

8 Study on the Ways of Protection of Post-Genome Research Products

In line with the recent progress of post-genome research, patent applications relating to its products are being filed in a manner unknown in the past, and it has been desired to promptly establish standards for their patentability.

Therefore, this study firstly attempted to clarify technologies subject to patents by reviewing the elementary technologies of protein's three-dimensional structure analyses and bioinformatics of which are the core technologies in the post-genome research, in consideration of their application to drug development and diagnostic methods. Subsequently, with an eyes on the distinctive feature of these technologies; information and its processing methods, this study extracted and discussed legal issues concerning to major types of claims likely to be made (including reach-through claims^(), function inferential type claims, pharmacophore type claims^(*) and virtual screening (in silico screening) type claims), and advised various problems and their solutions including the relationship between enablement requirement and the degree of function analysis, clarity of claims, and the relationship with the examination guidelines of computer software-related inventions.*

I Introduction

The research in the field of life sciences is moving from genome research focusing on the gene level in the direction of what is called post-genome (following genome analysis) research focusing on information relating to protein.

Although most of scientific products can be applied to industrially applicable inventions, in the case of the life sciences, there are many cases in which academic research products in particular are directly linked to industry, such as a certain protein which can be used directly as a pharmaceutical. Thus, many investors for researches in the field of life sciences expect patent rights to be granted for those products.

Under these circumstances, since patent applications relating to post-genome research products having their characteristics in information and its processing methods are being filed one after another, and much more variety of information is contained in these applications than those in the past, the handling of which under the Patent Law is becoming issues. These issues can be specifically divided into the following three issues.

The first issue is how to handle the "identification" of the products (substances) and methods utilize the above mentioned information. The second issue is the extent to which the value of "inferential" obtained from the information using bioinformatics technology can be emphasized as compared with actual experimental results. Finally, the third issue is how to handle patent applications for

information itself or inventions that can only be characterized by information.

II Protein's Three-Dimensional Structure Analyses and Bioinformatics - Products, their Value and Potential -

1 Protein's Three-Dimensional Structure Analyses Technology and Structural Proteomics Project

Proteins are only able to demonstrate their functions as a result of adopting a three-dimensional structure in which a primary sequence of amino acids is spatially folded over on itself. Thus, protein's three-dimensional structure analyses technology is extremely useful for inferring the function of that protein. When considering proteins related to disease, protein's three-dimensional structure information leads to elucidation of the molecular mechanism of the disease, and can be used as basic information that is directly connected to treatment. Moreover, protein's three-dimensional structure information also serves as important information for the development of pharmaceuticals that regulate the function of proteins related to a disease state. In actuality, together with the formation of the International Structural Genomics Organization (ISGO) that has already begun as a result of numerous public subsidies, numerous venture corporations, including Structural GenomiX (SGX),

(*)1 Referring to claims that are described so as to contain all possible products and so forth obtained through the use of basic research means.

(*)2 Pharmacophore typically refers to the representation of the structure characteristics essential for indicating a certain pharmacological activity using multiple functional groups and their spatial positional relationships.

Syrrx and Astex, have been established to serve in core industries in the field of drug development, and are beginning to become increasingly active.

At present, the main method for analyzing protein's three-dimensional structure is X-ray crystal structure analyses. The next most commonly used method is nuclear magnetic resonance (NMR). Methods other than these are quite specific, examples of which include electron beam diffraction, electron microscopy and neutron beam crystal analyses. In addition, recent progress has also been made in the area of computerized three-dimensional structure prediction technology.

Due to the progress of protein's three-dimensional structure analyses technology, although three-dimensional structure information has been obtained for numerous proteins, this information is the result of gathering the individual research results obtained in accordance with the respective interests of each research group. On the other hand, the objective of the genome project is to comprehensively decipher the entire genetic repertoire in genomes along with their sequences irrespective of the interests of individual researchers. Therefore, if the three-dimensional structure information of proteins, which are the products of these genes, is also similarly covered in an efficient manner independent of individual research, it will result in the construction of an extremely useful infrastructure for protein function research. Consequently, the concept of structural proteomics is to promote the systematic, comprehensive and high-throughput determination of three-dimensional structures in an organized manner, and this concept is progressing rapidly through various international projects.

Examples of important application issues regarding high-throughput three-dimensional structure determination include: (1) screening and design of bound low molecular weight compounds having novel functions (such as the search for lead compounds in new drugs development), (2) modification of the molecular functions of proteins by amino acid residue substitution (protein engineering), and (3) elucidation of the effects of amino acid residue substitution accompanying cSNPs on phenotype such as disease susceptibility and drug responsiveness, along with the contribution to tailor-made treatment based on that.

In addition, examples of potential application fields to new drugs development using the above protein's three-dimensional structure analyses technology include: (1) inference of molecular function in terms of functional genomics, (2) protein function analyses by homology modeling and virtual screening of drug candidate compounds, (3) searching for lead compounds in new drugs development, (4) docking studies with metabolic

enzymes and so forth for ADME improvement, (5) modification of protein molecular function by primarily amino acid residue substitution, (6) elucidation at the molecular level of the effects of amino acid residue substitution accompanying cSNPs on phenotype such as disease susceptibility and drug responsiveness along with the contribution to tailor-made treatment based on that, (7) design of backup compounds having completely new structures, and (8) new drug applications.

On the basis of these, in the case of considering protecting patents of protein's three-dimensional structure analyses technology, it will be necessary to adequately discuss such issues as (1) the validity of so-called reach-through claims that claim rights extending to downstream research products, (2) utility (proof of function) and (3) the need for protection of three-dimensional structure information itself (these issues are discussed in detail in the following chapter III mainly from the viewpoint of requirements for patentability).

2 Bioinformatics

Bioinformatics originally referred to laboratory data management systems for handling DNA or genome information, tools for analyzing structure characteristics based on DNA base sequences, and that database environment. More recently however, bioinformatics has come to be interpreted in a broader sense, being based on molecular biology, information processing, statistics and mathematics, and referring to not only DNA sequence analysis, but also analytical software for information such as literature information processing. Moreover, in the broader sense, there are many cases in which it refers to the entire spectrum of information processing involving the analysis of information relating to biology, medicine and pharmacology, ranging from protein structure analyses to compound searches. Thus, its purpose is also changing to the efficient organization of vast amounts and numerous types of biological information, and the clarification of the biological or medical significance of that information through its analyses.

Although researchers have become able to access large amounts of information with the establishment of an information technology (IT) environment, as a result of conversely requiring information processing abilities that far exceed the limits of human ability, it has become necessary to rely on computers^(*). It is here where bioinformatics is truly needed, and is also the reason why bioinformatics has grown rapidly over the past ten years during which large amounts of DNA data have been analyzed experimentally.

Examples of the characteristics of bioinformatics

(*) T.K. Attwood & D.J. Parry-Smith, *Introduction to Bioinformatics* (Addison Welsley Longman, Edinburgh Gate, 1999).

include: (1) obtaining of comprehensive analyses results, (2) easy comparison with other information, (3) public disclosure of a considerably large amount of information (although the undisclosed newest data of private corporations also exists), (4) addition of integrated annotation, (5) obtaining of comprehensive information that links various databases, and (6) various service and business forms, including software, hardware, onsite access and the Internet.

Examples of the elementary technologies of bioinformatics include: (1) prediction of the gene regions and transcription control regions within all DNA, (2) comparative genome analyses accompanying function elucidation of the genes of model organisms and laboratory animals, (3) population genetics analysis of DNA using single nucleotide polymorphisms (SNP), (4) expression of genes at the RNA level by DNA chips, gene networks and gene searching, (5) prediction of protein three-dimensional structure from genomes, (6) elucidation of the relationship between ligands and protein three-dimensional structure, (7) analyses of the interactions between proteins, (8) comprehensive pathway analyses focusing on the correlation between substances and biological functions, and (9) simulation of cell functions focusing on the time-based changes in the amounts of various proteins. In addition, an example of a technology considered to be important in the future is the extent to which information analyses and experimental analyses, which have each developed individually, can be fused. Moreover, fusion with nanotechnology is leading to expectations not only related to simply functions of the living body, but even to the potential for artificial life through the use of machines or through the fusion of the living body and machines.

Important issues that must be confronted by these elementary technologies include: (1) the establishment of a database environment capable of organizing and integrating large amounts of data, (2) improvement of calculation algorithms for achieving greater efficiency of prediction and analyses of exon portions and transfer control regions, (3) construction of gene network information systems for gene expression profile analyses, (4) improvement of calculation techniques and physical models for application to configuration structure at the molecular and atomic levels, dynamics simulations and the molecular orbital method, and (5) introduction of statistical mining techniques for efficiently obtaining highly accurate results from limited clinical data when using population genetics techniques.

In the case of considering protection of bioinformatics patents on the basis of these, although other biological data is to a certain extent dependent on experimentation, it is necessary to consider that in the case of

bioinformatics, it has the characteristic of being unable to distinguish the source of the results (information) obtained, since information processing is frequently used. In addition, accompanying the progress of technology, numerous completely new findings that far exceed the level of common sense of the past will be discovered or are expected to be created, in the case of bioinformatics, when a result is obtained that is completely different from anything in the past. However, it is difficult to determine whether it is the result of an artificial defect in a computation model, due to error that enters when making calculations, or truly a significant, new discovery. Thus, this will become the issue with respect to how the ambiguity is to be treated in terms of the Patent Law.

III Discussion of the State of Protection of Products - Issues Relating to Requirements for Patentability

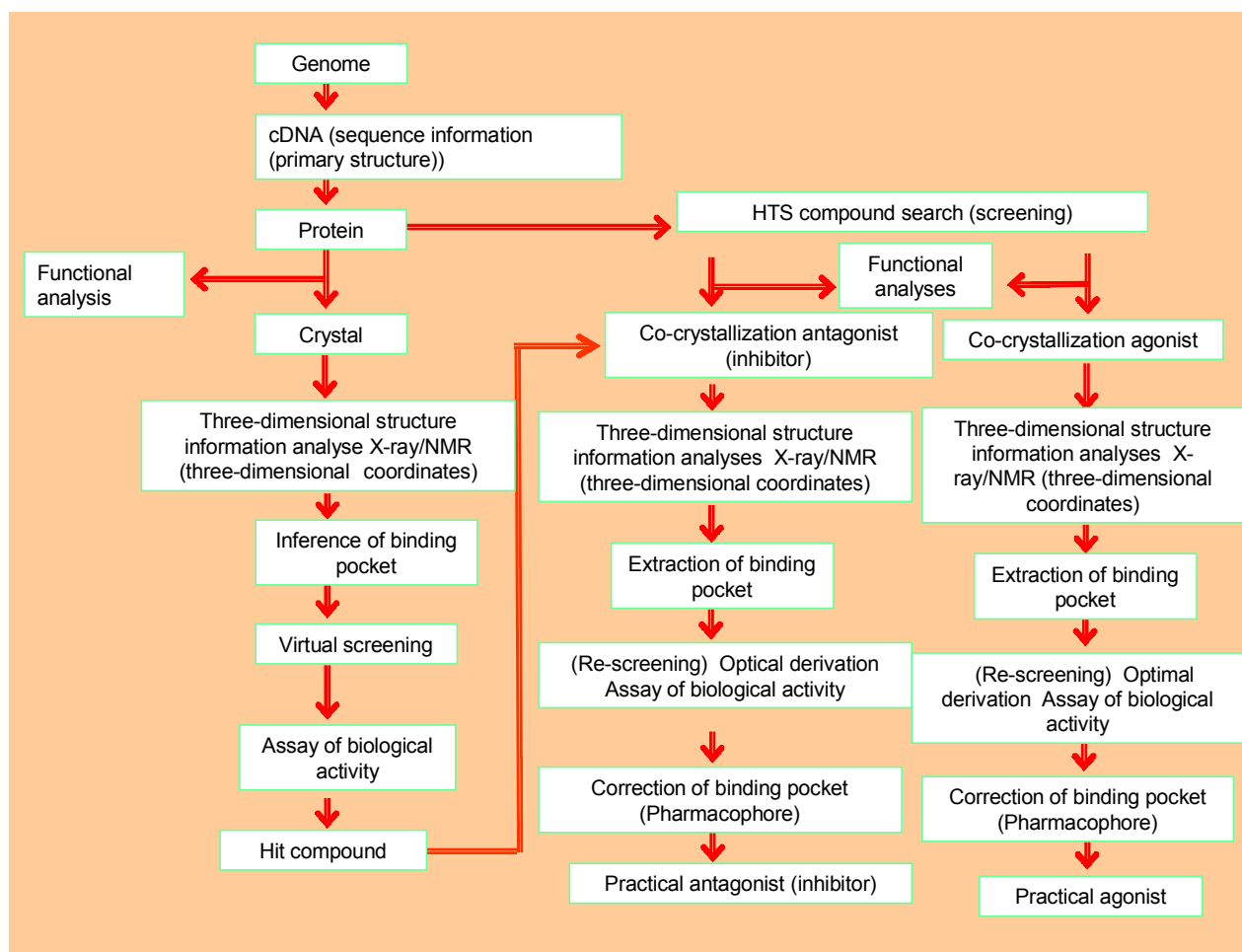
A Transforming Products into Claims

1 Claims of Protein's Three-Dimensional Structure Information, New Drugs Development and their Products

In line with the progress of the above-mentioned protein's three-dimensional structure analyses technology, one of the results anticipated by industry is first the searching for molecules that bind with target proteins. Namely, this involves searching for molecules for regulating biological functions, and with respect to the pharmaceutical industry, refers to new drugs development, and more specifically, to the development of new enzyme inhibitors as well as the development of new receptor agonists and antagonists. Secondly, the progress of protein's three-dimensional structure analyses technology is expected to contribute to the modification of proteins into more useful molecules. The properties of a protein can be changed by converting an amino acid at a specific site or by interchanging the structure of a specific domain, making it possible to, for example, extend the half-life of the protein in the body. Thirdly, another example of the utilization of this technology involves contributing to the diagnosis and prediction of diseases.

A schematic diagram of the actual manner in which new drugs development using protein's three-dimensional structure information proceeds is shown in Fig. 1 from the time a gene is obtained until a chemical substance in the form of a pharmaceutical is developed using the crystal structure.

Fig. 1 Flow of Genome Drug Development Research Using Three-Dimensional Structure Information



In line with the progress of genome-related sciences, once the base sequence of a gene is first determined, the amino acid sequence of the corresponding protein is estimated followed by function analyses of that protein. In the post-genome era, even under conditions in which function is unknown, since the form (structure) of the target molecule can be determined, it becomes possible to focus on those molecules that bind with that structure, thereby making it possible to derive and focus on more suitable compounds. In actuality however, there are numerous hurdles to be overcome. To begin with, at the stage in which function has yet to be adequately determined, a study must be conducted to determine which protein is to be the target protein to confirm that the target protein is suitable for the purpose of treatment (also referred to as target validation). Moreover, even if the target protein has been determined, there are frequently cases in which the protein has more than one three-dimensional structure, at least consisting of that when biological activity is demonstrated and that of a precursor or inactive form when there is no activity, and these structures are often quite different. In addition, the protein's three-dimensional structure may undergo considerable distortion depending on the

properties of the molecules that bind to the protein. Thus, even when a certain protein has been selected and its three-dimensional structure has been elucidated, this does not immediately signify the development of a new drug. Drug development takes considerable time in order to satisfy all requirements placed on pharmaceuticals relating to a high degree of safety and so forth.

The following provides an introduction to examples of patent claims that contained protein three-dimensional structures while focusing primarily on previously disclosed patents.

(1) Claims relating to a protein crystal itself:

These refer to claims that only specify a "protein sequence or name and its crystal", claims that indicate a crystal lattice, namely the packed state of molecules, and claims that are represented with parameters obtained from X-ray crystal diffraction ($1/2Q$ values), three-dimensional coordinates of results of interpreting diffraction images and X-ray diffraction images themselves.

(2) Claims describing active sites, or with respect to binding pockets, amino acid residues involved with a binding site:

These refer to claims that specify the "coordinates of amino acid residues" or "mutual distances", as well as those that use molecules that

bind to active sites to specify “molecules having specific functional groups capable of hydrogen binding with amino acid residues by indicating those amino acid residues at the binding site with coordinates”, “distances between specific functional groups of binding molecules” and “allowed spatial coordinates of a binding pocket”.

(3) Claims that apply the above in the form of “a method for identifying binding molecules using structure coordinates”, “a treatment method using compounds specified with structure coordinates”, “a computer system for displaying molecules that incorporates three-dimensional structures”, and “a method for inhibiting enzyme activity characterized by three-dimensional structure”.

(4) Claims such as “a recording medium capable of being read by a computer for recording atomic coordinates” and “database that accumulates compound information”.

(5) Claims relating to compounds which, instead of analyzing three-dimensional structure directly, are specified by synthesizing a large number of bound molecules (to a specific protein) and then superimposing those molecules to derive a structure (pharmacophore) (a detailed description of the patentability of pharmacophore-type claims is provided in the following Section B, Part 2 of Chapter III).

(6) Use (treatment agent) claims in which specification by three-dimensional structure has been added to structure specification by an extremely broad Markush form.

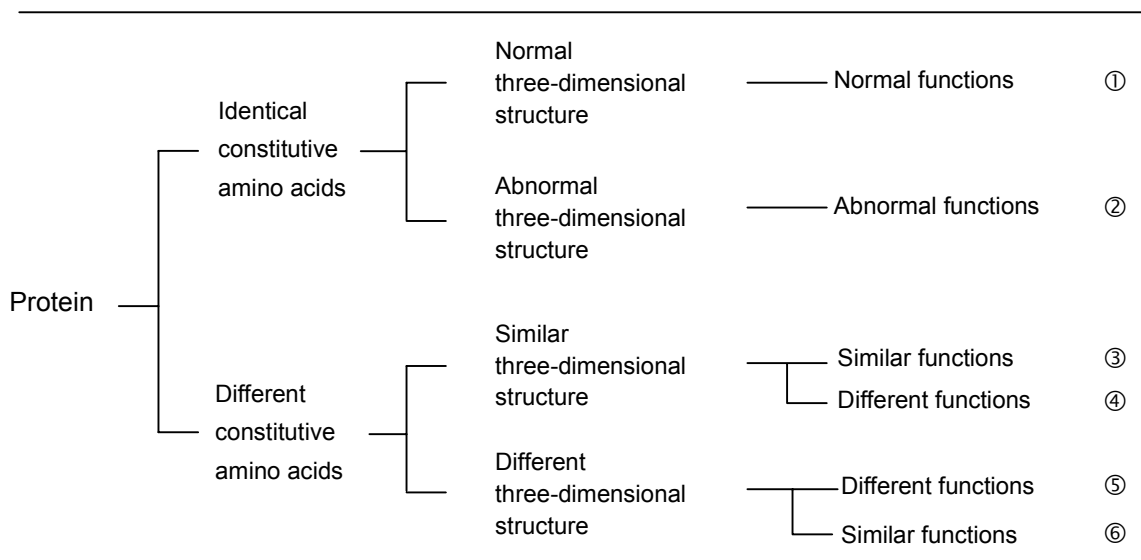
2 Three-Dimensional Structure Information and its Application to Protein Determination and Diagnostic Methods

A portrayal of the relationship between protein three-dimensional structure and its function can be broadly classified into ① through ⑥ of Table 1.

When inferring the function of a protein from its three-dimensional structure, caution is required with respect to ②, ③ and ④ in Table 1. In the case of ③, the resulting protein group is inferred to have a similar three-dimensional structure and similar function even though the constitutive amino acids differ. At the present stage, although it is possible to make a general classification based on the characteristics of three-dimensional structure such as proteins belonging to the super family of serine proteases and seven transmembrane receptor proteins, it is difficult to determine their actual pharmacological function. Moreover, it is also necessary to consider that it has been recently shown that proteins cannot be accurately determined based only on information relating to the primary structures or three-dimensional structures, etc. of immature proteins, and that information including the three-dimensional structure of the mature protein following translation is indispensable for determining the function of that protein. In addition, in the manner of ④ in particular, it is also necessary to consider that it is possible for proteins to have different functions despite having similar three-dimensional structures. Thus, although it is possible to a certain extent to determine a protein from its three-dimensional structure, verification of that protein through scientific experimentation is also important. Furthermore, there are hardly any proteins known to be applicable to the example of ⑥ in which they have different three-dimensional structures but demonstrate similar functions.

In addition, since the definition of similarity between structure and function as previously discussed in the field of genome science is extremely ambiguous, there is a need for studies on evaluation criteria for similarity between structure and function in order to evaluate requirements for patentability of proteins for which function has been

Table 1 Protein Three-Dimensional Structure and Function



inferred. One area of potential interest is whether or not it can be treated in the same manner as the sequence homology of genes and proteins.

In recent years, diseases have been demonstrated to exist that are based on metabolism being inhibited due to differences in protein's three-dimensional structure even though there are no differences in the constitutive amino acids after going through the normal protein processing pathway (conformation diseases). Examples of such diseases include Prion disease and Alzheimer's disease, and such diseases fall under example ② described above.

In the future, it is predicted that conformation diseases based on the formation of abnormal three-dimensional structures due to misforming or the formation of different molecular complexes due to abnormal association of protein molecules, even though protein components are normal, will be discovered, and that their three-dimensional information will be accumulated. Examples of diagnostic methods that have been developed which use this three-dimensional information include positron emission tomography (PET), fluorescent staining assay, immunoassay and electron microscopic assay, and their utilization is expected to contribute to preventive medicine. Naturally, new types of patent applications are also expected to appear relating to treatment methods, preventive methods and diagnostic methods of conformation diseases.

Similar to genetic diagnoses, it is necessary to accumulate normal three-dimensional structure information as well as abnormal three-dimensional structure information of various disease-related proteins in order to enable diagnosis of protein three-dimensional structure. The use of this information is expected to lead to the development of low molecular weight compounds and protein chips, etc. that demonstrate affinity for proteins having abnormal three-dimensional structures.

B Discussion of Requirements for Patentability of Claims

1 Requirements for Patentability of Reach-Through Claims and Function Inferring Claims

New drug development research prior to the genome era primarily adopted an approach based on a target for which the disease mechanism had been determined, and screening for compounds having the potential to become pharmaceuticals was primarily carried out through so-called wet experimental systems both *in vitro* and *in vivo*. However, in the post-genome era, due to the proliferation of bioinformatics technology, the process itself of new drug development research has changed since proteins capable of becoming the targets of drug development are identified both in

large quantities and rapidly.

Accompanying this change in the process of new drug development research, claims of patent applications in pharmaceutical-related fields have also clearly undergone a change. In addition to patent applications comprising compound claims of the conventional Markush form, a large number of patent applications have come to be filed that describe screening method-specific claims (said to be a kind of reach-through claim) so as to include all compounds screened by the use of screening methods.

Further, patent applications have also come to be seen that described so-called function inferential type claims which infer the function of a protein and so forth based only on its similarity to the sequence or three-dimensional structure of a known protein, etc.

The following indicates examples of typical claims that can be considered in the case of specifying the three-dimensional structure of a novel receptor protein having the potential of becoming a target of new drug development, while also providing a discussion of the patent requirements of reach-through claims and function inferential type claims.

[Examples of Claims]

Claim 1 A receptor R represented by the atomic coordinates of Fig. 1.

Claim 2 A screening method for a compound which activates or inhibits the receptor R wherein the screening is carried out by using the atomic coordinates of the receptor R represented in Fig. 1 for identifying the compound.

Claim 3 A compound obtained by the screening method as claimed in claim 2.

Claim 4 A receptor R activator or inhibitor (XX therapeutic/preventive agent) comprising the compound obtained by the screening method as claimed in claim 2 as an active ingredient.

(1) Novelty

The atomic coordinate data in claim 1 is a "means of specifying a product", and in the case an identical three-dimensional structure is not known, claim 1 is considered to have novelty. However, this novelty is questioned in the case the protein itself in the form of receptor R is known by specifying its amino acid sequence and so forth. In general, as long as the subject of the claim is a "product" in the form of receptor R, claim 1 is not considered to have novelty if its three-dimensional structure is simply specified with atomic coordinates.

On the other hand, in the case of analyzing the three-dimensional structure of a known protein based on its crystals, novelty can be considered to be recognized in the case structure differences between the known state and the analyzed state are clarified by the applicant, and it is clearly shown to be a different entity.

In addition, it is necessary to create a standard

for assessing identity between three-dimensional structures. This is because, since assay values naturally change according to the conditions and are accompanied by error, acknowledgment of the range considered to be substantially identical presents an issue, and results having different levels of analyses accuracy (also referred to as resolution) present an issue as to whether they should be considered to be different in terms of the Patent Law. In this case, the latter applicant generally must demonstrate that the three-dimensional structure relating to the invention of that applicant has significant structure differences as compared with the known three-dimensional structure (of the prior application) even when considering error and conditions.

Since claim 3 is a claim that relates to a novel substance, it is necessary that it is a claim which does not include known substances. In the case of a substance claim that merely specifies only a screening method, however, there is a high probability of a known compound being included, thereby making it difficult to satisfy novelty. Thus, in order for novelty to be acknowledged for claim 3, other requirements that specify a compound other than the screening method are thought to be required.

(2) Inventive Step

In the case a certain three-dimensional structure of receptor R is already known, and the claimed three-dimensional structure of receptor R is different from that, the inventive step of claim 1 presents an issue. In general, however, since a person with ordinary skill in the art would not be able to easily obtain a protein having the three-dimensional structure of claim 1 simply by using ordinary skill, claim 1 can be determined to have an inventive step provided the effect obtained by that protein could not be easily predicted by a person with ordinary skill in the art.

At present, a three-dimensional structure can be predicted if there is 25-30% sequence homology. Thus, in the case there are only substantial differences in three-dimensional structure information, it is possible to apply criteria that assess the predictability of a three-dimensional structure or the potential for acquiring three-dimensional structure information by using, for example, sequence homology between proteins. However, as is described in the previously mentioned Table 1, since three-dimensional structure information itself does not unconditionally lead to a specific, concrete application, adequate examination regarding the application of such criteria is required.

With respect to other claims, it seems that there are more cases where their relationships with enablement requirement, clarity, etc. are questioned than cases where their inventive steps are questioned on their own.

(3) Enablement Requirement and Clarity

If utility (industrial applicability, enablement) is fulfilled with respect to claim 1, it will be reasonable to consider that the utility of claims 2 through 4 would also be fulfilled. With respect to claim 1, the specific function of receptor R is generally required to be clarified on the basis of verification or scientific evidence. However, in the case the three-dimensional structure of receptor R has been obtained, questions arise concerning the case of searching a database^(*4), comparing with the three-dimensional structures of other receptors and then inferring its function. When three-dimensional structure were attempted to be compared for two proteins for which homology of their amino acid sequences was not known, it is certain that there are many cases in which the structures are extremely similar and molecular functions are conserved^(*5). However, as is described in the previously mentioned Table 1, it is necessary to note that just because three-dimensional structures may be similar, this does not necessarily mean that functions are also similar.

Furthermore, since it is not possible for a method that identifies agonists or antagonists of a receptor having unknown functions to satisfy the requirements of utility, in case the utility of claim 1 is not satisfied, the utility of claims 2 through 4 is considered not to be satisfied, either.

If the utility of claim 1 is satisfied, and a description is provided in the specification to an extent that allows a person with ordinary skill in the art to obtain receptor R with reproducibility, then the enabling requirement and clarity are considered to be satisfied.

With respect to claim 2 and the following claims, it is considered to be reasonable to refer to the results of the Trilateral Patent Office Comparative Research Report on Reach-Through Claims of November 2001^(*6). According to this report, although the screening method of claim 2 is not necessary required through its examples, with respect to claims 3 and 4, all three patent offices have indicated that in the case of simply being a screening method, claims of a specified compound and an application having that compound for its active ingredient do not satisfy the enablement requirement and clarity. Here, as a means of avoiding reasons for rejection with respect to

(*4) An example of a publicly disclosed database is the Protein Data Bank (PDB; <http://www.rcsb.org/pdb/>). A total of 17,082 structures were registered in this database as of January 15, 2002.

(*5) Shigeyuki Yokoyama: "Kozou Genome Kagaku ga mezasu Mono (Objectives of Structural Genome Science)", Jikken Igaku (Experimental Medicine), Vol. 19, pp. 930-933 (2001).

(*6) http://www.jpo.go.jp/saikine/tws/report/report_start_page.htm

enablement and clarity, both the Japanese and European Patent Offices require the claims to be restricted to compounds of the range described in the specification. Namely, in contrast to denying the validity of reach-through claims themselves that have been specified with a screening method only, the US Patent and Trademark Office indicates a method of avoiding rejection other than claim restriction. The US Patent and Trademark Office has stated that it is possible to avoid reasons for rejection with respect to enablement and clarity by submitting objective evidence that demonstrates that a receptor agonist specifically disclosed in the specification is that which represents the structure of a compound that is detected or identified by the claimed method. Although it is believed that the submission of such objective evidence would not be easy, it is worth noting that at the US Patent and Trademark Office, that the validity of specified claims themselves of a screening method only are not denied, namely there is the possibility of compound claims specified with only a screening method being valid.

2 Patent Requirements of Pharmacophore Claims

A pharmacophore refers to an essential structure characteristic for indicating certain pharmacological activity, and due to the characteristic, drugs are able to interact with target proteins by a specific mechanism. A pharmacophore is typically represented by multiple functional groups and their spatial positional relationships.

Pharmacophore models of ligands have recently been determined from the results of X-ray crystal structure analysis of complexes of target proteins and ligands, and examples have been reported of the discovery of leading drug candidate compounds by screening three-dimensional databases *in silico*. The ultimately obtained chemical substances that are useful as drugs are one of the important products of genome structure scientific research.

Then, applications have come to be observed that claim all possible drug candidate compounds which can be obtained as a result of searching three-dimensional databases using pharmacophore models. These claims are considered to be a type of reach-through claim (refer to the above Section B Part 1 of Chapter III), and result in the potential for various problems in terms of the Patent Law.

The following indicates probable examples of claims based on the discovery of pharmacophore models.

(Claim Examples)

Claim 1 A pharmacophore model (and recording

medium on which it is recorded).

Claim 2 A screening method of a drug candidate molecule using the pharmacophore model.

Claim 3 A compound specified by the pharmacophore model (and compound obtained by the screening method of claim 2).

Claim 4 A compound specified by the combination of the pharmacophore model and pharmacological effect (and an agonist/antagonist specified by a pharmacophore model).

Claim 5 A composition for treating disease A containing a compound specified by the pharmacophore model.

(1) Patentability of Claims 1 and 2

The advocacy of a highly reliable pharmacophore model involves the providing of novel technical findings that are useful as a template for screening or designing a drug candidate molecule. However, from the viewpoint of patentability, the discovery of a pharmacophore model is that of the causative relationship between the structure characteristics of a drug molecule and the pharmacological effect, and is understood to be the providing of a law of nature itself or a mere presentation of information relating to a correlation between structure and function. Thus, a pharmacophore model itself (the above claim 1) is the “creation of a technical idea utilizing a law of nature”, which is not included in the concept of an invention in the legal sense. The transformation of a pharmacophore model into a tangible object by recording onto a recording medium is not still considered to be using a law of nature, and is therefore understood not to be included in the concept of an invention in terms of the Patent Law. Accordingly, an object like that described in claim 1 is not protected under the current Patent Law.

On the other hand, a screening method of a drug candidate molecule that uses a pharmacophore model (claim 2) is recognized to exhibit utilization of a law of nature, and can be therefore patented under the Patent Law. However, novelty is denied in the case the only difference with a known virtual screening method is the pharmacophore model (data contents)^(*), and there are also opinions that such methods should not be protected.

(2) Patentability of Claim 3

(i) Clarity

It is considered to be relatively easy for a person with ordinary skill in the art to judge in advance whether or not a certain specific compound has physicochemical structure features described in the claims (multiple functional groups and their spatial positional relationships), namely whether or not that compound is contained in the scope of claims of a compound specified with a pharmacophore model. Thus, with respect to this point, the

(*) “Tokkyo Jitsuyoshinan Shinsa Kijun (Patent and Utility Model Examination Guidelines)” Part VII, Chapter 1, Computer Software Kanren Hatsumei (Inventions Related to Computer Software), 2.3.6(2).

description of the claims may be able to be said to be clear on the basis of claim 3 of the above Section B Part 1 of Chapter III in which a compound is specified by a screening method only.

However, the description of a claim has important significance with respect to comparing with the prior art on the basis of that description, and examining patent requirements such as novelty and inventive step. In the case of being specified with a pharmacophore, it should be noted that a comparison with the prior art is generally very difficult at the examination stage.

In addition, in the case the specification of a compound is not completed only with the physicochemical structure characteristics of the compound itself, but rather is made with the manner of association with the corresponding target protein by introducing the three-dimensional structure of the binding pocket and so forth of that protein, similar to claim 3 of the above Section B Part 1 of Chapter III in which the compound is specified with a screening method only, it would be judged that a person with ordinary skill in the art would not be able to know in advance whether or not the specific compound is contained in the scope of the claim, thereby causing the description of the claim to lack clarity.

(ii) Enablement Requirement

A compound specified with a pharmacophore model can be said to be such that its structure is partially defined. However, since there is normally no specification of other portions that are not essential for pharmacological activity, when considering the entire compound itself, it cannot be said to be structurally defined. Thus, similar to claim 3 of the above Section B Part 1 of Chapter III in which the compound is specified with a screening method only, whether or not that compound can be produced and used by a person with ordinary skill in the art presents a problem.

In contrast to “screening” being an objective action between the compound and receptor, the objectivity of the person advocating the screening can be included in a pharmacophore model. Thus, some form of support relating to the reliability of the pharmacophore model (such as the indication of experimental data that clarifies the acquisition pathway) is considered to be required.

In addition, in the case of being specified by a pharmacophore model, there is also the problem the manner in which it is shown that all compounds included in claims can be produced. Even if typical production examples are described in the detailed description of the invention of the specification for several of the compounds included in the claims, the range of compounds that are confirmed to be able to be produced based on the preparation examples and the range of compounds represented by a pharmacophore model will not coincide.

Be noted that the essence of a chemical

substance invention is conventionally considered to be the providing of a chemical substance that is novel and useful, or in other words, can be used industrially, and in order for the validity of this to be recognized, that compound is confirmed by a chemical structure and so forth in the specification, is indicated as being able to be produced, and although authentication is not required that is as severe as in the case of use inventions, the disclosure of reliable utility (industrial applicability) is required. As long as an invention is claimed in the form of a compound (chemical substance), it is considered to be reasonable that such requirements be levied in order to be granted a patent. In cases where descriptions of examples of actually producing representative compounds included in the claims or the intended utility of compounds having a pharmacophore model that are adequate for convincing a person with ordinary skill in the art are not contained at all in the specification, in addition to the problem of satisfying the enablement requirement, it would be valid to examine that such an invention would inherently not be considered to be an invention that can be used industrially.

(iii) Novelty and Inventive Step

In general, since it is difficult to compare compounds specified by a pharmacophore model with compounds specified by a conventional chemical structure, and there are many cases in which applications are filed without adequately examining whether or not known compounds are included, there is an extremely high probability that known compounds are included in the scope of the claims.

(3) Patentability of Claims 4 and 5

With respect to pharmacophore models, a claim is considered to have patentability if it is like claim 5 represented in the form of a so-called use claim in the manner of “A composition for treating disease A comprising a compound specified by a pharmacophore model.” When considering that a pharmacophore model is found as a result of discovering a correlation between a certain structure and pharmacological effect, describing both structure characteristics and pharmacological activity (use) in the claims in some form is believed to be appropriate for clarifying the essential portion (technical idea) of the invention and making the scope of rights the scope recognized by the inventor.

On the other hand, specification by pharmacological effect is also thought to be allowed with respect to claim 4 as well on the premise that the compound included in the claims be a novel compound. At present, if a description of “a compound X having carcinostatic properties” states that carcinostatic properties are a unique characteristic of a specific compound X, a description of “having carcinostatic properties” is

not useful in specifying that substance, and this claim is understood to be referring to “compound X” itself at the examination level^{(*)8}. Although a compound specified by a pharmacophore model is only partially structurally defined, since the overall structure is not specified (and the essence of this conversely lies in not deciding the overall structure), there may be compounds that do not have the intended pharmacological effect among the wide range of compounds included in the claims. Thus, the specifying of a specific pharmacological effect may be able to be considered to be useful in demarcating the scope of an invention.

3 Patentability of Virtual Screening Inventions

The following provides an example of a claim of a virtual screening method (*in silico* screening method).

(Claim Example)

“A screening method for cancer therapeutic drug candidates comprising: a step of inputting the atomic coordinates of a specific three-dimensional shape to first storage means, a step of inputting the atomic coordinates of a candidate compound are input to second storage means, and a step of carrying out the selection of a compound that binds to a pocket by XXX by YYY means.”

Inventions related to computer software in Japan are defined as “inventions that require software for the enablement of the invention” in “Computer Software-related Invention Examination Guidelines”. According to this definition, in addition to conventional computer software-related inventions, the inventions of various fields, including business model inventions that include financial methods and bioinformatics inventions that include virtual screening, are also included in computer software-related inventions provided they require software. There are therefore cases in which the above virtual screening inventions would be judged to have patentability under the “Computer Software-related Invention Examination Guidelines”.

According to these Examination Guidelines, in the case the difference between a claimed invention and a known cited invention lies only in the contents of the data, the novelty of the invention is not acknowledged^{(*)9}. In other words, if only the data contents represented by the atomic

coordinates in the above claim are novel, there is the possibility of the claim being judged as lacking novelty.

However, as is described in the above Section B Parts 1 and 2 of Chapter III, when considering that data contents themselves that are represented by atomic coordinates and so forth are unable to obtain patent protection, there is also the opinion that the patentability of virtual screening claims should be recognized in order for a person who has invested in an analysis of three-dimensional structure to continue to be able to proceed with development or obtain a financial return by licensing to a suitable business partner. Consequently, it will be necessary to examine the distinction between virtual screening inventions worthy of patent protection and those that are not considered to be such inventions within the current legal framework by perceiving the essence of virtual screening inventions from various viewpoints, including not only the conventional approach of expanding the range of protection, but also with respect to utility (enablement, industrial applicability), novelty and inventive step^{(*)10}.

IV Conclusion

1 Protein Three-Dimensional Structure Information and Bioinformatics

In the structural genome project, research products are aggressively publicity, and structure information obtained by government institutions is disclosed six months after that information has been acquired. The wide-ranging publication of research products itself is also desirable based on the need for publicity of government institutions. However, since this structure information has value as an intellectual property, adequate caution is required in the handling of that structure information.

More specifically, caution is required with respect to (1) confidentiality until publication of three-dimensional structure information, (2) handling of the products of function analyses research using three-dimensional structure information, and (3) protection of the three-dimensional structure information itself as an intellectual property.

(*)8) supra note 7 - Examination Guidelines, Part II, Chapter 2, Shinkisei Shinposei (Novelty and Inventive Step), 1.5.2(2) ②Example 1.

(*)9) supra note 7

(*)10) A specific proposal regarding this distinction, which states that such a distinction can be made by dividing computer software-related inventions into inventions whose technical essence utilizes laws of nature and those that do not, by focusing on the importance of using laws of nature in virtual screening inventions, is described in detail in a report of this study published by the Institute of Intellectual Property entitled, “Post Genome Kenkyu Seikabutsu no Hogo no Arikata ni kansuru Chousakenkyu Houkokusho Study on the Ways of Protection of Post Genome Research Products”, pp. 130-140, Institute of Intellectual Property, 2002.

Although cautions relating to the above (1) and (2) are generally forced to be left to accommodation through contracts, with respect to (3), it is possible to attempt to protect three-dimensional structure information in the form of a trade secret provided confidential protection is maintained.

In addition, since the requirement of protecting three-dimensional structure information as a trade secret is no longer required to be satisfied after that information has been published, it may be possible to protect that information in the form of a database. In Japan, although it is possible to protect information having creativity as a database (information selection or organizational structure) under Copyright Law as a copyright, since databases merely consisting of the collection of information are not recognized to have creativity and are not qualified as being copyright, they are not protected under Copyright Law. However, since the latter database also has value as a property, it is necessary to examine legislation for protecting the information itself.

With respect to bioinformatics, technology development is proceeding at a rapid pace, and at present it is considered to be difficult to infer the functions and three-dimensional structures of proteins using bioinformatics technology alone for fields where there is currently little accumulation of empirical knowledge in particular. However, since it is becoming easier to infer the functions and three-dimensional structures of proteins due to progress in the development of technology, it is necessary to adequately consider the relationship between requirements for patentability and this progress in the development of technology.

2 Problems Relating to Requirements for Patentability

(1) Patentability of Proteins Specified with Atomic Coordinates

It is necessary to adequately examine the validity of applying the conventional approach to the patentability (novelty, inventive step) of proteins specified with atomic coordinates.

It is necessary to examine novelty with respect to ① a determination of novelty based on the difficulty in determining the identity of three-dimensional structures, and ② the approach to novelty in the case where a protein itself is known by a primary sequence and so forth.

In addition, it is also necessary to sufficiently examine inventive step with respect to ① a determination of inventive step in the case where the three-dimensional structure of a protein is novel, ② determination requirements for inventive step including demonstration of safety, differences in pharmacological effects and so forth, and ③ the relationship with a description requirement of claims.

(2) Requirements for Patentability of Compounds Specified by *In Silico* Screening Methods

With respect to the patent requirements of compounds specified by *in silico* screening methods, in addition to it being necessary to adequately examine requirements for claim description from the viewpoint of clearly eliminating known compounds and specifying compounds having specific activity, it will be also necessary to adequately examine the enablement requirement of the relevant claims when considering requirements for claim description.

(3) Requirements for Patentability of Function Inferring and Structure Inferring Claims

Among the requirements for patent relating to function inferring or structure inferring claims in the case of protecting the products of post-genome research in the form of patents, those requirements that present the greatest issues are utility (industrial applicability, enablement) and clarity.

More specifically, it is necessary that adequate examinations be conducted with respect to numerous viewpoints including ① the standard of function inferential when determining utility, ② the degree of a use by elucidation of three-dimensional structure, ③ the approach to utility within the context of bioinformatics, ④ the relationship between technical progress, utility and inventive step, and ⑤ the relationship between homology and structure homology with enablement and clarity. Similarly, it is also necessary to examine the inventive step of function inferring and structure inferring claims from various viewpoints.

(4) Patentability of Pharmacophore Claims

Pharmacophore refers to structure characteristics required for indicating specific pharmacological activity. In the Patent Law, with respect to inventions that simply present information, patentability of them is denied. Consequently, even if an invention is a screening method for drug candidate molecules that uses a pharmacophore model, in the case where the only difference with a known virtual screening method is the pharmacophore model (data contents), there is believed to be the possibility of patentability being denied. However, since it is a fact that data itself in the form of a pharmacophore model is recognized to have value as a property, it is necessary to examine not only the potential for protection based on a patent, but also protection as another intellectual property.

In addition, since there is also the possibility of known compounds and compounds that cannot actually be made being included in claims of compounds having a pharmacophore, it will be necessary to adequately determine the manner in which claims are described from the viewpoints of clarity, enablement and so forth.

(5) Protection of “Jouhou (Information)”

Since the products of post-genome research frequently have the form of “Jouhou (information),” it will be necessary to discuss the protection of “Jouhou (information)” under the Patent Law in the broad sense.

Since numerous “software” is included in the products of post-genome research, there are those of the opinion that, rather than searching for ways to protect that software in the form of a “thing” or “process”, it would be reasonable to protect the “Jouhou (information)” itself under the Patent Law by perceiving it as an intellectual property. Consequently, it will be necessary to discuss how the protection of “Jouhou (information)” should be from a wide range of viewpoints.

More specifically, it will be necessary to determine the matter of requiring a revision of the system in the form of expanding the range of coverage of protection under the Patent Law in the form of a medium to long-range issue. However, at least for the time being, it will be necessary to conduct further studies in terms of operation, including the drafting of guidelines and the production of case studies and so forth with respect to the manner in which claims are described.

In addition, since the concept of “Jouhou (information)” includes various types of information such as that equivalent to information or knowledge and that merely equivalent to data, rather than considering general protection of all information, it will be necessary to conduct specific studies on how the protection should be in accordance with the nature of each piece of information. Furthermore, when discussing the protection of “Jouhou (information)” itself, it will be necessary to examine the validity of directly applying practices based on the conventional assumptions of “hardware” to patent requirements such as “industrial applicability” and “utility.”

Moreover, since the products of post-genome research are also frequently in the form of “databases,” in addition to examining the present state and problems associated with protection of “databases” under the Copyright Law and protection as a “trade secret” under the Unfair Competition Prevention Law, it will be also necessary to examine the need for a “database” protection law.

(6) Issues with Scope of Patent Rights and Enforcement of Patent Rights

There are also issues with respect to the scope of patent rights and the enforcement of those rights in the case of protecting the product of post-genome research with a patent.

For example, since the effect of patent rights differs between a production process and a simple process in the Patent Law, depending upon whether an *in silico* screening method is considered to be a production process or a simple process, the effect of

patent rights (whether or not it extends to a thing) is made different. Although screening methods are typically considered to be simple processes, when considered in this way, questions arise regarding the efficacy of patents of screening methods from the viewpoint of enforcement of the rights. Although it is not necessarily a problem to consider screening methods to be production processes from the viewpoints of the nature and effect of screening methods, it will be necessary to determine the scope of patent rights from the viewpoint of effectively exercising those rights with respect to the ease of establishing infringement and so forth.

In addition, since there is concern over creating considerable impairment of research activities as a result of granting patent protection when protecting the products of post-genome research in the form of patents, it will be also necessary to make a comprehensive determination from various viewpoints regarding problems relating to the scope of patent rights and the exercising of those rights, including the interpretation of “experiment and research” defined in Article 69 of the Patent Law.

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