

ANNEX 2: Comments of the JPO

Trilateral Project WM4 Comparative studies in new technologies

Theme: Comparative study on
“protein 3-dimensional (3-D) structure related claims”

1. Introduction

As more 3-D structures are elucidated, such as the 3-D structures of proteins, it is expected that patent applicants will file increasing numbers of applications claiming inventions relating to such 3-D structural information. Given this expectation, the three Offices agreed to conduct a comparative study to enhance mutual understanding concerning the examination of 3-D structure related claims.

2. Questions Common to All Cases

The answers to the following questions are intended to set forth the perspective of each Office in addressing the patentability of 3-D structure related inventions. Please provide an answer to each question.

1. Are the following claims directed to patent eligible subject matter? If not, explain why and answer questions 2-4 below to the extent possible. If yes, answer questions 2-4 below.
2. Do the following claims satisfy the industrial applicability or utility requirements? If not, explain why.
3. Do the following claims satisfy clarity, enablement, support and written description requirements? If not, explain why.
4. Do the following claims satisfy novelty requirement and the inventive step or nonobviousness requirements? If not, explain why.

5. If there are any comments on the kind of evidence, argument, and/or claim amendment that may overcome any rejection for failure to satisfy the requirements of 1-4 above, please state them.

3. Provision

Japanese Patent Law Sect. 2(1): Definition of Invention

(Guidelines Part II, Chap. 1, 1.) Patent Law Section 2(1) defines a statutory invention as a highly advanced creation of technical ideas utilizing a law of nature.

Japanese Patent Law Sect. 29, First Sentence: Industrially Applicable Inventions

(Guidelines Part VII, Chap. 2, 1.3.1) "Inventions ... whose utility is not described in a specification or cannot be inferred, do not meet the requirements set forth in the first sentence in Section 29(1) of the Patent Law."

Japanese Patent Law Sect. 29(1): Novelty

Any person who has made an invention which is industrially applicable may obtain a patent therefor, except in the case of the following inventions:

- (i) inventions which were publicly known in Japan or elsewhere prior to the filing of the patent application;
- (ii) inventions which were publicly worked in Japan or elsewhere prior to the filing of the patent application;
- (iii) inventions which were described in a distributed publication or made available to the public through electric telecommunication lines in Japan or elsewhere prior to the filing of the patent application.

Japanese Patent Law Sect. 29(2): Inventive Step

Where an invention could easily have been made, prior to the filing of the patent application, by a person with ordinary skill in the art to which the invention pertains, on the basis of an invention or inventions referred to in any of the paragraphs of Subsection (1), a patent shall not be granted for such an invention notwithstanding Subsection (1).

Japanese Patent Law Sect. 36(6): Clarity of Claims

(Guidelines Part VII, Chap. 2, 1.1.1) "According to Section 36(6)(ii) of the Patent Law, the invention for which a patent is sought shall be clear, therefore, scope of claim shall be described so that an invention is clearly identified on the basis of statements of each claim."

Japanese Patent Law Sect. 36(4) :Description, Enablement

(Guidelines Part VII, Chap. 2, 1.1.2.1) "Section 36(4) of the Patent Law states that "the detailed description of the invention shall be stated...in such a manner sufficiently clear and complete for the invention to be carried out by a person having ordinary skill in the art to which the invention pertains." ...For an invention of a product, the definition of "being able to

carry out the invention" is to make and use the product..."

4. Cases

Case 1: 3-D structural data of a protein per se

[Claim 1]

A computer model of protein P generated with the atomic coordinates listed in Fig. 1.

[Claim 2]

A data array comprising the atomic coordinates of protein P as set forth in Fig. 1 which, when acted upon by a protein modeling algorithm, yields a representation of the 3-D structure of protein P.

[Background]

- The specification asserts that protein P is a novel protein.
- The description gives experimental data and explains that the protein, when active, lowers blood pressure.
- Protein modeling algorithms are well known in the art.
- The description also gives the atomic coordinates of protein P, and asserts these coordinates would be useful in *silico* (computer-assisted) screening methods.

[Prior Art]

- A search of the prior art did not identify any references that teach or suggest protein P.

Claim 1

Statutory Invention - No

Our Guidelines state that a mere presentation of information (where the technical feature is found only within the contents of the information, and the main purpose of the invention is to present such information) without any technical feature in the presentation or the means or method of presentation, is not an "invention" in terms of Section 2 and 29, first sentence ("a creation of technical idea utilizing a law of nature").

In the present case, the claimed computer model is a mere presentation of information, and it is neither directed to a presentation of information with some technical feature in the presentation or the means or method of presentation, nor is it directed to a data structure which concretely realizes information processing using hardware resources. Thus, the present claim is not a statutory invention.

Industrial Applicability, Clarity, Enablement, Novelty and Inventive Step – N/A

Claim 2

Statutory Invention - No

The claim is directed to a “data array.”

Data arrays are logical structures of data defined by the interrelationship among data elements. In order for a data array to be a statutory invention, it must concretely realize information processing using hardware resources.

In the present case, the data array acted upon by a protein modeling algorithm is itself a data element and not a statutory invention.

In addition, there may be cases where data is a statutory invention if it is featured by a data structure (logical structure of data defined by interrelationship among data elements) and information processing by the data structure is concretely realized using hardware resources.

Industrial Applicability, Clarity, Enablement, Novelty and Inventive Step – N/A

Clarity – No

Claimed “data array” is not considered as data having a structure by which information processing by software is concretely realized using hardware resources. The invention cannot therefore be defined as an invention of a product.

In this case, the category of the invention for which a patent is sought is unclear, or an item that falls under neither products nor processes is stated in a claim.

Japanese Patent Law Section. 2 breaks inventions down into products, processes, and processes which produce products. Therefore an invention that falls under neither products nor processes violates the clarity requirement (Section 36(6)(ii) of the Patent Law).

Case 2: Computer-readable storage medium encoded with structural data of a protein

[Claim 1]

A computer-readable storage medium encoded with the atomic coordinates of protein P as shown in Fig. 1.

[Background and prior art]

Same as in Case 1.

Claim 1

Statutory Invention - No

Our Guidelines state that a mere presentation of information (where the technical feature is found only within the contents of the information, and the main purpose of the invention is to present such information) without any technical feature in the presentation or the means or method of presentation, is not an "invention" in terms of Section 2 and 29, first sentence ("a creation of technical idea utilizing a law of nature").

Industrial Applicability, Clarity, Enablement, Novelty and Inventive Step – N/A

Case 3: Protein defined by its tertiary structure

[Claim]

An isolated and purified protein having the structure defined by the structural coordinates as shown in Fig. 1.

[Background]

- The description sets forth the 3-D structure of protein P, including the coordinates of the amino acid side chains, the source organism for protein P and the molecular weight of protein P.
- The description gives experimental data and explains that administering protein lowers blood pressure.
- The structural coordinates were derived from a solution phase protein by NMR at 0.2nm resolution.

[Prior art]

- A search of the prior art did not identify any references that teach or suggest the 3-D structure of protein P.
- The prior art teaches a protein from the same source organism having the same specific function and approximately the same molecular weight.

Statutory Invention - Yes

A protein is a statutory invention.

Industrial Applicability – Yes

A protein that lowers blood pressure is considered to be an "industrially applicable invention".

Clarity, Enablement - Yes

Novelty, Inventive Step - No

Our opinion is that merely defining a known protein by its 3-D coordinates does not make it novel.

Since the prior art teaches a protein from the same source organism having the same specific function and approximately the same molecular weight, there is a reason to suspect that the claimed protein would be identical *prima facie* with the protein of the prior art. As long as there is no other difference between the two, a notice of refusal would be sent based on lack of novelty.

On the other hand, if the applicant is able to submit enough evidence that the claimed protein is different than the protein described in prior art, the reason for refusal will be cleared.

Furthermore, if a claimed protein, having the same amino acid sequence as a known protein, has a different 3-D structure compared to the known protein (e.g., abnormal prion protein compared to a normal prion protein), the former is considered novel.

In such a case, however, we believe the applicant would rather define the protein by its amino acid sequence and physical properties other than its structural coordinates.

Case 4: Crystals of known proteins

[Claim]

A crystalline form of protein P having unit cell dimensions of $a=4.0\text{nm}$, $b= 7.8\text{nm}$, and $c= 11.0\text{nm}$.

[Background]

- A nucleotide sequence encoding the amino acid sequence of protein P was known in the art.
- The description explains that the activity of protein P was previously known to result in lowering blood pressure.
- The inventors assert they have newly produced a stable crystalline form of protein P.
- Protein P in crystalline form is inactive.
- The description gives experimental data with explanations of how to make the crystals.
- Common prior art methods used in protein P crystallization were unsuccessful, and there was clearly a technical difficulty in producing the claimed crystalline form of protein P.

[Prior art]

- There was no prior art reference teaching or suggesting a crystal of protein P or related proteins.
- There was no prior art reference concerning the crystallization method.

Statutory Invention - Yes

A protein and its crystalline form are statutory inventions.

Industrial Applicability – Yes

There was no violation of industrial Applicability requirement.

Clarity – Yes

Enablement - Yes

Even if protein P that is able to lower blood pressure in active form is inactive in crystalline form, it is considered that the protein is able to be restored to the active form by well known art.

Protein P in crystalline form can be made with the description.

Therefore, the claim meets enablement requirement.

Novelty, Inventive Step – Yes

The protein crystal is considered novel, since it differs its form and structure from the protein itself (a compound). Since the prior art does not teach any crystalline forms of protein P or any methods to obtain the claimed crystalline protein P, and since common methods used in protein crystallization were unsuccessful, the crystal involves inventive step.

Case 5: Binding pockets and protein domains

[Claim 1]

An isolated and purified molecule comprising a binding pocket of protein P defined by the structural coordinates of amino acid residues 223, 224, 227, 295, 343, 366, 370, 378 and 384 according to Figure 1.

[Claim 2]

An isolated and purified polypeptide consisting of a portion of protein P starting at one of amino acids 214 to 218 and ending at one of amino acids 394 to 401 of protein P as set forth in SEQ ID NO: 1.

[Background]

- Protein P is a previously known protein whose amino acid sequence was also previously known.
- The description explains that administering protein P was previously known to result in lowering blood pressure.
- The inventors assert they have newly discovered that the active residues in the binding pocket of protein P consist of amino acids 223, 224, 227, 295, 343, 366, 370, 378 and 384.
- The description teaches that the possible peptides that begin with any amino acid from position 214 to 218 and end with any amino acid from position 394 to 401 of SEQ ID NO: 1 are protein domains that are able to fold into an active binding pocket of protein P. This ability was confirmed by X-ray diffraction data.
- The description also indicates that the above domain alone shows a significantly higher signaling activity compared to the whole protein P when activated by a natural ligand of protein P.

[Prior art]

- Prior art suggesting the position of the binding pocket of protein P was not found.
- Prior art suggesting a protein structure domain containing said binding pocket was also not found.

Claim 1

Statutory Invention - Yes

A protein and its parts are statutory inventions.

Industrial Applicability – Yes

A protein and its parts are able to output a signal lowering blood pressure in an active form.

Therefore, the claim meets industrial applicability requirements.

Clarity – No

Except for binding pockets, concrete conformation of the molecule is unclear. Therefore, the claim does not meet clarity requirements.

Enablement - No

“A binding pocket” will not fold into its proper 3-D structure unless you have the whole protein or a whole structural domain (meaning that you have to “cut” the amino acid sequence at the right place in order to have a structural domain that folds into the cor-

rect 3-D structure). Protein P in crystalline form can be made with the description. It is not possible to make the real compound defined by the structural coordinates of said amino acid residues with referring to the description. Therefore, the claim contains parts that does not meet enablement requirement.

Novelty, Inventive Step – No

The protein P in the prior art is a compound comprising the claimed “binding pocket”. Any distinction between the claimed invention and protein P are not made.

Claim 2

Statutory Invention - Yes

A polypeptide is a statutory invention.

Industrial Applicability – Yes

A protein and its portion are able to output a signal lowering blood pressure in an active form.

Therefore, the claim meets industrial applicability.

Clarity – Yes

Claimed invention is a polypeptide defined by a structure containing specific amino acid sequence. Therefore, the claim does not meet clarity.

Enablement - Yes

Polypeptides are protein domains that can fold into an active binding pocket of protein P. By expressing the said polypeptide, a person skilled in the art can get easily protein which has active binding pocket.

Therefore, the claim meets enablement.

Novelty, Inventive Step – Yes

We can understand the difference between the claimed polypeptide and the whole protein P. Thus the claimed invention is considered novel.

Prior art does not teach any polypeptide which consists of a specific part of protein P, or methods to specify parts of the polypeptide, and the claimed polypeptide shows a significantly higher signaling activity compared to the whole protein P.

Therefore, the claimed polypeptide meets involves inventive step requirement.

Case 6: *In silico* screening methods directed to a specific protein (1) [Claim 1]

A method of identifying compounds that can bind to protein P, comprising the steps of:
applying a 3-dimensional molecular modeling algorithm to the atomic coordinates of protein P shown in Fig. 1 to determine the spatial coordinates of the binding pocket of protein P; and

electronically screening the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket to identify compounds that can bind to protein P.

[Background]

-Protein P is a previously known protein whose amino acid sequence was also previously known.

-The description explains that the activity of protein P was previously known to result in lowering blood pressure.

-The description gives the atomic coordinates of protein P (raw data of the protein itself without any ligands bound to it) but does not describe the position of its binding pocket.

-Instead, the specification gives general information on programs which predict the binding pocket of proteins (which often give a relatively large number of amino acids related to the binding) and general information on commonly used *in silico* screening programs.

-Methods of peptide modeling and binding using rational drug design are well known in the art.

-There was clearly a technical difficulty in obtaining the claimed atomic coordinates of protein P.

-The specification speculates that by using the binding pocket prediction program and *in silico* screening program, the person skilled in the art can identify compounds binding to said protein.

-The description gives no working examples of identifying compounds using the atomic coordinates of protein P.

[Prior art]

-No prior art suggesting the 3-D coordinates of protein P was found.

-The prior art teaches computer programs that predict the binding pocket of proteins.

-Several *in silico* screening programs using the predicted binding pocket of proteins are also previously known.

Claim 1

Statutory Invention - No

To be qualified as "a creation of technical ideas utilizing a law of nature," a claimed in-

vention must be concrete enough to accomplish a certain purpose.

In case where the claimed invention is considered to be computer software-related inventions where information processing by software is not concretely realized by using hardware resources, the claimed invention does not constitute "a creation of technical ideas utilizing a law of nature."

Therefore, the claim is not a statutory invention.

Industrial Applicability – N/A (Yes)

Claimed invention is a method of identifying compounds that bind to protein P and may normalize blood pressure.

Therefore, the claim meets industrial applicability.

Clarity – N/A

Enablement - N/A

Novelty, Inventive Step – N/A (No)

If the claimed invention is considered a software-related invention it only differs from the prior art by the limitation based on Figure 1 coordinate data.

Case 7: *In silico* screening methods directed to a specific protein (2)

[Claim 1]

A method of identifying compounds which can bind to protein P by comparing the 3-D structure of candidate compounds with the 3-D molecular model shown in Fig. 5 which comprises the following steps:

- (1) ...
- (2) ...
- (..) ...
- (n) ...

(The 3-D molecular model of Fig. 5 presents the positions of heteroatoms in the amino acids constituting the binding pocket of protein P (i.e., amino acids 223, 224, 227, 295, 343, 366, 370, 378 and 384) wherein said heteroatoms can form hydrogen bonds with hydrogen bonding functional groups in a candidate compound.

Steps (1) through (n) describe a data processing method in which

a) the coordinate data of the 3-D molecular model of Fig. 5 is input in a data structure such that the interatomic distances between the atoms of protein P are easily retrieved, and

b) the distances between hydrogen-bonding heteroatoms of different candidate compounds and the heteroatoms that form the binding pocket in the 3D molecular model are compared thereby allowing the identification of those candidate compounds which would theoretically form the most stable complexes with the 3-D molecular model binding pocket of protein P, based on optimal hydrogen bonding between the two structures.)

[Claim 2]

A compound identified by the method of claim 1.

[Claim 3]

A database encoded with data comprising names and structures of compounds identified the method of claim 1.

[Background]

- Protein P is a previously known protein whose amino acid sequence was also previously known.
- The description explains that the activity of protein P was previously known to result in lowering blood pressure.
- The description gives the atomic coordinates of protein P as a co-crystal with its natural ligand, and gives a logical explanation that the active residues in the binding pocket of protein P consists of amino acids 223, 224, 227, 295, 343, 366, 370, 378 and 384.
- The description explains how the 3-D molecular model of Fig. 5 includes the 3-D structure of the binding pocket of protein P.
- The description gives working examples of the claimed method in which a number of compounds are identified.
- The description also shows experimental data of the actual binding affinities of the compounds identified. According to the data shown, the person skilled in the art can understand that the claimed method can actually identify a number of compounds which bind strongly enough to protein P so that some biological effect can be expected.

[Prior art]

- No prior art suggesting the 3-D coordinates of protein P was found.
- The prior art teaches *in silico* screening programs comparing the 3-D structure of candidate compounds with a 3-D molecular model of possible ligands.
- The method of storing coordinate data to optimize the interatomic distance informa-

tion is taught by the prior art.

Claim 1

Statutory Invention - Yes

To be qualified as "a creation of technical ideas utilizing a law of nature," a claimed invention must be concrete enough to accomplish a certain purpose.

If the claimed invention is considered to be a computer software-related invention and where information processing by software using hardware resources is not concretely described, the claim is a statutory invention.

Industrial Applicability – Yes

Claimed invention is a method of identifying compounds that bind to protein P and may normalize blood pressure.

Therefore, the claim meets industrial applicability requirements.

Clarity – Yes

Enablement - Yes

The description gives an evidence that compounds identified by using the atomic coordinates bind strongly enough to protein P so that some biological effect can be expected

Therefore, the claim meets enablement requirement.

Novelty, Inventive Step – No

The claimed invention is considered a computer software-related invention with the technical feature of an information processing method by software.

The difference between the prior art and the claimed invention as a whole is limited to the 3-D molecular model shown in Fig. 5.

Data that does not alter the processing method should be considered as mere contents. Technical specifications cannot be affirmatively inferred even if the limitation of a 3-D molecular model is added to the claim.

Claim 2

Statutory Invention - Yes

A compound is a statutory invention.

Industrial Applicability – Yes

It is understood by the description that the claimed compound heightens or lowers

blood pressure.

Therefore, the claim meets industrial applicability requirements.

Clarity – No

Claimed invention is a compound defined by only identification method.

At the time of filing, a person having ordinary skill in the art is not able to conceive a concrete chemical compound that has activating abilities, even taking common general knowledge at the time of filing into consideration.

Therefore, the scope of the invention is unclear.

Enablement - No

Accordingly a specification without examples nor contents of key information that makes it possible to obtain active ingredients of such compounds requires a trial and error effort beyond what is expected of a person having ordinary skill in the art.

Novelty, Inventive Step – N/A

Claim 3

Statutory Invention - No

Where a database is encoded with data comprising names and structures of compounds, the feature of the database resides solely in the content of the information, and the main object of the database is to present information.

The claim is neither directed to a presentation of information with a technical feature in the presentation or the means or method of presentation, nor is it directed to a data structure which concretely realizes information processing using hardware resources.

Therefore, the claim is not a statutory invention.

Industrial Applicability – N/A

Clarity – No

Same as in Claim 2.

It is unclear whether “database” means data itself or a data processing system.

Enablement - No

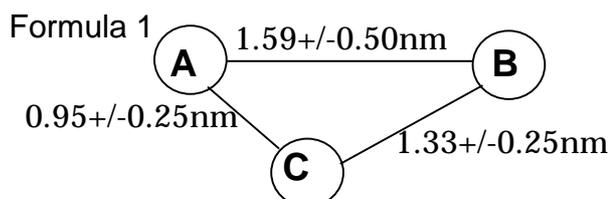
Same as in Claim 2.

Novelty, Inventive Step – N/A

Case 8: Pharmacophores and pharmacophore - defined compounds (pharmacophores defined by the distance between atom- groups)

[Claim 1]

A pharmacophore having a spatial arrangement of atoms within a molecule defined by the following formula:



in which A and B both represent an electron donor atom, C represents a carbon atom that is part of a hydrophobic group, and the distances represent the distances between the centers of the respective atoms.

[Claim 2]

An isolated compound or its salt defined by the pharmacophore in claim 1.

[Background]

- A pharmacophore is a description of a generalized concept of molecular features in terms of information on spatial arrangement of chemical elements (e.g. hydrophobic groups, charged/ionizable groups, hydrogen bond, donors/acceptors, and substructures) that are considered to be responsible for a desired biological activity.
- Protein P is a previously known protein whose amino acid sequence was also previously known.
- The description explains that the activity of protein P was previously known to result in lowering blood pressure.
- A search of the prior art did not identify any references that teach or suggest the 3-D structure of protein P.
- The description teaches that the pharmacophore shown in formula 1 was evaluated from the 3-D structure of the ligand binding pocket of protein P.
- The description also teaches that the structure of the ligand binding pocket of protein P was estimated using conventional methods.
- The description also describes that a novel ligand was designed based on the pharmacophore, and shows experimental results that the ligand binds to the protein with relatively high affinity.

[Prior Art]

-A document showing an agonist of protein P was found.

Claim 1

Statutory Invention - No

A pharmacophore itself is a mere display of information, thus not a statutory invention (the only technical features are found within the contents of the information). Refer also to Case 1.

Industrial Applicability – N/A

Clarity – N/A

Enablement - N/A

Novelty, Inventive Step – N/A

Claim 2

Statutory Invention - Yes

A compound and its salt are statutory inventions.

Industrial Applicability – Yes

It is comprehended that the claimed compound is made use of heightening or lowering blood pressure by the description.

Therefore, the claim meets industrial applicability.

Clarity – No

Claim 2 lacks clarity since it is not clear to a person having ordinary skill in the art what sort of compound would fall under the claim.

Enablement - No

a) Since formula 1 merely defines the position and characteristics of three atoms, it would require a trial and error effort beyond what is expected of a person having ordinary skill in the art to envisage a ligand structure other than the one described concretely in the examples, and make such compounds.

Therefore, claim 2 does not meet enablement requirements.

b) It is also possible that molecules that fall under the definition may still not actually fit into the binding pocket of protein P, since there may be other factors within these mo-

lecules that cause static and/or other hindrance.

Novelty, Inventive Step – No

Novelty and inventive step may be destroyed since the agonist found in the prior art search binds to the ligand binding pocket of protein P. Thus there is a high probability that this agonist falls under the pharmacophore definition.