Open Innovation Business Model in Drug Discovery

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1. Introduction

The purpose of this study is to consider the ideal business model and the inter-organisational relationships among various players in drug discovery from the viewpoint of open innovation through international comparative research.

In preceding studies about the business model of drug discovery, the limit of the model in pursuit of large-scale research, represented by Pfizer, was pointed out. On the other hand, the number of successful biotech venture companies around the world has not increased very much (Pisano (2006), etc.).

Our research project team thought that such concepts as open innovation (Chesbrough (2003), etc.) and/or the platform business model (Gawer & Cusumano (2002)), which were successful in the IT industry, could be effective in the pharmaceutical industry to activate drug discovery research and development. The research project team consists of researchers from universities and the Japanese National Institute of Biomedical Innovation, which is a key player for the Osaka biotech cluster in Japan. The team members split up and visited several pharmaceutical companies and bio-clusters for the field survey.

2. Review of previous works and hypothetical deduction

For pharmaceutical companies to survive, they must continue to produce new drugs. There are several paths that lead to the creation of new drugs, such as creating new drugs from a company's own research or introducing the concepts of another company through merger and acquisition or an alliance. Usually, however, a company creates new drugs from its own designs.

New drug creation is becoming increasingly difficult due to the enlargement, advancement, and complication of pharmaceutical exploitations, as well as tighter requirements for approval. The productivity of research and development in pharmaceutical companies has been studied for many years. These studies report a jump in research and development costs. Research and development costs rose suddenly beginning around 1990 and have since risen to reach an average of 15 to 20% of gross sales in major pharmaceutical companies, which is markedly higher compared to other industries.

Some of the reasons for decreasing new drug discoveries are complications during the drug discovery, enlargement of research and development, and tightening of regulations. European and American companies tend to access various resources (research seeds, talented people, etc.) more easily than Japanese companies. In Japan, there are few cases of the kind of venture companies and clusters that developed on the world level. Many factors, such as the cultural environment and governmental

policies, have influenced this, and authors Nakamura and Asakawa (2006) have indicated the weakness of this external environment. Moreover, European and American companies have worked to maintain exploitative resources (pipelines, research and development funds, etc.) through mergers and acquisitions or alliances. Japanese companies have seldom undertaken mergers and acquisitions or strategic alliances. However, since 2005, large resource acquisitions by Japanese corporations, such as Astellas Pharma or Daiichi Sankyo and purchases of overseas drug companies by Japanese corporations, have been increasing.

2-1. Previous works on the productivity of research and development in the drug industry.

The definition of research and development productivity in pharmaceutical companies is made in each study. It is difficult to compare productivity by same criteria.

For pharmaceutical companies to survive they must produce highly profitable products or products that will produce blockbuster sales, and the origins of the compounds may not matter. Yabuki et al. (2004) insisted that the productivity of a company with one product whose annual sales total 100 billion yen can be considered equivalent to the productivity of a company that has two products grossing 50 billion yen. However, pharmaceutical companies are manufacturers with the important function of research and development, and it must be important from the standpoint of profitability that new drugs are invented from their own research activities.

It is common to separate research and development into an early phase and a late phase. The early phase ranges from seeds searching to clinical development or sometimes to the ascertainment of clinical proof of concept. The late phase is the phase of checking the effectiveness of medicines for cases. In the early phases and late phases, the key factors for success are completely different (Bonabeau et al. 2009). Evaluating these phases by the same conditions is not helpful. Hereinafter, in order to distinguish the two phases, the early phase of research and development will be called research, and the late phase will be called development.

2-2. From economies of scale to economy of scope

Generally, since larger companies can invest more in research and development costs, they tend to get larger returns compared to small companies. The relation between the amount of investment and the return is explained through "economies of scale" and "economy of scope." "Economies of scale" is the cost spread concept holding that the cutback effect of the product cost per unit expands with the quantity of production. The pharmaceutical industry is an industry of limited production with wide variety, and each production method is also a part of the application for approval. Therefore, there are few degrees of freedom for reducing costs through production concentration such as in the auto or electric industry. Since the demand responsiveness to the price of a new drug (except generic drugs) is not very high, the price competition is not easily successful.

Henderson and Cockburn (1996) of MIT indicated that past researchs were inconclusive because they did not treat the right information sufficiently, and they tried surveying for comparative precision and exhaustibility. They surveyed the productivities of research and development based on the recording of about 5000 drugs for 38 research projects by averaging 20 years for ten European and American

R&D-oriented companies and verified the "economies of scale", "economy of scope", and "spillover effect." They especially focused on the research part of research and development. As a result, they predicted that a certain "economy-of-scale" effect exists. In addition, they claim that "economy of scope" and "spillover effect" influences the productivity of research. The spillover effect, they pointed out, means the ease by which therapeutic drug research for one sickness condition is applied to the therapeutic drug research of another condition. They claimed that when the scale was large, the effect of "economy of scope" became possible by diversifying and continuing the portfolio of research projects that harness knowledge spillovers between internal and external organisations. However, they have not made references to the ease of application.

The discussions so far are summarised as follows:

- As a result of verification, if conditions are the same, the research and development of large companies are more productive than those of small corporations. However, the market powers of big companies are exceeded by superior innovation competence under some certain situations (Economy-of-scope > Economies-of-scale).
- In the research activities in big companies, "economy of scope" comes out of the viewpoint that the sharing of knowledge capital that accumulates in the company and internalises the competence of external information, is more profitable than “economies-of-scale,” which arise from the distribution of fixed cost. Although productivity may be higher if a company carries out a lot of research and development projects, excessive concentration or diversification may create a negative effect.
- Further, it has also been verified that the spillover effects of the knowledge in a company is the driver of economical outgrowth.

Okada and Kawahara (2002) have also reported the same research results in Japanese pharmaceutical companies.

2-3. Economy of scope and the economy of experience

The business style of the drug industry changed gradually with the evolution of biotechnology and the bio-industry around 2000. Research and technologies of biotechnology or pharmacogenomics were less developed when Henderson and Cockburn (1996) examined, and mergers and acquisitions were not as prevalent as they are now. The current external environment is considered to be very different from that time.

Danzon et al. (2005) argued it is impossible to apply the verification results of Henderson and Cockburn to present pharmaceutical companies because of the altered environment. They stated that improving the success and accuracy of clinical development was improving the productivity of research and development, and investigated the data of more than 900 companies from 1988 to 2000. They concluded that productivity depends on the probable success of each phase of clinical development and how a product is marketed. The hypotheses they held are as follows:

1) The compounds produced by the companies that have significant research and development experience as a whole or within a specified-diseases area succeeded at high rates in clinical development (economics of scale).

2) The compounds produced by the companies that straddled the sickness areas and have done various researches and developments succeeded at high rates in clinical development (economics of scope).
3) Alliances improve R&D productivity, and the effect of it at the clinical 2nd & 3rd phase is more remarkable than at the 1st phase.

According to the results of their verification, in phase I, the spillover effect of knowledge is important and development experience was the important factor in the clinical later phases (the 2nd phase, the 3rd phase). With regard to alliances, the alliances between big companies and small companies contributed to high success in later clinical phases (Ph2-3). They indicated that experience and alliances are important factors in improving the probability of success in and after the development phase. Conversely, in the research phase, it can be said that the experience of a company is not so important. This is also explained as "external accumulation of knowledge", or "accumulation (clustering) theory," mentioned later.

2-4. "The selection and focus strategy" (investigating widely and narrowing down before development late phase)

The Japanese drug industry has also produced pharmaceuticals that have been taken globally in recent years.

For example, Mevalotin of Daiichi Sankyo (Sankyo of those days) and Aricept of Eisai became blockbusters. Kuwajima et al. (2006) investigated two companies, and considered the management of highly uncertain pharmaceutical research and development by conducting interviews to research and development persons, etc.

The late phase of clinical development spends the greatest amount of resources (people, materials and money) among the phases of research and development. Therefore, it is inefficient to advance too many highly uncertain projects to later clinical development phase recklessly. However, in view of the history of drug discoveries, the success percentage of drug discoveries is not always high. Some standpoints are completely dependent on fortuity. It is important for companies to understand how the success probability in late development phase is improved in such a situation.

On this point, Kuwajima et al. indicated that companies should prepare many candidates by running various projects and extending the target areas in the early phase of research and development. Before entering the late development phase, the projects should be sifted out through precise investigations, and narrowed down to only the projects with a highly predicted rate of success. They argued that the superiority or inferiority of a company to narrow down their choice is based upon the competence of the company. They indicated, "It is important to stretch a net widely and to narrow down brietly with sufficient timing." Competence is related to two essences, "accumulation of knowledge about causation" and "decision system." However, such management is effective especially at the late phase of research and development. The only key success factors at early phases are individual spite, fate, and chance. More discussions are needed.

Hitoshi Yabuki et al. (2004) of The Boston Consulting Group also performed the same kind of verification, and supposed that there are three points which lower the productivity of research and development: the smallness of the value per item, the absence of research and development efficiency,

and the height of the cost of failure. They indicated that the impact to reduce the third point, "cost of failure," is the largest. It is important for low productivity companies to raise their competence to make earlier decisions about potential failure.

It is common in these verifications that the management capability to narrow down projects before the late research and development phase, and the ability to stop lower probability projects early is enhanced by the competitiveness of the company. The following can be said from the above-mentioned verifications concerning the productivity of research and development of drug discoveries.

- The productivity of research and development in a large-scale company is basically high (economies of scale).
- However, under certain situations, the spillover effect and economy of scope of the knowledge are the drivers.
- Since a large amount of development costs is needed in the late phase of research and development, it is important to spread out the net of seeds and themes in the early phase of research and development, and to narrow down the projects properly before the late phase.
- Since outsourcing, research and development, mergers and acquisitions, and alliances have prospered recently, the difference of alliance skills has affected the success probability in the late clinical development phase in addition to the development experience.

Small-scale companies cannot invest research and development resources like big companies, and cannot always spread out the net widely. If success probability does not change among companies, the company that runs many projects can put out more products. As a result, small-scale companies must try to connect few seeds to late development phase somehow, and expect the last return. Then the problem is how the accuracy of the project, which shifts to development (late phase) from research (early phase), is raised. At this point, it is still a black box regardless of the scale of the company. In fact, even in big companies, new drugs run short and it becomes difficult for them to keep in growth. As a result, European and American big companies began to seek external seeds. They concentrated on enclosing good materials in the earlier phase as much as possible, and are investing large sums of money. Big companies have funds to support enclosure, and economies of scale work first for them, followed by economy of scope and the spillover effect. Although there are not many studies that only consider the productivity of the research phase of research and development, some reported the benefits of organisational theory and management theory. The chorus model of Eli Lilly and metrics model of Wyeth Pharmaceuticals are just some examples of the productivity drive that pharmaceutical companies are performing.

2-5. Collapse of in-company management in the productivity drive of research and development

The new-drug depletion phenomenon of pharmaceutical companies is seen all over the world. Therefore, the strategies of major pharmaceutical companies have tended to change towards seeking external resources, such as pipeline reinforcement through mergers and acquisitions, collaborative studies with bio-ventures and universities, and the training of start-up ventures. The following can be considered the background of such situations.

Although the pharmaceutical industry is called knowledge intensive industry, science and

technology progresses very slowly? and it becomes difficult to collect knowledge and technology by self-completion in one company. In particular, enlargement, advancement, and complication of research and development became prominent with the evolutions of genome and biotechnology in the latter half of the 1990s. That progress is rapid, and it has become difficult to actually maintain in-company management. As a result, each company is being forced to understand the external environment as being important. Modularisation progresses from the viewpoint of the value chain of pharmaceuticals industry. Research modularisation is advancing especially in biotechnology and genome-based drug discovery. However, the trait of modularisation in the pharmaceutical industry is a "modularisation of process." It is not just the same as the modularisation of other industries, which is mainly the modularisation of product (Takahashi (2004)).

Nakamura and Asakawa (2006) focused on the "collapse of in-company management" and "rise of cluster theory" as the external environment changed in the drug industry:

1) In-company management is beginning to collapse because companies need to lower the cost and risk of research and development, while knowledge is actively accumulated out of a company.
2) The significance of the cluster's role is increasing in the industry where one company cannot perform every research and development by oneself.

Nakamura and Asakawa also pointed out the importance of thinking how to manage resources efficaciously. According to the Resource-Based View (RBV) of Barney, it is possible to make a difference by accumulating one's own internal management resources and gain economically. In Japan, very few enterprises or clusters start up. According to the Structure-Conduct-Performance logic of Porter, companies try to move to attractive positions to maximise their performances. However, management resources cannot be transferred overseas readily.

On the other hand, due to the change in external environment, UMN (unmet medical needs) of pharmaceuticals has decreased greatly in the areas of hypertension, infectious disease, diabetes mellitus, and some psychiatric disorders, which had much large patient loads until now and whose markets were large. The change to generic pharmaceuticals progressed with the pressure of medical cost containment, making the market more competitive and lowering the amount of sales. The time in which forerunner companies can gain first-mover advantage (Schumpeter Lent) is becoming short. As a result, big companies are moving their target to the carcinomas and immunopathies where UMN are large. This means that companies have to move their strategic positions too early to build their internal resources, which can secure competitive advantage. As a result, acquisition of resources (talented people, knowledge, an information, etc.), through either mergers or acquisitions or the borrowing of resources by alliances or networks, is happening even more. Therefore, as stated, the capability to accumulate new findings outside the company—through clustering, etc.—is becoming important to cultivate as a core competency in companies. However, if a company depends too much on external resources, the risks of weakening the intelligence in a company will increase. Therefore, a system that complements this weak point is required.

2-6. The capability that drug discovery companies should have

How should drug discovery companies build resources and capabilities in their own companies?

Capability here refers to the competence that a company masters in combining management resources suitably. The significance of organisational capability is shown by the framework of VRIO (Value, Rareness, Imitability, and Organisation) in the Resource Based View theory (Barney (1997)).

According to Collis and Montgomery (1995), organisational capability is the complicated combination of the property, talented people, and processes to change input into output.

Ken Kusunoki (2001) distinguished "know-how" and "know-what" by paying attention to such types of knowledge as organisational capability. If organisational capability is considered to be the convergence of organisational special resources, "know-how" can be transferred to some extent, and it should not be an organisational special resource. He indicated that the organisational special knowledge in a true sense is "know-what", which is the knowledge to diversify and/or integrate the product system. Knowledge in connection with value differentiation is organisational capability. Moreover, he insisted that relativisation with the others who have different know-what is important to create and improve know-what of oneself. Linkage with the others becomes important.

Henderson and Clark (1990) divided knowledge into Component Knowledge (knowledge about each component) and Architectural Knowledge (knowledge about the total system), and verify the significance of the latter.

Clark & Fujimoto (1991) have pointed out the significance of a "heavy weight product manager" who has an integrated competence. They found the significance of it based on the survey of types of management in the auto industry. According to them, the more architecture of products or processes become complicated, the more the superiority or inferiority of the management competence of the relationship in an organisation and inter-organisation affects competitive advantage.

According to Cohen & Levinthal (1990), when an alliance with another company is managed, the coefficient of self-fulfilment of one's own resources affects absorptive capability. The absorptive capability should be improved and funded as one's own resources. Leonard-Barton (1995) introduced core rigidity, which means that innovation became difficult to occur only by internal learning. He indicated that the transaction of internal learning and external learning is necessary to promote innovation.

The styles for cooperating with a company for external information are divided generally into two areas. One is individual tie-up style, and the other is cluster network style. The merits of individual tie-up alliance are the possession of exclusive information, and clarified rights. On the other hand, the risk is that limiting networks may decrease the chance of innovation. Through network type, the researchers can communicate widely with other researchers who may have the same research themes, and the probability of innovation may increase. The demerits of network type include the risks the leadership to hastening the project, and differences in goals among participants.

In conclusion, the necessity for the competence to gain and manage the external resources efficiently becomes so high as to exceed the limitation of in-company management. They are considered to consist of the following competencies:

- Organisational capability, which can build and manage necessary alliances (Alliance-Management).
- Capability to transform external knowledge to the internal resource (the competence to convert the

input from an alliance into in-company project) (Intelligence-Conversion)

- Competence to generate output from input (Integration-Capability).

3. Quantitative analysis

3-1. The synopsis of the survey

This survey is a survey about the relationships between the business model and profitability of drug discoveries. We collected survey data from the data that the independent administrative agency Pharmaceuticals and Medical Devices Agency (Tokyo) exhibits on the homepage. Here are found the examination reports of drugs and pharmaceutical companies approved in the past, which have recently been exhibited with the expansion of the official information disclosure system of Japan.
http://www.info.pmda.go.jp/shinyaku/g0810.html

As items to be surveyed, the following were read in the application data about 137 new drugs (generic drugs omitted) approved in the past three years (from 2006 to 2008).

- The company that developed the original substance.
- The company that did pre-clinical and clinical assessments.
- The company that applied to the certification organisation.

Clearly written about the above were 77 items (because of confidentiality of information etc.). Among them, the amount of investment and profit (pretax base) were investigated from the financial data of each company, etc.

3-2. The result of a survey

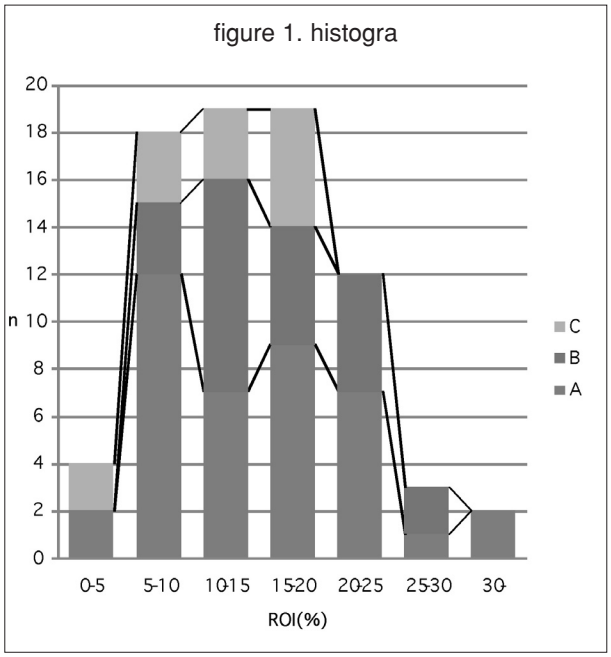
The business model of the drug discovery was classified into the following three models:

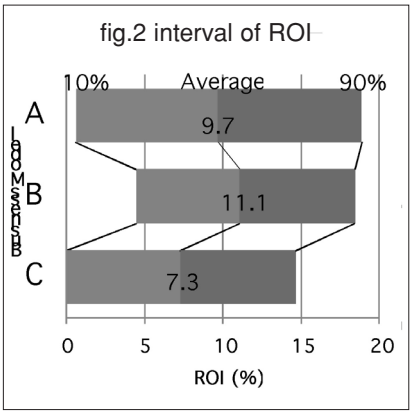
- Business model A: vertical integration type of drug-discovery business model; the company that applied performs all the processes of R&D (from a development of a substance).
- Business model B: cooperation model; the company that applied takes charge of clinical development and later phases.
- Business model C: the company that applied is not performing drug discoveries or clinical development.

Among each model, the specimen population's means were 9.7, 11.1, and 7.3, respectively. The most profitable model was business model B, the next was business model A, and business model C was the lowest. Each specimen population's distribution is as figure 1.

As a whole, profitability is broadly distributed from the determination of distributions. In model C, there are comparatively few drugs with high profitability compared with business models A and B. Since business model C is a model where the company purchases the substance after clinical development has finished from the other company, this is considered to be a situation where high profitability is hard to raise. Moreover, between business models A and B, the number of drugs with low profitability seems be less in B than A.

To make these tendencies more distinct, fig.2 indicates the ranges of ROI of each model, by





excluding 10% of the epistemic and 10% of the inferior, respectively.

From the specimen population's basic statistics and trend analysis, it is assumed that business model B is dominant from a point of profitability to other models. Business model B has the following traits.

- Pharmaceutical companies cooperate with other companies about high contingency research.
- The pharmaceutical company itself performs the phases from development to sales, to which experience and management competence contributes well. The lead time of the phases from development to sale is a rather long period, usually more than 10 years. It is difficult for venture businesses to perform them all.

However, at the performance of this survey, there was no statistical significance (5%) in the population. The form of distribution shows that the values of profits of each business model varied widely. It is thought that whether the company has chosen business model B is not enough of an explanation for profitability. Furthermore, it is thought that the skill of management, etc., influence the results. It is necessary to survey them more individually.

4. Qualitative analysis

The field work of some bio-clusters or drug discovery companies was carried out by qualitative analysis as above-mentioned. The cluster of Basel district in Switzerland especially should attract attention from the viewpoint of cooperation between organisations.

The biotechnology industry in Switzerland is one of the leaders in Europe. The headquarters of the multinational companies that act globally, including Novartis, Roche, Lonza, and Syngenta are located

there. Moreover, the small biotechnology companies progress nationally, constituting a huge network, and furthering the latest research and development. Tens of start-up companies are born in fields, such as functional genomics and bioinformatics. The biotechnology companies in Switzerland exist in all 20 states. There are three concentrated regions, Basel, Zurich, and the lakefront region. Although many bio-clusters exist all over the world and many seem to have not achieved results easily, the bio-cluster of Basel is a rare exception.

In the Basel region, approximately 80 companies are located around multinational companies, and at least 40% of the pharmaceutical companies in the world are found in the same region. Many related companies, including Novartis, are building a surveillance study centre on the largest scale in Europe with Basel University, where many global authorities in this field were born. The Zurich Federal Institute of Technology has also installed a bio-associated system theoretical centre.

It is thought that face-to-face relations in a comparatively narrow region has been created over several years among players such as universities, companies, and administrations, such as is seen in the bio-cluster of Basel. I felt this sort of confidential relationship from all whom I met. Roche and Novartis play the roles of a “platform,” which produces and supports spinout ventures in addition to Basel University. From those companies, support funds are offered based on a confidential relationship. Moreover, many spinout ventures which achieve superior results again came back into the pharmaceutical companies through mergers and acquisitions. As a result, researchers can do research and development based on their own views comparatively freely. It has become the trend that big companies support research on drugs that need a long time to achieve success. Big companies manage a diversified network and integrate the seeds and needs. Furthermore, many tool venture businesses have come out of universities like Basel University. Various players exist there who complement the value chain of drug discoveries, such as staff, skills, etc.

In IT clusters like Silicon Valley, investment systems by venture capitals which can cover rather short-term funds, functioned comparatively well. But in a bio cluster, the structure of risk management is a more necessary for the long term because drug discovery is high risk and requires a longer time reseach and development (RZD).

From the case study of Basel bio, one of the ideal business models in a bio cluster is as follows:

- Venture businesses produce various kind of "know how" based on trial & error.
- The gatekeepers (Allen (1977)), talented people with rich experiences in big companies, invest in outside ventures based on "know who" confidential relationships.
- And, based on experiences, the connoisseur capabilities of gatekeepers discern "know what"—what the findings can be used for.

The above eco-systems are formed in the overall Basel community.

5. Discussions and the tasks left

The following are considered from the results so far:

5-1. Open innovation is effective for the high-risk area of drug research & development. Innovation by just a conventional large company has become severely restricted. The modularisation of the drug

manufacturing has process has progressed to concentrate its own resources and lower the risk. The technical cluster (Porter (2006)) that plural networks intersect can be effective.

5-2. However, in drug research and development, the effective model of open innovation is different from that in the IT industry. In successful biotech clusters, the participants consist of not only universities, start-ups, and venture capitals, but also pharmaceutical companies and hospitals. Drug research and development is characterised by long lead times, high uncertainty, regulation, and the difficulty of the management of intellectual property rights. The player who manages the value system, from fundamental research to clinical application, is important. It should be a company that has high knowledge absorptive capacity (Cohen and Levinthal (1990)).

5-3. Some kind of intermediate model (like the keiretsu system in Japanese automobile industries) is effective, and is characterised by longterm and multiple relationships between external organisations. Modularisation of the business process is effective for innovation in the IT industry, but integral and wide variety interface is effective in drug research and development. The type of system needed to share the uncertain tacit knowledge (Nonaka (1997)) between organisations is important.

5-4. In the pharmaceutical industry, the lightweight product manager was said to be suitable because the initial research strategy is the most important (Clark and Fujimoto (1991)). But the importance of the heavyweight product manager is increasing. Project management by the discerning person has become important for pushing forward open innovation.

Some useful ideas were obtained through this survey of the business model of drug discovery. However, statistically significant explanations are not sufficient, and it is thought that explanatory models are still insufficient.
I would like to advance quantitative and qualitative survey further, and to continue to push for the more explanatory model.

Bibliography

Allen, Thomas J. (1977), *Managing the Flow of Technology: Technology Transfer and the Dissemination of Technological Information within the R. & D. Organization*, MIT press.

Annalee Saxenian (2006), *The New Argonauts: Regional Advantage in a Global Economy*, Harvard Univ Pr.

Barmey, J. B (1997), *Gaining and Sustaining Competitive Advantage*, Addison Wesley.

Bonabeau, E., N. Bodick and R. W. Armstrong. 2008. A more rational approach to new-product development. *Harvard Business Review* (March): 96-102.

Chesbrough, Henry (2003), *Open Innovation: The New Imperative for Creating and Profiting from Technology*, Harvard Business School Pr

Chesbrough, Henry (2006) et al., *Open Innovation: Researching a New Paradigm*, Harvard Business School Pr.

Chesbrough, Henry (2006), *Open Business Models: How To Thrive In The New Innovation Landscape*, Harvard Business School Pr.

Clark, K. B. and T. Fujimoto (1991) *Product Development Performance: Strategy, Organization, and Management in the World Auto Industry*, Boston: Harvard Business School Press.

Cohen, W. and D. Levinthal. (1990), "Absorptive capacity: a new perspective on learning and innovation." *Administrative Science Quarterly* 35(1) pp 128-152.

Collis, D. J. & Montgomery, C. A. (1995), Competing on resources: Strategy in the 1990s, *Harvard business review*, July (Aug), 118 - 128.

Danzon P.M., Nicholson S., Pereira N.S. (2005) "Productivity in pharmaceutical – biotechnology R&D: the role of experience and alliances" *J. Health Economics* 24, pp317-339

Henderson R., & Cockburn I. (1996) "Scale, scope, and spillovers: the determinants of research productivity in drug discovery" *RAND J. Economics* 27(1), pp32-59

Henderson, R. and K. B. Clark (1990) "Architectural Innovation: The Reconfiguration of Existing Product Technologies and the Failure of Established Firms," *Administrative Science Quarterly*, Vol. 35, No. 1, pp. 9-30.

Ishikura Y. (2003) *et al., Strategy of industrial cluster in Japan*, Yuhikaku Publishing.

Kimura H. edits. (2008), *Medical business*, Kanki publication.

Kusunoki, K. (2001) "Value differentiation and restrictions colocalization", in Hitotsubashi University Innovation Research Center, *The knowledge and innovation*, Chapter 2, Toyo Keizai Shinpo-Sha.

Kuwajima K. (2006), *Management of Uncertainty*, Nikkei Business Publications.

Leonard-Barton, D. (1995), *Wellsprings of Knowledge: Building and Sustaining the Sources of Innovation*, Harvard Business School Press, Boston, MA.

Mizuho industrial research (2005), *"Reorganization trend of European and American drug industry and implication to our country pharmaceutical industry "*, (http://www.mizuhocbk.co.jp/fin_info/industry/sangyou/m1017.html)

Mizuho industrial research (2007) *"Trend of European and American major pharmaceutical companies, strategy, and viewpoint of business reinforcement"*, (http://www.mizuhocbk.co.jp/fin_info/industry/sangyou/m1025.html)

Nakamura H. & Asakawa K. (2006), *"Conquest of minor external environment like by R&D management in pharmaceutical and biotech industry"*, RIETI DPS 06-J-019

Okada, Y. & Kawahara, Y. (2002), "Research-and-development productivity of Japanese pharmaceutical industry", *Office of Pharmaceutical Industry Research, research paper* (9), http://www.jpma.or.jp/opir/research/article09.html

Pisano, Gary P. (2006), *Science Business: The Promise, the Reality, and the Future of Biotech, Harvard* Business School Pr.

Porter, Michael E. (1999), *Competitive Advantage of Nations*, Free Press.

Ross DeVol and Armen Bedroussian, et al. (2006), *Mind to Market: A Global Analysis of University Biotechnology Transfer and Commercialization*, Milken institute.

Shook, Robert L. (2007), *Miracle Medicines: Seven Lifesaving Drugs and the People Who Created Them*, Portfolio.

Takahashi Y. (2004), "A suggestion cooperation management of drug discovery company", *The Japan Society for Science Policy and Research Management, collection of annual scientific convention speech summaries*, 19, pp.642-645.

Yabuki H. et al. (2004), "Crisis of research-and-development productivity", Boston Consulting Group, http://www.bcg.co.jp/publications/globalreport/2004/gr_040702_1.pdf.