22 Current Situation Surrounding Patents on Genes and Proteins – Protection from the Innovational Viewpoint

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It has been suggested that the scope of rights for biotechnology-related patents are typically broad and cover a high level of accumulation of technology. For gene / protein patents, however, there has been no clarification of specifically which points have the broad scope of rights, or of the consequences of this situation. For this study the claims were analyzed for about 600 gene / protein patents registered with the Japan Patent Office (JPO) between 1996 and 2003, and the problem points were identified and assessed. Furthermore, in order to assess the impact of current gene / protein patents on life-science research in academia and industry, an analysis was made of the characteristics of inventions, from the properties of the gene / proteins to the derivation. Social systems and appropriate approach for protecting intellectual property to encourage innovation are considered and proposed.

Gene / Protein Patents and Protection from the Innovational Viewpoint

The twenty-first century may be called the Century of Biology, as major advances in life science research continue to be made around the world. The majority of the attention is on genes and proteins. In particular, the release of DNA sequence information that was decoded by the Human Genome Project completed in June 2003 sparked an international explosion of gene and protein research, as well as a rush to patent the results. However, there are many points that are not clear regarding the effects of the current patent activities and situation on life science innovation. This report considers the current status of gene / protein patents both from the perspective of intellectual property and from the scientific perspective, to consider how best to provide effective patent protection.

The world has seen gene / protein patents increasing every year. For example, according to the database Derwent GENESEQ containing information on nucleic acid and amino acid patents from the patent issuing agencies in 38 countries, the European Patent Office (EPO) and the World Intellectual Property Organization (WIPO), as of 2001 more than 2,400,000 nucleic acid and amino acid sequences were registered. Furthermore, the sequences added between 1999 and 2000 accounted for about 75% of the total number registered in the database. This illustrates the momentum of gene / protein patents. A report by the United States Patent and Trademark Office (USPTO) stated that about 6000 patents related to genetic sequences have been issued up through the year 2000, and that through the year 2002 about 1500 full-length gene patents are being established. How many gene / protein patents are being established in Japan? A search was performed at the Japan Patent Office (JPO) gazette test search page on-line using the keywords “gene” and “protein”, and the cumulative number of patents in each year was investigated. The results show that about 100 patents per year are being established in Japan, with 627 gene / protein patents established between 1996 and 2003. Since a gene / protein patent is a materials patent, it is typical for a wide range of rights to be granted, including the patents on the manufacturing method. However, there are frequent criticisms that the range of rights granted by gene / protein patents is too broad. Many infringement suits have been initiated. Specifically, in the USA there was a patent infringement suit involving Genentech and Genetics Institute over whether the range of rights for the full-length sequence for recombinant human tissue plasminogen activator (t-PA) included modified sequences. Another case involved the University of California and Eli Lilly over whether the range of rights for insulin genes obtained from rats covered all mammals, including humans. Still another suit was fought between Plant Genetic Systems N.V. and DekalbGenetics Corp. over whether a genetically-modified plant patent obtained for dicotyledons was applicable to all plants, including monocotyledons. In Japan as well, although the number of lawsuits is much smaller than in the USA, the same types of lawsuits are arising. In all these cases the problems arise from the wide range of latent rights in the gene / protein patents. In order to investigate the specific points of the gene patents for which the range of rights is broad, and the consequences, an analysis was made of the claims in the detailed specifications of the retrieved 627 gene / protein patents.

The results indicated that the typical gene / protein patent tends to be composed of claims that can be roughly categorized into the following 9 types; 1) gene sequence, 2) recombinant vectors with the gene inserted, 3), transformants (cells) having a recombinant vector, 4) amino acid sequence of polypeptides (proteins), 5) production methods for the applicable protein, 6) antibodies for

the applicable protein, 7) animals lacking the gene encoding for the applicable protein, or partially-modified animal, 8) methods for producing an animal lacking the gene encoding for the applicable protein, or partially-modified animal, and 9) a screening method for the applicable polypeptide, or for an antagonist, agonist, or ligand of the applicable polypeptide making use of an applicable portion of a peptide, or for a function modulator. This makes it clear that gene / protein patents are generally composed of many claims, including manufacturing patents for items other than the sequence, gene vectors, cells and animals with the insertion/modification/lack of the gene, and screening methods. It can be said that, perhaps, as a materials patent, the properties are well presented. However, upon close analysis of the individual claims, it is apparent that for some claims there is a potential for an excessively broad range of rights being granted, depending on how they are stated. In particular, it became clear that vague functional descriptions in the two types of claims regarding 1) gene sequences and 4) amino acid sequence of proteins have a high probability of allowing a single patent to cover many groups of genes, including gene families and alternative splicing gene products. Furthermore, with regard to 6) claims of antibodies recognizing proteins, highly-progressive monoclonal antibodies are being including within the range of rights, as well as methods that make use of antibodies, suggesting that the existence of the claims may greatly exceed the original concept of the invention. In addition, it is claimed that gene / protein patents are likely to grant a broader range of rights as a result of particular properties derived from the sequence information. This is not occurring only in Japan, but seems to be common throughout the world. One possible reason for this is that is it easy to specify a range of rights that exceeds the inventor's concept because of vague function specifications caused by inadequate claim descriptions and deficiencies in the prior art and knowledge at the time the patent application is submitted. In the past it has been pointed out that the claims for bio-related inventions are significantly broader than for other fields. It is expected that this tendency will become increasingly apparent as a result of the increases in gene / protein patents.

What kind of effect will these broad ranges of rights for gene protein patents have on innovation in the life sciences? To date there have been several reports on the relationship between the range of patent rights and innovation. Some of the topics that are still being debated include Kitch's "Prospect Theory", and Merges & Nelson's "Innovation Competition Theory". According to the Prospect Theory, the patent system is based on a prospecting system that resembles a mining method, rather than on incentives of financial reward. If broad intellectual property rights are granted to the basic patent holder, this has the advantage of allowing the original inventor to avoid redundant investment to promote further improvement of the invention in order to create business applications, and efficient innovation can be performed. In comparison, the Innovation Competition Theory is based on the premise that "for innovation, faster is better". This argument states that basic patents should not be granted a wide range of rights because incentive for later inventors to make improvements is eliminated when a broad patent is granted in a field with multi-layer technologies. However, there are certainly patterns of technological innovation in each technical field, and there should also be differences in the effect that the breadth of the range of rights will have on the innovation. Here, we will first analyze the characteristics and properties of research and development in the life sciences field, and discuss what effects there will be on innovation when a broad range of rights is granted in a gene / protein patent.

A point that is important when considering life science innovation is the fact that most of the progress in life science research is being carried out in 2 sectors, academia and industry. In academia, basic research is being advanced with the goal of uncovering truth and knowledge. In industry, application research is being conducted with the goal of creating products based on the results of the basic research. What is important here is that the life science industry has a structure based on scientific research-driven innovation. Therefore, when considering innovation in the field of life sciences, an understanding of the structure of scientific research itself is important. The key point is that the subject of scientific research in the field of life science is "life". Life consists of extensive chemical reactions. At the heart of these complicated chemical reactions are the proteins that are the main units of the gene functions. Understanding these functions has become the ultimate goal of life science research. Along with this, there is currently a major shift in life science research from genes to proteins. When considering the structure of scientific research, it has become important to have an understanding of the special characteristics of the research process and the properties of the proteins.

The most characteristic feature of proteins is that they are multifunctional. A protein is a large chemical substance with a complex tertiary structure made up of 23 different types of amino acids. There are large variations in the properties through interactions with various factors, such as metallic ions, small-compound bonding, and post-translational modification, and many functions are obtained. In this way, many proteins typically have multiple functions. From the viewpoint of an

invention, there is a high probability of many application and improvement inventions being discovered. In addition, proteins form complexes through interactions with other proteins, and a variety of functions are derived through combinations of proteins consisting of these complexes. As a result, proteins are even more likely to have properties leading to the discovery of many application and improvement inventions. Proteins also have distinctive characteristics with regard to the research process. As previously mentioned, it is rare for a protein to have a single function, and many functions are exploited through the formation of complexes. This is why complex analysis is becoming important for understanding protein functions. In the past, there have been many technical problems, and complex research and analysis has been difficult. Recently, however, there is vigorous advancement due to remarkable technological progress. When the function of a protein complex is analyzed, it is usual to first identify each of the individual proteins in the complex, and form a hypothesis about the function of the complex based on the known functions of the identified component proteins. This is why the verification research requires the use of the many proteins that form the complex, and, of course, the opportunities to use the material increase. The cumulative nature of the information also plays an important role in protein functional research. As a result of the shift in the functional analysis of proteins to complex analysis, and the fact that biological phenomena comprise enormous signal transduction pathways, protein research is becoming a research field with a higher dependence than before on the accumulation of information, technology and the materials used.

In light of these characteristics, what kind of effect does a broad range of rights for a patent have on life sciences research? First, since a protein typically has multiple functions there are many opportunities for many inventions. Therefore, the grant of a broad range of patent rights is likely to suppress progress on many applications and improvements derived from the patented gene / protein. Furthermore, since the research process has a high reliance on the accumulated materials, technology and information, if each individual protein is patented with a broad range of rights, subsequent researchers will be required to obtain many licenses. This will create unreasonable obstacles for subsequent inventors, including increases in research and development costs due to the cumulative licensing fees, and complete blocking of research and development because of licensing refusals. What is the impact of this situation on academia? In academia there is a "research freedom" that is assured, and there has not been a large effect from patents. This is largely due to Article 69, Paragraph 1 of the Patent Law in Japan, which states "The validity of the patent rights shall not extend to implementations for the purposes of testing or research". Specifically, the use of patents for the purpose of improvement or development by universities has been considered to be exempt. In addition, if a company sued a university for conducting research that did not have a goal of making a profit, there would be criticism from academia and a negative image created for the company. This is probably one of the main reasons for the tendency for companies to tacitly consent to the use of patented technology by universities. However, in recent years the situation has been changing. This is due, in part, to the fact that genes and proteins are used as research tools. The use as a research tool is not for the purpose of improvement or development, so it falls outside the scope of Article 69, Paragraph 1, meaning that there is no testing exemption, and that the patent is being infringed. Furthermore, in many cases it is difficult to differentiate use of a gene or protein as a research tool from use for the purpose of improvement or development. If there is a difference in the interpretation of the user and the patent holder there are likely to be various problems with licensing, contracts and lawsuits. As a result, the use of many genes / proteins as research tools for a lot of scientific research has become a serious issue, in which research advances are being delayed by restrictions on the use of genes / proteins due to the patents. A factor that is exacerbating this situation is the strengthening of collaborations between academia and industry in Japan. Since there is a transfer of many inventions created at universities to businesses through these collaborations, there is a growing connection between the basic research and the applications research, and research that can be considered purely academic is become rare. On top of this, since the national universities are being converted to independent administrative entities starting in April 2004, the patents are reverting to the universities. This means each university will collect royalties and conduct licensing activities at their own responsibility, as part of the university operations. Furthermore, there will be an increase in joint research between universities and companies as a means of raising funds, which will further blur the boundaries between profit and non-profit activities. Under such circumstances, it is anticipated that businesses that were previously hesitant to initiate lawsuits against universities will probably be more likely to sue for patent infringements. A good example of this is the case of the patent infringement suit brought by a U.S. company regarding some joint research by the Hamamatsu University School of Medicine and a company. Since universities will be required to carefully handle patented gene proteins in the future, it will become difficult to maintain the

research freedom achieved in academia. In addition, there is also the fear that the research results that have been published and distributed by universities in the past will now be delayed until the patent applications have been filed, eliminating the prompt sharing of information. If patents cause this loss of research freedom and prompt sharing of information, it is very likely to obstruct scientific research activities and stifle the progress of science and technology.

What is the impact on the industrial world? First, the most important difference between research in industry and research in academia is that the basis of the existence of research in industry is the pursuit of profit. Since the research results created by a company are closely related to the profits of the company, rather than quickly publishing research results companies have strong incentives to maintain the secrecy of the research results until the products are developed, or to obtain a monopoly. Therefore, if patents are not granted for genes / proteins, since the company will make it a business secret, this perpetuates exclusive use. The patenting of a gene / protein grants exclusive rights for a specified period of time, in return for which the inventor publishes the secret information. This has the important industrial strategy function of promoting further research and development by others. In the industrial world the recognition of gene / protein patents as an effective means of recovering the huge investment in research and development costs is also important. For this reason the granting of patents for gene and proteins is a major incentive for research and development in the industrial world. In this way there are large advantages for industry as a whole from gene / protein patents, resulting from the cycle of [Return on investment due to broad range of rights] → [Stimulate incentive to perform research & development] → [Patent application] → [Stimulate improved inventions through publication of information]. The question then becomes, however, are there any disadvantages? When considering this question, the important point becomes the large differences in the return on investment depending on the type of gene.

The most representative industry making use of gene / protein patents is probably the pharmaceutical industry. The ultimate goal of the pharmaceutical industry is to create technology and medications to treat disease. Therefore, genes / proteins can be roughly classified into two types according to the relationship to the disease. The first category is the type of gene / protein for which a disease occurs when the function of that gene / protein is lacking. Examples of this type are insulin, t-PA, and erythropoietin. For this reason these gene proteins are effective as a means of rapidly recovering investment costs, because the gene proteins can be commercialized as direct medications. However, this type is relatively rare, as is clear from the fact that few examples of this kind of gene protein have appeared on the market. The other category includes the genes / proteins that cause a disease through activation or expression. In these cases the gene / protein itself cannot be used as a medication. In order to establish treatment methods for these kinds of diseases the relevant complex signal transduction pathways for the gene protein must be analyzed, and the protein functional domain and tertiary structure must be studied so that an inhibitor can be developed to block the activity of the gene / protein. In addition, it is generally rare for a disease to be caused by a single gene, and in many cases diseases are multifactor, resulting from the interactions of several genes. This means that for a company to establish a disease treatment method the researchers must analyze the functions of multiple genes as well as the multiple relevant signal transduction pathways. This means that the research and development in the pharmaceutical industry can be said to have many of the characteristics of academic research. Under these circumstances, if several of the genes / proteins are already patented and excluded from being used, this can create a situation in which the research and development must be abandoned. At present the signal transduction pathway networks contributing to diseases are basically unknown. Monopolization of gene proteins through patents has the potential to greatly suppress the progress of disease research. In particular, this effect is likely to be especially large in fields such as diabetes, cancer and AIDS where the competition in research and development is very keen.

Thus far we have surveyed the current situation for genes and proteins and the impact. The area most likely to be affected by patents is the scientific research conducted in academia and industry. Especially in recent years there have been many opinion papers issued throughout the world on the problems of gene / protein patents and research freedom, raising questions about fears of limitations on scientific freedom due to the interference of gene / protein patents on the scientific research sector. Let us now consider the kinds of patent protection that will be demanded in the future. First, when considering the relationship between the range of patent rights and innovation it is important to be aware of the 2 types of competition that exist with regard to the creation of new technology. In order to promote creative activity, it is good to provide incentives through patent protection (pre-invention competition). On the other hand, it is also good for new knowledge and technology to be utilized once it has been created (post-invention competition). If there is stagnation in either the pre- or post- competition,

innovation cannot be sustained. An excessively broad range of rights in gene / protein patents promotes the pre-invention competition, but also suppresses the post-invention competition, causing progress on improved inventions to be stifled. For the fields of life science, from which improvement inventions are especially dependent on the cumulative advances, it is even more important to promote post-invention competition. Based on this, even if a broad range of rights is recognized for gene / protein patents and pre-invention competition is promoted, it is still important to stimulate post-invention competition by limiting excessively broad ranges of rights. As an adjustment mechanism for these kinds of ranges of rights, the examination department of the patent offices has such a function before the patents are granted. Therefore, there must be clearer examination criteria for inventions related to genes / proteins, which address the various problems. Specifically, with regard to antibody claims, it is important to set more limited descriptive criteria to support the development of antibody research and antibody medical treatment. With regard to gene sequence and amino acid sequence claims, there should probably be a requirement for more specific functional descriptions. However, since it is anticipated that there will be difficulties in making the correct judgments on functions at the examination stage due to the lack of prior literature, it is also important to devise a rapid and qualified review system that can restrict a broad range of rights even after a patent is granted. In addition, clarification of government guidelines to partially limit the range of patent rights is also an effective method. It is also important to make sure that not only the range of rights, but also the validity of the patent does not extend to academic research. In particular, since limitations on the use of genes / proteins as research tools may significantly obstruct the progress of scientific research, it is necessary to devise some means of handling this. Therefore, there is a need to clarify the definition of "testing and research" in Article 69 Paragraph 1 of the Patent Law. It is considered to be especially important to ensure that patent validity not extend to purely scientific research. Furthermore, in order to prevent unnecessary limitations on the use of research tools at universities after they become independent entities, it is important for the national universities to create clear patent and licensing policies with regard to research tools. In particular, for the use of research tool patents with many opportunities for use in scientific research, if it is established that there will be "freedom for non-profit research by non-profit research organizations", this will help release the scientific world from use restrictions on many genes / proteins. Furthermore, when the use is for the purpose of profit, considering the substitutability of technology in the market in the future, non-exclusive licenses or exclusive licenses (priority non-exclusive licenses) should be granted. In this way it will be possible for venture enterprises or large companies to embody the technology developed in academia, and promote a return to society. However, since there are often new functions discovered later for genes / proteins, if an exclusive license is granted, there is some likelihood that it will significantly hinder research to analyze the other functions. For this reason, for the licenses of gene / protein patents to profit-making organizations, it will probably be effective to grant exclusive rights with limitations on the function or field of application.

The sharing of intangible assets in the form of patent rights as a means of achieving the research freedom currently found in academia was mentioned previously. In the bio-fields, the distribution of tangible assets, such as genes, proteins, cells, animals, etc. is also an important factor. For gene / protein patents, even if the sequence information is published and can be used freely, preparation of the gene / protein from cells and tissue requires a lot of time and effort. In the case of a gene / protein that only appears in patients with a specific disease, obtaining the gene / protein itself can be difficult. MT (material transfer) systems to rapidly distribute such research resources and reduce the burden on researchers are expected to make a large contribution to the promotion of life science research, which requires a great deal of time for research and development. However, if each university develops their own MT system, since the user will have to investigate whether there are fees and enter agreements with several different research organizations, this could become a complicated and troublesome system. Therefore, as each research organization develops an MT system, it will be important to build a system that allows all the information to be searched at one time, and contracts to be made easily. In 1996 the US National Institute of Health (NIH) began negotiating agreements called Material CRADA (Cooperative Research and Development Agreements). Under this system in exchange for allowing the NIH to use samples (genes, proteins, cell stock, genetically-modified animals) that they own, businesses are given priority in the licensing of patent inventions that are created from the research using the samples. As a result, since the scientific research agencies can freely use the research samples held by business, it is possible to achieve a greater research freedom for public research agencies. Furthermore, since this increases the opportunities to promptly return the patents arising at the scientific research agencies to industry, it is possible to achieve an efficient cycle of basic and application research. However, the effectiveness of the Material CRADA

in the U.S. is largely due to the fact that the host NIH is an enormous research agency. When a business enters an agreement with the NIH, the research samples owned by the business are freely utilized by the 27 research organizations that compose the NIH, and there is no need for the business to make agreements with multiple research organizations. In comparison to the U.S., the scale of one research organization in Japan is small. Even if the Material CRADA was introduced, there would be limitations and only some research organizations would be able to use the research samples from business. The distribution of the research samples of business to the academic world is an important factor related to the advancement of research and development. A future MT system for Japan is an issue that should be carefully considered, including promotion of cooperation with several universities.

We have discussed the effect of a broad range of rights for a gene / protein patent, and policies to resolve the problems. Since the life science field is particularly susceptible to the impact of patents, it is probably necessary to establish a new upper-level agency to coordinate policy research / establishment and to deal with the issues from both a scientific technology and an intellectual property perspective. The Council for Science and Technology Policy established within the Cabinet in January 2001 is expected to be instrumental in filling this role. Their current focus is on the design and planning of science and technology policy. In the future there are expected to be specialty divisions created to handle the overall coordination, including intellectual property, such as license agreements for academia and industry, the formation of patent pools, technology transfer policies for universities, and how to handle arbitration, which should promote and facilitate the utilization of patent technology for scientific research.