Structural Characteristics of the Patent Applications and Examinations of Important Upstream Inventions in Life Science Area[1]

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Abstract

In this paper, 47 key patents in the life science field are analyzed for the types of applicants, the state of applications and registrations at the trilateral patent offices of Japan, Europe and the United States, the use of continuing applications in the United States and their effects. We have found that the main source of the key patents in upstream fields has shifted to private firms, in particular, biotech firms, from universities and that there is a significant difference in the rates of registrations of key patents across the trilateral patent offices (the difference is more pronounced if we focus on the patents in the families related to the key patents).

1. Introduction

In life science fields, patenting of research results has been actively pursued even in upstream fields close to basic research. Such patenting of the upstream research may increase the profitability of basic research, and promote the voluntary research investment by universities and private firms in such fields, thereby enhancing their contribution to the development of the fields. On the other hand, as expressed by the term of "the tragedy of the anticommons", there is also the possibility that the combinatorial use of significant technologies of a range of research organizations will be impeded, resulting in the constraints on the research in downstream fields. At the very least, these debates on how to best design the system of patent protection in upstream fields should be based on proper collection of and understanding of the factual data.

However at present, it cannot be said that there exists a sufficient understanding of the facts, which can provide a good foundation for such debates. For an example, the basic information is not available, as to the level of patenting in upstream fields, the types of research organizations conducting research and patenting, and what differences in examination exist between the trilateral patent offices.

In this paper, we try to clarify the structural characteristics of upstream patents in the life science field, based on detailed analysis of bibliographic information of 47 key patents which made considerable contribution to the development of the life science field. More precisely, the types of organizations conducting the research and patent

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applications for key inventions will be analyzed. Identification of the types of organizations gaining rights on key inventions in the life science field are required for assessing the entry of private firms in such research field and for assessing the potential threats due to the "tragedy of the anticommons" in upstream fields. Following this, the state of the patent applications and the registration of key inventions in three offices will be analyzed. It is submitted that the patenting of upstream inventions may be sometimes limited by description requirements or utility requirements of a patent law. More generally, problems with respect to upstream inventions (such as patentability and patent scope) may well be affected by the examination standards or patent system itself of respective national patent offices. Thus, there remains a very important issue to understand how globally such patents are granted. Although there is a few important literature in which quantitative international research has been conducted to compare patent office examination[2], focusing on highly important patents such as key patents in the life sciences will open up the possibility of debating differences purely arising from examination standards, independently of the limitations caused by invention quality.

Finally, how extensively continuing applications are used before and after the grants of key patents in the United States will be analyzed. In upstream fields in the life sciences, there is a high potential for cumulative discoveries after the initial invention. Furthermore there is a high potential for discovering new market uses which were not originally imagined. Consequently, it may be more important than in other fields for the patent system to enable strengthening the invention and expanding the scope of the claims after the initial patent application. Our analysis will be performed with respect to the United States which allows extensive use of continuing applications, regarding both the level of the use and the effect of using such system (continuation applications, divisional applications) which enables a broadening of the scope of the claims after the initial application for patenting of an upstream invention, or a continuation-in-part application which enables the addition of new matter.

The structure of this paper is the following. In the second section, we clarify how the key patents have been selected from the Japan Patent Office reports on key patents in the life sciences. In the third section, an analysis by applicant organizations for key patents is performed. In the fourth section, the state of applications to and registrations in the Trilateral Patent Offices is analyzed. In the fifth section, the state of the use of continuing applications and their effects are examined. In the sixth section, the results are summarized and discussed.

2. Selection of Life Science Key Patents for Analysis

In this paper, 47 key patents listed in "Life Sciences, 2003 Edition" in the Reports on Technical Trends in Patents Applications from the Japan Patent Office have been used for analysis. We have identified the applicants , the characteristics of the technology, presence or absence of government subsidies in research and development, the state of application and examination by the Patent Offices of Japan, Europe and the United States and the number of times the patent is cited. First, the selection process of the key patents by the report will be summarized. The report divides the field into a total of 18 fields, including four basic fields (biotechnology key patents) and 7 applied fields such as post-genomic technologies (technologies related to post-genomic techniques and other technologies) (Refer to Table 1). It searched for key patents by field and finally selected a total of 47 patents comprising 19 patents in basic fields and 28 patents in applied fields. In comparison to applied fields, basic fields tend to be research in upstream fields. Regarding the poolof the candidate patents for such key patents, the following four sources were used.

1. Japan Patent Office Annual Report (1998), Japan Patent Office

2. Biotech Key Patents (March, 1998), Japan Bio-industry Association
3. Highly cited US patents
4. Interviews with the specialists in the field

The list of the key patents identified by the Report is shown in Table 2. The list contains key technologies which have been essential for the development of the fields, such as the Cohen Boyer Patent of Stanford University, the Axel Patent of Columbia University, the patents for the PCR methods and that for DNA chips. Fig. 1 shows the patterns of applications for these patents divided into basic and applied fields by priority year. According to this figure, it can be seen that a similar number of key patents for both basic and applied fields were filed almost simultaneously, indicating that the researches oriented to basic fields and those to applied fields were made almost simultaneously. The structural characteristics of such key patents in the life sciences will be examined below.

Table 1 Structure of Life Science Fields

Basic Fields	Applied Fields
genetic engineering genetic functional analysis developmental engineering glycotechnology	genetic therapies and diagnosis nano-biotechnology microbials and enzymes recombinant plants recombinant animals biotech pharmaceuticals biotech chemicals

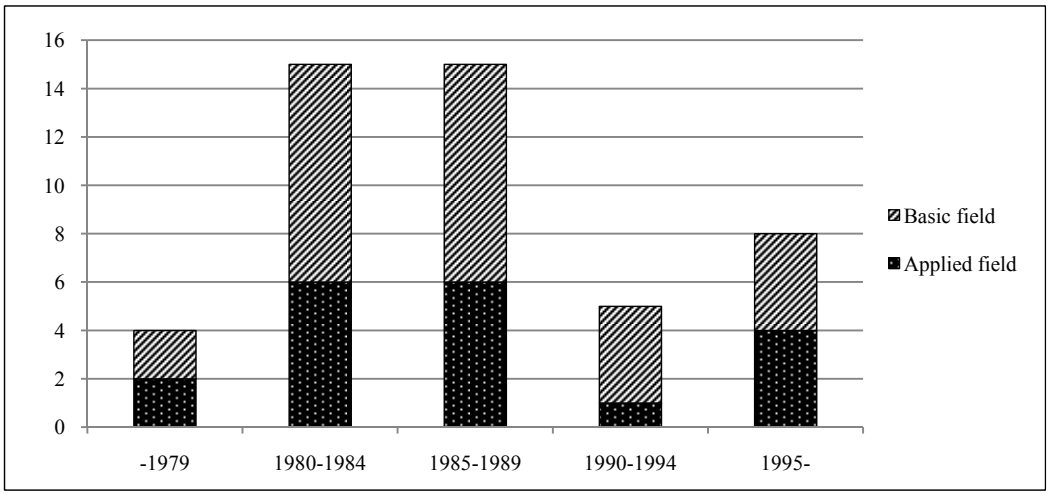
Table 2 List of Key Patents in the Life Sciences

name of technology	core techniques	short description	Patent Nos.
genetic engineering	method of genetic recombination	method of replication and expression of exogenous genes in microorganism, basic technique for genetic recombination	US4237224
genetic engineering	protein production using recombinant DNA	production and secretion of desired protein in bacterial cell	JPA-62-46160
genetic engineering	method of protein recombination	—	US4399216
genetic engineering	method of gene cloning	—	US4394443
genetic engineering	genetic transformation of zygotes	—	US4873191
genetic engineering	ribozyme methods	suppressing gene expression and cleaving genes	US4987071
genetic engineering	introduction of genes using particles	—	US4945050
genetic engineering	PCR methods	techniques for exponentially amplifying specific nucleic acid sequences using specific primers	US4683202
genetic engineering	display methods	—	US5223409

genetic engineering	isothermal PCR	method of amplifying genes by improving specificity using novel primers to which a plurality of oligonucleotides is mutually bound	JPA-10-337186
genetic functional analysis	DNA chip	planar, non-porous solid support mounting probes differing by at least 4 bases on at least 400/cm2	US5744305
genetic functional analysis	human ESTs/Gene sequencing Methods Data System	gene fragment patent identifying a DNA sequence with a novel human kinase expressed in human cells and tissues/ computer system used when computing the gene full length sequence from the fragment	US5817479
genetic functional analysis	full length cDNA	provision of a primer enabling synthesis of full length cDNA and 830 full length cDNA encoding human complete protein	JPA-2002-17375
developmental engineering	manufacture of animal with introduced genes	non-human mammalian animal with introduced genes prepared by introducing genes activated oncogenes at embryonic stage	US4736866
developmental engineering	manufacture of cloned animals	manufacture of cloned animal by selective propagation of mammalian stem cells	US6146888
developmental engineering	cloned sheep	production of cloned sheep by transferring nucleus from quiescent donor cells into a suitable recipient cells	US6147276
glycotechnology	beta 1, 4-galactosy1 transferase human	cDNA coding for N-actylglucosamine (beta 1-4) galactosy1 transferase	JPA-2-27987
glycotechnology	variant EPO	erythropoietin analog performing variation of number of added sugars by substitution of amino acid residues	Japanese Pat. No. 2938572
glycotechnology	ST3Gal III human	cDNA coding for novel alpha 2 → 3 sialyltransferase	US5494790
genetic therapies and diagnosis	diagnostic agent for hepatitis C	use as diagnostic agent identifying amino acid sequence and isolating hepatitis C virus	JPA-5-81600
genetic therapies and diagnosis	methods of gene therapy	preparation of chimeric protein by fusion of ADA gene to human MDRI gene and use in gene therapy	Japanese Pat. No. 2949440
genetic therapies and diagnosis	antisense methods	mutual interaction of genes and suppression of genetic expression	Japanese Pat. No. 2547714
genetic therapies and diagnosis	methods of gene therapy	methods of therapy by introducing recombinant human cells producing and expressing therapeutic active protein into humans	US5399346
nano-biotechnology	highly sensitive biosensors	detection of minute variation in material surface by measuring device having a tunneling tip piezo and measuring the effects of environmental changes	US5103174
nano-biotechnology	drug delivery	polymers and compositions thereof having polymethacrylate esters having functional groups on an terminal end	Japanese Pat. No. 3310303
nano-biotechnology	semiconductor nano particles	use of semiconductor nanocrystals as detectable label in chemical and biological applications	US6274323
microbials and enzymes	*E. coli* producing threonine	method of manufacturing L-threonine by culturing *E. coli* strain as L-threonine producer in the presence of antibiotic penicillin	JPA-1989-20871
microbials and enzymes	Method of culturing *Pseudomonas* bacteria	Method of culturing *Pseudomonas* bacteria having high nitrile-hydratase activity	JPA-61-43998

microbials and enzymes	extreme thermophile DNA polymerase	thermostable DNA polymerase originating in *Thermotoga maritima* and the producing method	JPA-7-108220
recombinant plants	Ti plasmid	Ti plasmid having high transformation efficiency obtained from plant pathogen *Agrobacterium tumefaciens*	JPA-2-58917
recombinant plants	electroporation	method of stimulating membrane porosity by application of DC pulses and introducing DNA into cells	Japanese Pat. No. 3038479
recombinant plants	herbicide resistant plants	transformation of plant cells to have resistance to herbicide glyphosate by plants and plant cells	Japanese Pat. No. 2615013
recombinant plants	plant antisense regulation	tomato with improved shelf-life using antisense techniques with respect to polygalacturonase DNA	Japanese Pat. No. 2702921
recombinant plants	particle Gun	introduction of genes into cells by firing high-speed metallic particles coated with DNA	Japanese Pat. No. 2517813
recombinant plants	method of multiple introduction of genes	use of genes inducing morphological aberrations as marker genes into a vector for plant gene transfer	Japanese Pat. No. 3256952
recombinant plants	antibody production by plants	production of antiorganizations by transgenesis and expression of antibody genes in plants	US6417429
recombinant plants	oncomouse	preparation of transgenic animal having oncogene by introduction of oncogene into embryo of animal	JPA-5-48093
recombinant plants	exogenous protein expression in milk	preparation of transgenic animal for expressing exogenous protein in milk of mammalian animal	Japanese Pat. No. 2874751
biotech pharmaceuticals	recombinant interferon	production of alpha-interferon in recombinant mouse cells or in microbes using DNA having specific DNA sequence	JPA-3-21150
biotech pharmaceuticals	recombinant human TPA	production of human TPA using recombinant DNA techniques	JPA-62-16931
biotech pharmaceuticals	recombinant EPO	DNA sequence encoding amino acid sequence for human erythropoietin	JPA-2-17156
biotech pharmaceuticals	recombinant G-CSF	DNA including amino acid sequence for human granulocyte colony simulating factor and human base sequence encoding same	JPA-3-31437
biotech pharmaceuticals	Hepatitis C vaccine	K1 protein expected to have greater efficinecy	Domestic Publication of International Application 7-508423
biotech pharmaceuticals	insulin derivative	insulin derivative bonding lipophilic groups of 12 – 40 carbon atoms to B chain N terminal amino group	Domestic Publication of International Application 11-502110
biotech chemicals	method of manufacturing acrylamide	obtaining acrylamide by contacting microbes having affinity with acrylonitrile	JPA-62-31913
biotech chemicals	method of manufacturing 7-amino cephalosporanic acid	production of 7-amino cephalosporanic acid directly from cephalosporin C using *Pseudomonas* microbes	JPA-5-27395
biotech chemicals	method of manufacturing 1,3-propanediol	manufacturing the compound from a single carbon source using recombinant microbes	Domestic Publication of International Application 2001-503636

Figure 1 Shift in Number of Patent Applications by Technological Field



3. Structure of the Applicants for the Key Patents

3.1 Types of Applicants

First, we will analyze what types of organizations are involved in inventions and applied for the 47 key patents. Fig. 2 shows the number of patents by applicant organization. In the figure, the applicants are divided into the five categories: universities, national research institutions, private non-profit research institutions such as foundations, biotech firms such as startup firms, and large pharmaceutical firms[3]. Universities obtained a majority of patents (10 of 19 patents) in basic fields while only 1.5 patents of 28 patents in applied fields. University patents are concentrated strongly in basic fields which are more upstream in research processes. Conversely, biotech companies obtained 4.5 patents in basic fields and 10 patents in applied fields, with significantly more patent patents in applied technologies. Only 12 key patents were acquired by large pharmaceutical firms which is smaller than that for biotech companies. In the basic research in life science fields, universities and biotech companies played a larger role than large pharmaceutical firms.

Next, Fig. 3 and Fig. 4 show the composition of applicants in basic and applied fields by half a decade (every five years). In basic fields, all of the eight patents in basic fields were filed by universities by the first half of the 1980s. However by the second half of the 1980s, patent filings from universities had fallen to two patents and the number of patents by biotech companies and large pharmaceutical firms had increased. After the second half of the 1980s, it can be seen that biotech companies and large pharmaceutical firms became very significant in basic research fields too[4]. On the other hand, as shown by Fig. 4, the majority of patent applications from the 1970s in applied fields have been made by these firms and the contribution of universities or public research institutions have been low. Thus, although there wer a division of research up to the first half of the 1980s: basic fields by universities and public research institutions and applied fields by biotech companies and large pharmaceutical firms, this distinction broke down later due to the entry by the latter group into basic fields.

Finally Fig. 5 shows the number of patent applications by the nationality of applicants. The applicants from the United States account for 70% (12 patents) of all patents in basic fields and 50% (14 patents) of all patents in applied fields. Thus, the development and the patenting of key technologies have been mainly engaged by the US applicants.

Figure 2 Number of Key Patents Acquired by Applicant Type

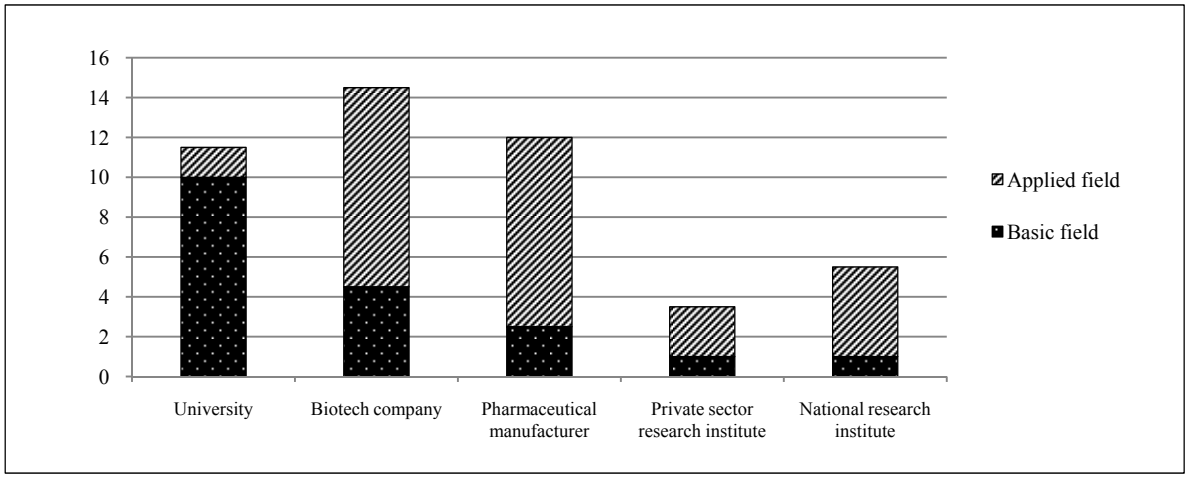


Figure 3 Trend in Number of Patent Applications by Applicant Type (Basic Fields)

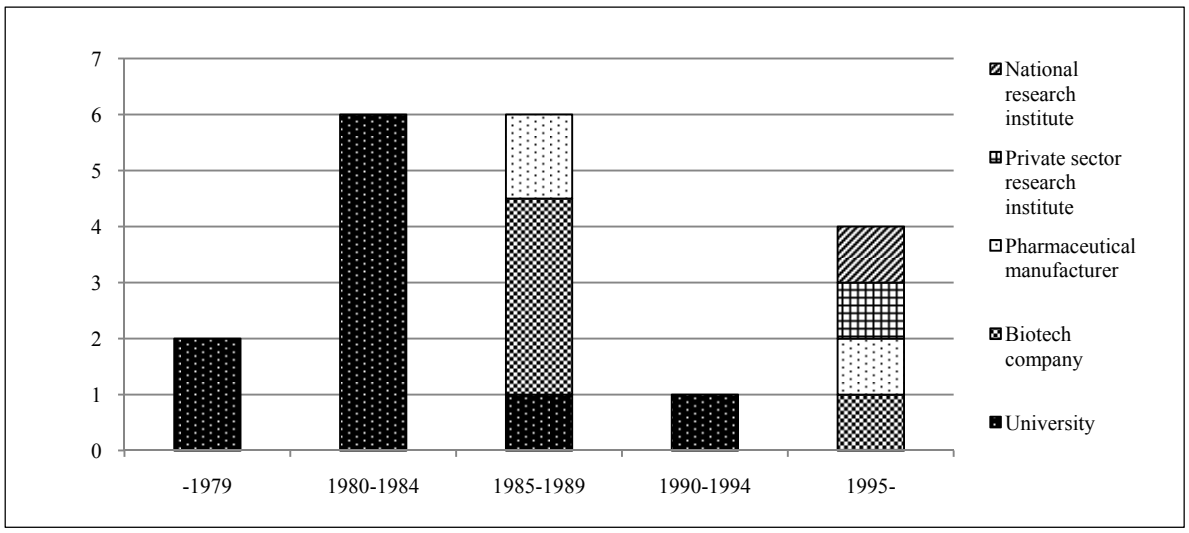


Figure 4 Trend in Number of Patent Applications by Applicant Type (Applied Fields)

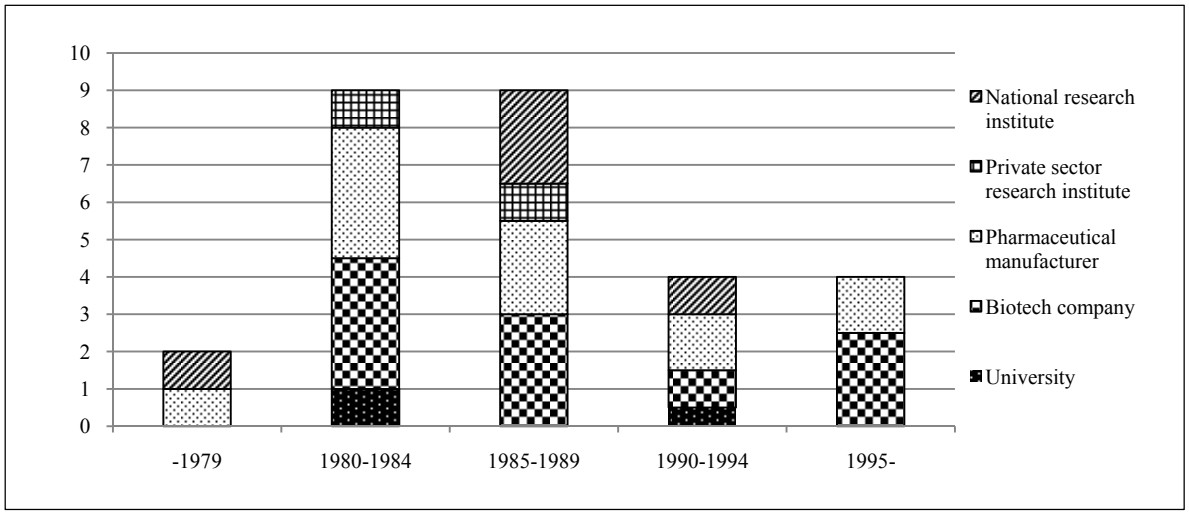
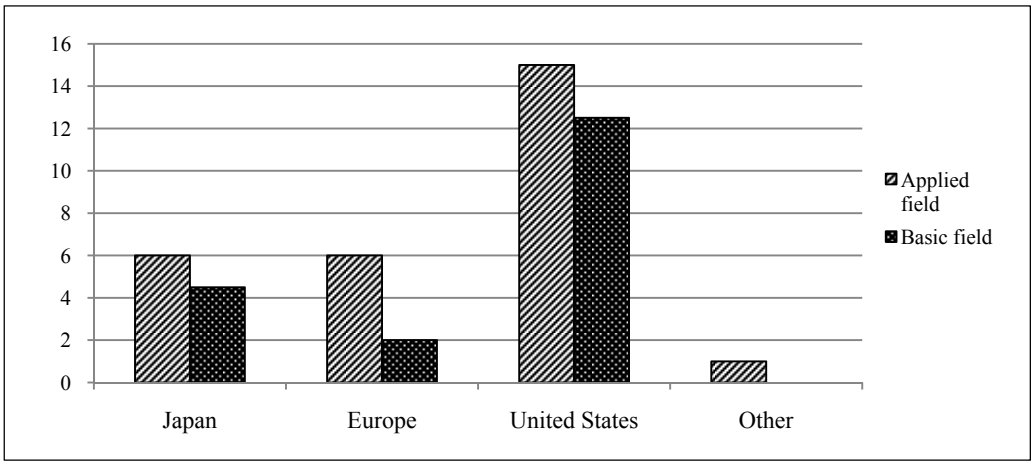


Figure 5 Number of Patents Acquired by Applicant Nationality



3.2 The Proportion of Research Tool Patents

When analyzing the structure of the ownership of key patents, the more important consideration may be whether the patent relates to a research tool rather than whether the patent is a patent in a basic field or in an applied field. A patent covering an important research tool with little alternatives, such as the Cohen Boyer Patent, may impede the development of broad-based research by limiting the user to a single organization or by increasing the royalty burden on research costs, although it .may also increase the profit made by a research organizations for such invention.

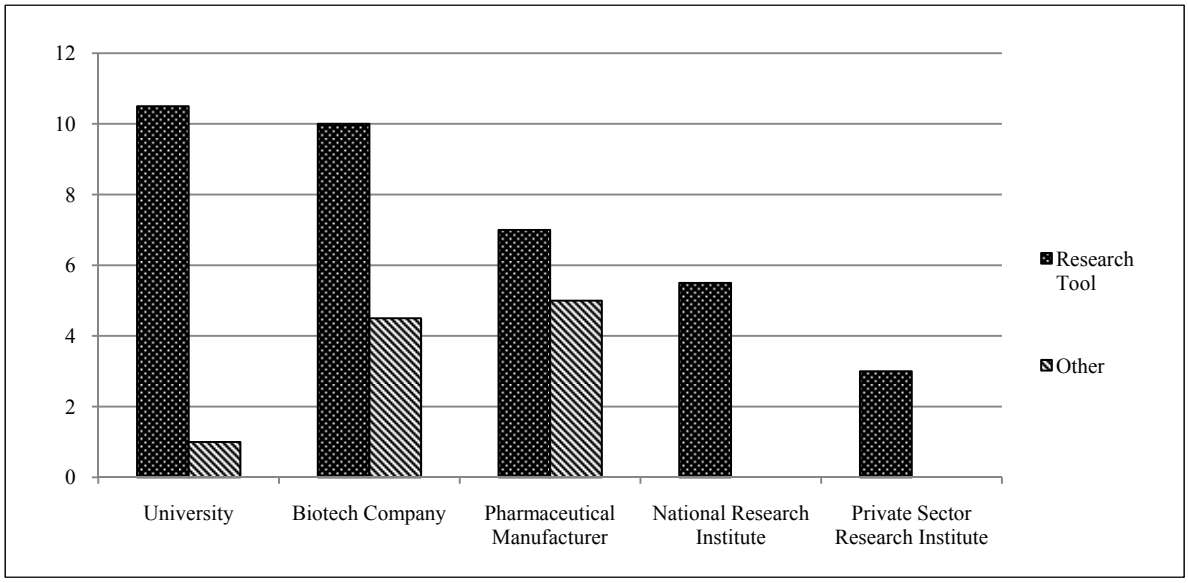
We classified the key patents from this perspective of whether it covers a research tool or not[5]. Table 3 shows the 47 key patents classified into the three categories: pure research tool patent, dual patents having direct commercial use in addition to its use as a research tool and the patents not related to research tools. Of the 47 key patents, pure research tool patents accounted for 21 patents (44.7%) and the dual patents accounted for 15 patents (31.9%). Thus, when pure research tool patents are combined with dual patents, research tool patents accounted for 70% of the all key patents. In particular, in basic fields, 18 out of 19 patents are related to research tools. In applied fields, the ratio of research tool patents is also high (18 out of 28 patents). The difference of the applied fields from basic fields is that the proportion of pure research tool patents is low and the proportion of dual patents is high. There were no research tool patents in the fields of bio-chemical products and bio therapeutic substances, which are directly related to drug discovery, even in applied fields.

Fig. 6 shows the ownership distribution of research tool patents by type of applicants. All patents acquired by government and private sector research institutes are related to research tools and 90% of the patents acquired by universities are related to research tools. In addition, the the number of research tool patents acquired by biotech companies and pharmaceutical firms is also high (10 patents were acquired by biotech companies and 7 patents were acquired by pharmaceutical firms). The patenting of research tools by biotech companies and pharmaceutical firms may result in the monopolization of research based on those technologies and may result, from the point of view of the broader society, in the possibility that research by various organizations may be impeded.

Table 3 Research Tool Patents by Technological Field

	Technical Field	Purely Research Tool Patent	Dual Patent	Other Patents	Total
Basic Field	genetic engineering	2	1		3
	genetic functional analysis	8	2		10
	developmental engineering	3			3
	glycotechnology		2	1	3
Applied field	nano-biotechnology	1	2		3
	genetic therapies and diagnosis		4		4
	microbials and enzymes	2	1		3
	recombinant plants	1	1		2
	recombinant animals	4	2	1	7
	biotech chemicals			3	3
	biotech pharmaceuticals			6	6
Total		21	15	11	47

Figure 6 Patent Research Tool Applications by Applicant



3.3 Level of Involvement of Government Subsidies

When considering the problems of upstream patents, one important consideration is whether or not the research results have been obtained using public subsidies. As is stipulated by the NIH Guidelines, it is required in the US that non-exclusive licenses be granted to a licensee for the technologies developed using public subsidies, with the exception of the case where the investment requirement for the commercialization justifies an exclusive right. For these cases, the problems associated with the limited access to research tools would be avoided[6]. In Japan, the Council for Science and Technology Policy formulated a "Policy related to Facilitating Use of Research Tool Patents in the Life Science Field" in March 2007. The policy states that "the royalty for non-exclusive licenses for research tool patents

shall be reasonable, based on the characteristic of the research employing the patent and on whether or not the patented invention to be licensed was developed using public funds. Sufficient considerations shall be given to avoid impeding the use of such patents. In particular, for a license among universities, it is desirable that such license shall be granted for free (except for covering the actual costs associated with the provision of tangible materials) from the point of view of promoting academic research . The granting of a license may include reasonable license conditions other than royalty"[7].

In the United States, when the patents are applied for the results of the research using public fund, such facts must be stated in the applications, according to Bayh-Dole Act. Thus, the identification of whether the patents rely on public subsidies is possible by checking for the presence or absence of such a statement. The 26 patents having American applicants were examined for the presence of this statement. It was found that a statement of reliance on public subsidies (government interest) was present in 5 of 9.5 (53%) of patent acquired by U.S. universities. On the other hand, in the applied field, public subsidies were associated with only one patent granted to a private sector research institution and are very rare, irrespective of whether the entity is a university or a corporation. These results show that almost all research tool patents acquired by private firms are not subject to the application of the NIH Guidelines and, in particular, that considerable cumulative license royalties may be incurred in the event that the research tool patent s of a number of organizations is required for a research project.

4. State of Applications to the Trilateral Patent Offices and Examination Results

4.1 State of Applications to Trilateral Patent Offices

The technical details and/or the specific uses of upstream inventions in the life sciences are often unknown at the application stage and consequently, they may sometimes fail to satisfy patentability conditions with respect to the description requirements or utility. What therefore are the examination results in the three trilateral patent offices in view of these characteristics? Before examining the state of registration at the trilateral offices, we shall provide an overview of the state of applications for key patents at the trilateral offices. Firstly, Fig. 7 shows the state of application to the trilateral patent offices by basic or applied field. In the applied field, there are 20 patent applications which were made to all of the three offices and this represents 70% of the total. In contrast, in the basic field, there are only eight such applications, only 40% of all. In the basic field, there are six applications to a single office and approximately 30% of the applications do not involve applications to a foreign country. As far as the key patents are concened, the more upstream an invention is, the smaller the tendency for an international patent application. However, according to Fig. 8 which shows the state of applications to trilateral offices by every 5 years, in comparison to the 1970s, the proportion of applications to all trilateral patent offices increased throughout the 1980s and 1990s. These results demonstrate the development of the globalization of patent applications.

Fig. 9 shows the state of application to the trilateral patent offices by type of an applicant. As shown in the figure, the number of patent application to all trilateral patent offices by biotech companies and pharmaceutical firms considerably exceeds the applications only to one or two offices. However there are relatively few applications made by universities, private sector research institutes and national research institutes to all of trilateral patent offices. Thus, it is clear that the applications to all three offices center on private firms.

Figure 7 Trends in Trilateral Applications by Technological Field

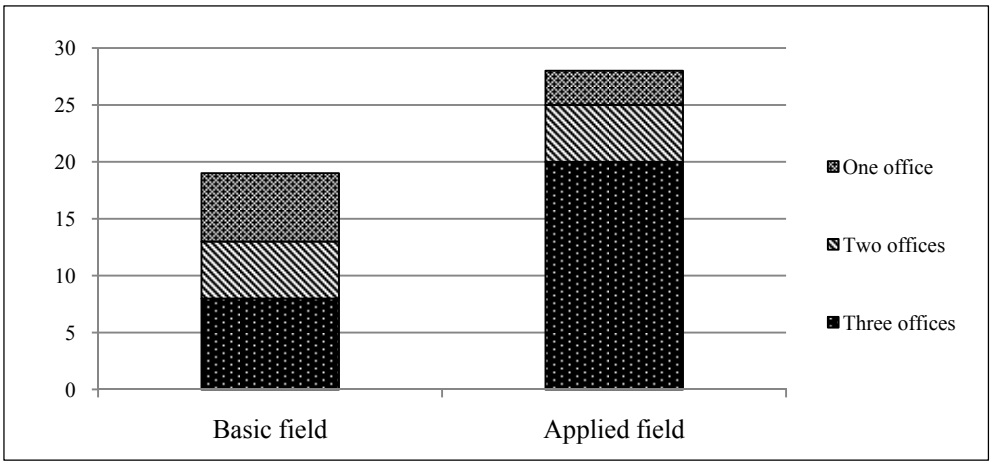


Figure 8 Distribution of Trilateral Applications by Decade

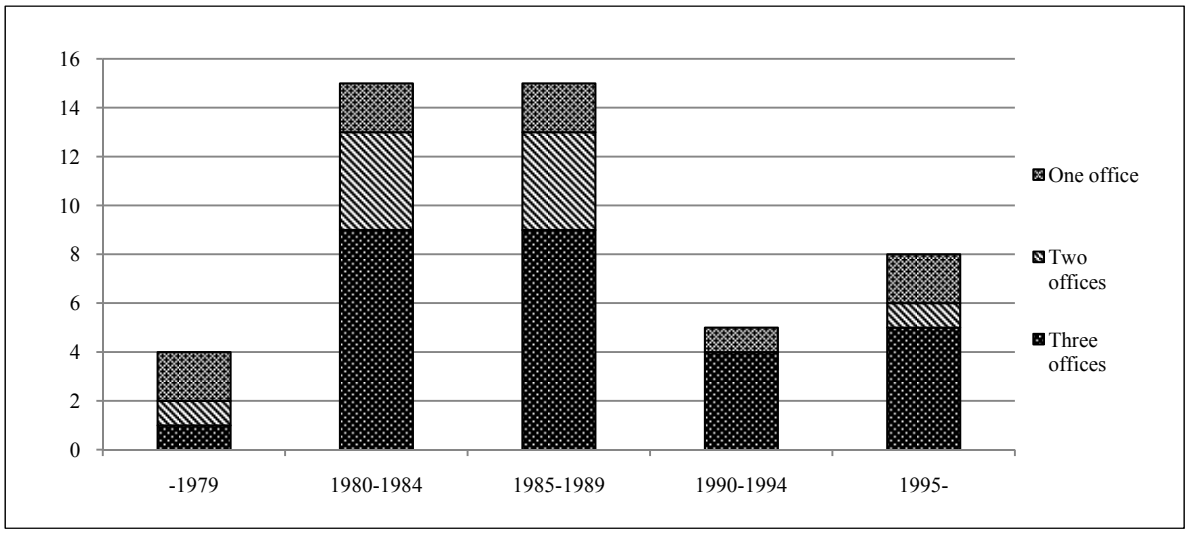
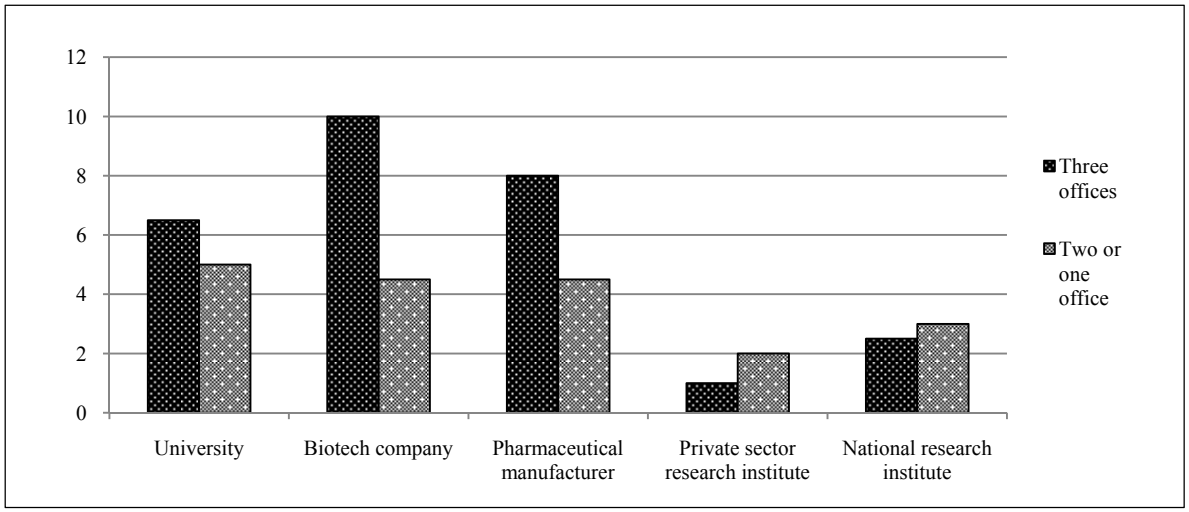


Figure 9 Trilateral application by Applicant Type



4.2 State of Registration at Trilateral Patent Offices

Table 4 shows the number of registrations and rejections at the patent offices of Japan, the United States and Europe for key patents and the associated patent families by units of patents (the entire patents in the family including the key patent)[8]. Summing the number of patents for both basic and applied fields, 28 patents for the key inventions are registered at the Japan Patent Office (the ratio relative to the number of applications is 74%) and 64 patents for the patents in the families (70%). By the EPO, there were 25 registered patents for the key patents (70%) and 26 such patents in families (51%). The overall rate of registration for applications is higher in Japan, although not in basic fields. The reasons for rejection by the EPO include "new matter" (one application), "inventive step" (two applications), and "description requirements" (one application), with one unknown reason (one application). By the JPO, eight applications were rejected for "novelty and inventive step", six applications for "description requirements", and one application for "industrial applicability", with one unknown case. Although the results are from a small sample, it is suggested that in both the JPO and EPO the specificity of the invention such as description requirements or industrial applicability played an important role for a rejection by the patent office.. As for the USPTO, although there is no public information for the patents subject to rejections until recently due to the absence of automatic disclosure, we believe that few of the patents which are granted by the JPO or the EPO are rejected by the USPTO, so that the granting of patents by the USPTO for these patent applications is certainly higher.

Table 4 State of Patent Grants by the Patent Offices of Japan, Europe and United States

		USPTO	JPO			EPO		
		Registration	Application	Registration	Rejection	Application	Registration	Rejection
Basic field	Key patent	15	12	7	0	13	9	1
	Family patent	37	17	12	0	20	10	1
Applied Field	Key patent	24	26	21	3	23	16	2
	Family patent	73	74	52	16	31	16	4

What are the mechanisms for rejection before the EPO and JPO? The effect of the opposition system which forms (and used to form) an important part of the patent system in Europe and Japan will be examined below[9]. 8 Oppositions were filed before the EPO by 2006 against 13 key patents in basic fields (60%) and 11 oppositions against 23 patents in applied fields (50%). Although the corresponding figures in Japan are considerably lower, 2 oppositions were filed against 12 key patents in basic fields (17%) and 6 oppositions against 26 in applied fields (23%). Furthermore all 5 applications rejected by the EPO were opposed and at least three applications were amended after the oppositions when the patent reached registration. Similarly, of the 16 applications subject to the final rejections in Japan, three applications were opposed. Thus, the opposition system is likely to be one reason for the lower number of (final) registrations of the patents in Japan and Europe[10].

5. Use of Continuing Applications in the United States and Related Results

Since research and development in the life sciences consumes considerable time, there is a considerable desire

by those wishing to patent the inventions to be able to add experimental data, improvements or embodiments which could not be prepared at the time of invention subsequently to the initial patent application. Thus, there is a high latent need for the provisional applications, domestic priority or continuing applications. Furthermore since there is a similarly large scope for the development and improvement of the claims after the completion of an invention, there is also likely to be a strong desire for continuing applications after the grant of the patent to a key invention. In this context, we have examined the use of continuing applications for 15 applications in basic fields in the US.

Before the grant of the key patent, there is a high frequency of the use of a continuation in part application to add new matter and such procedures involved 4 of out of 15 applications (as a frequency, 8 times), that is, in 30% of patents. On the other hand, simple continuation applications (involving no new matter) were only used in two patents (as a frequency, twice) before the grant of such patent. After the grant, 9 of 15 patents used continuation applications, with the highest frequency of usage reaching 43 times per such key patent. On the other hand, the use of continuation in part applications was relatively infrequent for 4 patents (of 9 patents).

The above results show that continuation in part applications are relatively frequently used before the grant of the key patent and continuation applications are more used after the grant. These results may be interpreted to indicate that in many cases the key patent is granted after the addition of new matter to an original invention[11]. After the grant of the key patent, a continuation application for the purpose of expanding the rights are often used.

Finally the effects of expanding rights via continuing application in the United States will be discussed. In this article, we examined the number of citations of all the descendants after the grant of the key patent.

Firstly, Table 5 shows a list of top 5 key patents in the number of (forward) citations. The number of citations for PCR methods is the highest, reaching 1,416 citations. The average number of citations for 15 key patents in basic fields is 242. On the other hand, the average number of citations for the 10 patents which made use of continuing or divisional applications was 329 (209) (the latter figure in the bracket is the average figure, excluding PCR methods for which the citation number is exceptionally high). In contrast, the average citation number for the groups of the descendants is 3195 (62). When including PCR methods, the average number of citations for the groups of descendant patents is substantially the same as that for the parent patent (thus the number of citations doubles on the average). Even when excluding PCR methods, the number of citations is 30% greater due to the use of continuing applications. Thus, the expansion of patent rights by using continuing applications after the grant of the basic patent is very important in increasing the value of the invention.

Table 5 Ranking of Top 5 Key Patent by Number of Citations

Patent	Key Patent	Descendent Patent Family
1. PCR Methods (Cetus Inc.)	1416	2566
2. DNA Chip (Affymetrex Inc.)	313	28
3. Display Method (Protein Engineering Inc.)	312	214
4. Cohen Boyer (Stanford University)	251	-
5. Genetic Cloning Method (Yale University)	221	1
5. zygote Transgenesis Method (Ohio University)	221	0
Average of 15 patents	242.3	318.5

* As at February 17, 2006 using Delphion

5. Conclusion

In this paper, we examined 47 key patents in the life sciences (19 in basic fields and 28 in applied fields) with respect to their applications to the trilateral patent offices and the status of their patent grants , the use of continuing applications in the United States for these patents and their effects.

The analysis has demonstrated that the research and development and the applications for these key patents were performed by a variety of organizations, including universities, biotech companies and large pharmaceutical firms. In addition, although initially all key patents in basic fields were filed by universities, after the 1980s, the number of patents acquired by private firms became to exceed those by universities and the research scope by private firms centering on biotech companies clearly expanded to cover upstream fields. Considering the strong effect of the profit on the entry decision by private firms, this increasing role of these private firms in the research in upstream fields is very likely to originate from the increased profitability of entry which in turn has been significantly due to increased availability of patent protection for the upstream inventions in the US. The entry of private firms is to be welcomed from an economic perspective in that it increases the level of research and development and increases the variety of research organizations in this field.

It should be noted that the rise of private firms does not mean a decrease of the role and functions of universities in life science fields. As shown by the recent invention of the iPS cell, university research has opened a frontier research field. In addition, there are many examples in which university researchers were included in the inventors of the key patents acquired by biotech companies or pharmaceutical firms (Nagaoka, Onishi 2009).

If we are to identify one source of concerns regarding the effects of patent on the research in the life science field, the majority of patents are held by private firms and furthermore only a minority of university patents received the investment of public subsidies, in spite of the fact that 70% of the key patents are related to research tools. Consequently the license conditions will be subject to the negotiations between the parties. The facilitation of licensing is important for promoting research in the life sciences and innovation in that field. It is important that research tools developed with public support would be licensed on a broad basis indiscriminately either for free or at a reasonable price. Furthermore when a number of patents are required for a research, the formation of a patent pool is important in which a package of licenses is granted for a price set for a bundle of the necessary patents.

The analysis of the applications and registrations of key patents at trilateral patent offices show that, although patent applications tend to become more global, the propensity for trilateral applications is lower for patents in basic fields. Furthermore when an application is made, the grant rate relative to patent applications is lower in Japan and Europe, which is at a level of 70% of the overall key patents. Furthermore the grant rate for the entire patents belonging to a family is even lower for them. In Europe, at least 50% of the patents granted are opposed (in Japan, this is approximately 16%) and this opposition system is an important mechanism constraining the patent rights in Japan and Europe. Consequently even for key inventions, which has contributed significantly to the development of the life sciences field, there exist cases in which the patent is not granted in Japan or Europe. This suggests that there is a considerable international difference in examination standards. The practice of patent examination in leading-edge fields (addition of new matter, grace periods, continuing applications) remains an important topic for further research.

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Notes

1 This paper relies in part on the patent research activities 2005 ("Research into the State of Patent Protection of Upstream Technologies such as Research Tools", Hitotsubashi University, Research Representative, Sadao Nagaoka)

2 As an exemption, see Webster et al. (2007) and Commissioned Research from the Japan Patent Office (International Association for the Protection of Intellectual Property Japan (2007))

3 For joint applications, a partial count was performed.

4 As will be shown later in this paper, 18 out of the 19 basic field patents are research tool patents.

5 We acknowledge the cooperation of Mr. Hajime Morioka (at the time, Deputy Manager of Ajinomoto Company Intellectual Property Center) for the identification of research tool patents. In that regard, we would like to express our heartfelt thanks.

6 See NIH Guidelines http://ott.od.nih.gov/policy/rt_guide_final.aspx. For an introduction and analysis thereof see Nagaoka (2005).

7 See http://www8.cao.go.jp/cstp/output/iken070301.pdf.

8 The definition of a patent family uses the classification of the Derwent patent citation index.

9 In Japan, the pre-grant opposition system was abolished and replaced with a post-grant opposition system in 1996. In 2004, all were integrated into trials for invalidation. The majority of the patents subject to the analysis of this paper reached the application and the registrations prior to 2004 and therefore there is almost no effect of the above institutional changes.

10 For the usefulness of opposition in the life sciences field, see Harhoff and Reitzig (2004).

11 Hegde et al. (2007) indicate that start-up companies in fields related to biotechnology use CIP applications frequently and that the value of patents using CIP applications is higher than the other patents. The results of the analysis in this paper are consistent with this evidence. In contrast, Lemely and Moore (2003) indicate that continuing applications increase the uncertainty regarding the patent enforcement against competing companies and forms a basis for submarine patents.