On a personal note, my first encounter with the Belgian life science industry was in 2017 when I spoke with the late Mr. Goro Takeda and Mr. Jean Claude Deschamps, who greatly contributed to the writing of this article.

To be honest, I first had felt that this may be a type of story in which countries around the world state the strengths of each area. However, I can understand why I came to hear such stories in Japan at that time by looking at the recent trends in Belgium, which has created a system that allows research and development funds to flow into the life sciences.

In discussions of ecosystems in the life sciences, systems made in the United States naturally take precedence. In particular, the size of the venture capital industry is at a level that makes it difficult even for Japan to think about catching up. There are so many things to learn from that system, but at the same time, while knowing the essence of it, I feel the need to consider a model that can be applied in Japan as well.

It has probably been more than five years since the term “ecosystem” became widely used in the Japanese life science field. As a person in a financial institution, I focused on trying to grasp the overall structure of “ecosystem” in that context, while searching for a theoretical basis for that ambiguous term.

In the overall structure, one discovery is that in the life sciences, the expansion of the scale of large companies preceded the expansion of scale in academia and venture capital (or at the same time). This is highly compatible with the ecosystem theory that the actor is not alone. In the end, when each actor continued to make best efforts, those disparate efforts coalesced to form the current global ecosystem.

When thinking about "what can be done in Japan", a clear question is, “How can we connect to the global system?” However, that question only addresses a goal, and what is truly important is ingenuity in the process. The case study in Belgium has much to teach in that regard. The most important message is Dr. Jo Bury's quote, "Put your resources in people, not projects". This word of advice is also linked to the recent human resource development project in Belgium.

I hope that this article will serve as an opportunity for lively discussion for future creativity and the formation of Japan's unique life science ecosystem.

[References] ※Documents written only in Japanese are omitted.

Chapter 1

Tamas Bartfai, Graham V. Lees (2006), "Drug Discovery", Elsevier Academic Press
Daria Mochly,Rosenm Kevin Grimes (2014), "A Practical Guide to Drug Development in Academia: The SPARK Approach"
Paul G. Yock, Stefanos Zenios, Josh Makower et al (2015), "BIODESIGN 2nd edition", Cambridge University Press

Chapter 2

Zucker et al (1998), 'Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises', NBER WORKING PAPER SERIES
Zucker et al (2002), 'Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology', Management ScienceVol. 48, No. 1
Mika Kulju (2002), "Oulun Ihmeen Tekijat", Ajatus Kirjat
Gary P. Pisano (2006). 'Can science be a business', Harvard Business Review Oct.2006
Gary P. Pisano (2006), "Science Business", Harvard Business School Press
Ron Adner (2006), 'Match Your Innovation Strategy to Your Innovation Ecosystem', Harvard Business Review April.2006
Ron Adner (2012), "The Wide Lens", Portfolio
Ron Adner (2021), "Winning the right game", The MIT Press
Steven Casper (2007), ''How Do Technology Clusters Emerge and Become Sustainable?: Social Network formulation and Inter-firm Mobility within the San Diego Biotechnology Cluster', Research Policy 36
Michael G. Jacobides et al (2018), 'Towards a theory of ecosystems', Strategic Management journal/Volume 39, Issue 8
Chi Heem Wong, Kien Wei Siah and Andrew W. Lo (2018), 'Estimation of clinical trial success rates and related parameters', Biostatistics
Andrew W. Lo (2021), 'Can Financial Economics Cure Cancer?', Atlantic Economic Journal 49, 3–21.
Andrew W. Lo et al (2022), 'Financing Corelated Drug Development Projects', The Journal of Structured Finance
Andrew W. Lo et al (2022), 'Financing Vaccines for Global Health Security', Journal of Investment Management, Vol 20. No.2
MIT Laboratory for Financial Engineering, 'Project ALPHA', https://projectalpha.mit.edu/

Chapter3

European University Association (2021), 'Innovation ecosystems for a sustainable Europe', eua website
European Commission (2022), 'SCIENCE, RESEARCH AND INNOVATION PERFORMANCE OF THE EU 2022', EC website
NVCA (2022), 'Yearbook 2022', NVCA website

OECD, ‘Science, Technology & Patents’, OECD website

Chapter4

Bernard A.Cook (2002), “Belgium A History”, Peter Lang Publishing
Essenscia website
VIB annual report

Chapter5

Tatsufumi Aoyama
“Method of Innovation for Japanese Med-Tech Industry: Essence of Silicon Valley Style and How Japan Can Tap IT”, Sep. 2015. DBJ Research Report
“Market Circumstances of Medical Device Industry and Logic for Building a Strategy for Innovation by Japanese Companies”, Jul. 2016. DBJ Research Report

[Interviewees] (List of only those who were directly reflected in this manuscript)

- Marc Dechamps, Philip Vergauwen (Academic Director, Solvay Brussels School) Aug 22 & 26, 2022
- Danny Gonnissen (Chief Operating Officer, Newton Biocapital) Aug 22, 2022
- Marc Dechamps (Director International Affairs, BioWin) Aug 23, 2022
- Frēdēric Druck (Director of essenscia wallonie and essenscia bruxelles, Secretary General bio.be) Aug 23, 2022
- Wouter Piepers (CEO, flanders.bio), Willem Dhooge (COO), Katrien Lorre (Programme Manager), Charlotte Pauwels (Data Manager) Aug 24, 2022
- Jo Bury (Director-Emeritus, VIB) Aug 25 & Oct 18, 2022
- Vinciane Gaussin (Managing Director, WELBIO(current WEL Research Institute)) Aug 26, 2022
- Graeme Fraser (CSO, Epics Therapeutics) Aug 26, 2022

[Accompanying and cooperating with the interview] Newton Biocapital

- Jean-Claude Deschamps, Chairman Emeritus and Advisor to the Board of NBC I and NBC II
- Alain Parthoens, Chief Executive Officer
- Els Hubloux, Chief Investment Officer
- Guy Heynen, Chief Medical and Regulatory Officer
- Tomoko Asaoka, Scientific Director
- Danny Gonnissen, Chief Operating Officer
- Pierre Detrixhe, Venture Director
- Kaori Sano, Global Relationship Director
- Toko Senna, Assistant to the CEO Office Manager (Brussels Office)
- Louis de Thanhoffer de Völcsey, Senior Advisor, Independent Directors
- Dirk Boogmans, Vice-Chairman and Chairman of the Audit Committee of NBC I and NBC II
- Sadashi Suzuki, Japan Representative