**ANNEX 3: Comments of the USPTO**

# 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 chemical 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 the 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.

SUMMARY OF APPLICABLE U.S. LAW:

**35 U.S.C. § 101: Patent Eligible Subject Matter**

To be considered patent eligible subject matter under 35 U.S.C. § 101, the claimed invention must be a process, machine, manufacture, or composition of matter that has a practical utility.

**35 U.S.C. § 101: Utility**

To comply with 35 U.S.C. § 101, the claimed invention must have at least one specific, substantial, and credible utility that is either asserted in the specification or is well-established.

**35 U.S.C. § 102: Novelty**

A claimed invention complies with the novelty requirement if there is no single reference that expressly, implicitly or inherently describes the invention including each claimed element.

**35 U.S.C. § 103: Nonobviousness**

A claimed invention complies with the nonobviousness requirement if there are no prior art references that, alone or in proper combination, teach or suggest the invention as a whole including each element of the claimed invention. In determining whether an invention would have been obvious, the examiner determines the scope and contents of the prior art, ascertains the differences between the prior art and the claims in issue, resolves the level of ordinary skill in the art, and evaluates any objective evidence of nonobviousness.

**35 U.S.C. § 112, first paragraph: Enablement**

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. Factors to be considered in determining whether any required experimentation is “undue” include the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the presence or absence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**35 U.S.C. § 112, first paragraph: Written Description**

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, the specification must describe the claimed invention in sufficient detail such that one skilled in the art reading the description would recognize that the inventor had invented the claimed subject matter and had possession of the invention as claimed at the time the application

was filed.  An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

**35 U.S.C. § 112, second paragraph: Claim Definiteness**

To comply with the claim definiteness requirement of 35 U.S.C. § 112, second paragraph, each claim must particularly point out and distinctly claim the subject matter which the applicant regards as his or her invention. A claim is definite if one skilled in the art would be reasonably apprised of the scope of the claim when the claim is read in light of the specification.

| SUMMARY OF USPTO ANSWERS | | | | | |
|---|---|---|---|---|---|
| Case | Subject Matter Eligible? | Utility? | (1)Enabled; (2) Adequately Described? | Novel and Nonobvious? | Patentable? |
| Case 1 Claim 1 | N | M | (1) N; (2) Y | N/A | N |
| Claim 2 | N | M | (1) N; (2) Y | N/A | N |
| Case 2 Claim 1 | N | M | (1) N; (2) Y | N | N |
| Case 3 Claim 1 | Y | Y | (1) Y; (2) Y | N | N |
| | | | | | |
| Case 4 Claim 1 | Y | Y | (1) M; (2) Y | Y | M |
| Case 5 Claim 1 | Y | Y | (1) N; (2) N | N | N |
| Claim 2 | Y | Y | (1) Y; (2) Y | Y | Y |
| Case 6 | Y | M | (1) N; (2) Y | N | N |
| Case 7 Claim 1 | Y | M | (1) M; (2) Y | N | N |
| Claim 2 | Y | M | (1) N; (2) N | M | N |
| Claim 3 | N | N/A | N/A | N/A | N |
| Case 8 Claim 1 | N | N/A | N/A | N/A | N |
| Claim 2 | Y | M | (1) N; (2) N | M | N |
| Y=Yes, requirement met<br>N=No, requirement not met<br>M=Maybe; additional facts needed to reach a definitive conclusion<br>N/A=Not addressed | | | | | |

## 3. 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 *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.

**USPTO ANALYSIS:**

A1: Claim 1, directed to a computer model, is not tangibly embodied and therefore is nonfunctional descriptive material *per se*. Descriptive material is considered to be an abstract idea and therefore the claim would be rejected under 35 U.S.C. § 101 as not claiming patent eligible subject matter. Claim 2, directed to a data array, claims a compilation or mere arrangement of data. The 3-D coordinates of a protein constitute nonfunctional descriptive material without physical structure, and therefore are abstract ideas that are not patent eligible subject matter under 35 U.S.C. § 101. See, e.g., In re Warmerdam, 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1760 (Fed. Cir. 1994) (descriptive material per se is not patent eligible subject matter).

A2: The specification asserts that the atomic coordinates of protein P would be useful in an *in silico* screening method. Thus the claimed inventions comply with the utility requirement if the compounds identified by the screening method have a specific, substantial, and

credible utility. While the specification teaches that protein P, when active, lowers blood pressure, there is no indication whether there is a correlation between binding activity and activation. The claims comply with the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be accepted as a specific, substantial, and credible utility. However, in the absence of a known or disclosed correlation between binding and activation, identifying compounds which can bind to protein P is not a specific, substantial, and credible utility.

A3: Based on the disclosure that protein modeling algorithms are well known in the art, and the complete description of the atomic coordinates of protein P, claims 1 and 2 are enabled for how to make the claimed method and are adequately described. With respect to the how-to-use prong of the enablement requirement, unless there is a specific, substantial, and credible utility for the claimed invention (as discussed with respect to A2), the specification would not provide an enabling disclosure for how to use the claimed inventions. If the claimed inventions do comply the utility requirement of 35 U.S.C. § 101, it would then be necessary to determine whether one skilled in the art could use the claimed inventions without undue experimentation.

## 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.

USPTO ANALYSIS:

A1: As noted in the analysis set forth with respect to case 1, the structural data of a protein is nonfunctional descriptive material. As claimed, the protein data stored on the computer-readable medium is merely stored so as to be read by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer. Thus the 3-D coordinates do not impart functionality

to either the data or the computer, and are therefore nonfunctional descriptive material. Nonfunctional descriptive material stored in a computer-readable medium is an abstract idea that is not patent eligible subject matter under 35 U.S.C. § 101.

A2 -A3: See Case 1 analysis.

A4: As noted in A1 above, the 3-D coordinates do not impart functionality to either the data or the computer, and are therefore nonfunctional descriptive material. When descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability, and therefore the claim would be rejected as being obvious over prior art that describes a computer readable storage medium. See *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983). See also the analysis in Case 6, A4.

## 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 the 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.

**USPTO ANALYSIS:**

A1: The claim is directed to an isolated and purified protein; a protein may be considered either a composition of matter or a manufacture and therefore is statutory subject matter

under 35 U.S.C. § 101.

A2: The claim is directed to an isolated and purified protein, and the specification teaches that the isolated protein P lowers blood pressure. Assuming that there is no evidence that the asserted utility of lowering blood pressure when administered lacks credibility, the claimed protein has a specific, substantial, and credible utility and thus complies with the utility requirement of 35 U.S.C. § 101.

A3: The specification discloses 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. Based on this information, a person of ordinary skill in the art would be able to make the claimed protein. With respect to the how-to-use prong of the enablement requirement, if the claimed isolated and purified protein P could be used to modulate blood pressure without undue experimentation, the claimed method would comply with the enablement requirement of 35 U.S.C. § 101.

With respect to the written description requirement, applicant has provided sufficient structural information so that one skilled in the art would recognize that applicant was in possession of the invention as claimed.

A4: Under USPTO practice, when an applicant claims a composition in terms of a property or characteristic, and the composition of the prior art appears to be the same as that of the claimed composition but the property or characteristic is not explicitly disclosed by the reference, the examiner rejects the claims as anticipated by, or, in the alternative, as obvious over the reference, supporting the rejection with evidence or reasoning supporting the inherency of the disclosed property. This shifts the burden to applicant to show a nonobvious difference over the reference. *See, e.g., In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985); *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977).

Those principles would be applied to this case. The initial search would generally be limited to a conventional prior art search. The examiner would do a text search with initial search terms directed to the genus and/or species of organism from which the claimed protein was prepared along with an approximate molecular weight. (Note: Searching on the basis of molecular weight is difficult because molecular weight estimations vary depending on the technique employed.) Evidence of effects on blood pressure associated with any protein found from this search would also be considered. If the 3D structure is sufficient to derive amino acid sequence information, a search against appropriate protein and nucleic acid databases would also be performed.

In this case, the prior art teaches a protein from the same source organism having the same specific function and approximately the same molecular weight. Although the prior art does not teach the atomic coordinates as claimed, the atomic coordinates are an inherent property or characteristic of the claimed protein in a particular state. Absent evidence that the state defined by the coordinates represents a form distinguishable from that for the protein present in the prior art, the claim would be rejected under 35 U.S.C. § 102 as being anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over, the prior art protein. This situation is analogous to the situation where a claimed protein is characterized by amino acid sequence, but is otherwise identical to a prior art protein that has not yet been sequenced.

A5: Applicant may overcome the rejection by submitting evidence showing that the prior art protein is not the same as, or an obvious variant of, the protein described in the prior art.

## Case 4: Crystals of known proteins

**[Claim]**

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

**[Background]**

-A nucleotide sequence encoding the amino acid sequence of protein P was known in the art.

-The description explains that administering 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.

**USPTO ANALYSIS:**

A1. The claim is directed to a composition of matter (crystalline protein) and therefore is patent eligible subject matter.

A2. Although the claimed crystalline form of protein P is inactive, the claimed form has a specific, substantial, and credible utility as an intermediate in preparing the active form of protein P assuming (1) that it is well established in the art that a crystalline form of a protein generally can be reconstituted into an active form, and (2) that there is no evidence that the utility of lowering blood pressure by administering a reconstituted active form of protein P lacks credibility.

A3. With respect to the enablement requirement, the specification teaches how to make the claimed crystals. With respect to the how-to-use prong of the enablement requirement, assuming that the claims comply with the utility requirement of 35 U.S.C. § 101, it is necessary to determine whether one skilled in the art could use the claimed invention without undue experimentation. If one skilled in the art could use the claimed protein crystal to make the active form of protein P and thereafter use protein P to modulate blood pressure without undue experimentation, the claimed method would comply with the enablement requirement of 35 U.S.C. § 112. The claim complies with the written description requirement because the structure of protein P is provided.

A4. With respect to novelty, it is recognized in the art that a crystal of protein P is different from previously known forms of protein P. Furthermore, the claim complies with the nonobviousness requirement of 35 U.S.C. § 103 because as noted in the fact pattern, there was no prior art reference teaching or suggesting a crystal of protein P or related proteins. Although there is a general desire to obtain the crystal structure of any protein, the methodology of doing so is highly unpredictable and specific to each individual protein. Therefore, without guidance in the art as to how to crystallize a particular known protein, the known protein in crystalline form would be nonobvious.

## 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 the activity of 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.

**USPTO ANALYSIS:**

A1: Claims 1 and 2 are each directed to a composition of matter (an isolated and purified molecule) and therefore are patent eligible subject matter.

A2: Claims 1 and 2 meet the utility requirement of 35 U.S.C. § 101 because polypeptides which have the binding pocket as defined in the claim were shown to have a higher signaling activity than protein P when activated by a natural protein P ligand, and protein P is known to lower blood pressure when active.

A3: Claim 1 would be rejected under 35 U.S.C. § 112, first paragraph as lacking written description and as encompassing a broader scope than is enabled by the specification. The claim lacks written description because it recites a “molecule” defined only by the “structural coordinates” of 9 amino acid residues from a source polypeptide of at least 161 residues.

The recited structure is open-ended and defines only a portion of the claimed molecule. The molecule may be a polypeptide but it may also include residues that are not amino acids or amino acid derivatives. Protein P and the 40 fragments shown to be active all have the naturally occurring amino acid sequence of protein P and do not constitute a representative number of species of the claimed genus, which includes polypeptide and non-polypeptide molecules, to allow one of skill in the art to envision all members of the genus. Thus they do not provide an adequate written description for the genus.

With respect to the enablement requirement, the specification enables the full-length protein P and the specifically disclosed fragments, but the specification does not enable all molecules encompassed by claim 1. For the binding pocket to function, the 9 residues must be in the same spatial relationship to each other as they are in the natural polypeptide or the polypeptide fragments disclosed in the specification. Because of the large number of residues within the pocket that can be changed to comprise any one of 20 amino acids (or possibly other unspecified structural elements), and the fact that additional unspecified moieties may be included on either end of the binding pocket, the total number of molecules that are encompassed by this claim is extremely large. Because of the vast number of species encompassed by the claimed genus and the lack of guidance as to what structural changes may be made in the amino acid sequence between and around the active residues such that the resulting polypeptide would retain the 3-dimensional structure and activity of the binding pocket, it would require undue experimentation to make and use the invention over the entire scope claimed in claim 1.

Claim 2 complies with the enablement and written description requirements because it is limited to fragments of protein P that contain the binding pocket and were shown in the specification to retain binding activity and the signaling activity of protein P.

A4: Claim 1 recites open “comprising” language, and thus the claim encompasses natural protein P, which is known in the prior art. Claim 1 is anticipated by protein P and lacks novelty under 35 U.S.C. § 102.

Claim 2 is limited to fragments of protein P that consist of the amino acid residues that make up the binding pocket and retain binding and signaling activity. These fragments were not disclosed in the prior art and would not have been obvious on the basis of the known amino acid sequence of the entire protein P.

## 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 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.

**[Claim 2]**

A method of identifying compounds that bind to protein P by using the atomic coordinates of Protein P shown in Fig. 1 in a method of rational drug design.

**[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.

**USPTO ANALYSIS:**

A1: To qualify as patent eligible subject matter, the invention of each of claims 1 and 2, as a whole, must accomplish a practical application. That is, it must produce a "useful, concrete and tangible result." *State Street Bank & Trust Co. v. Signature Financial Group Inc*., 149 F.3d 1368, 1373, 47 USPQ2d 1596, 1601-02 (Fed. Cir. 1998). Note that the "useful result" aspect of the practical application test requires significant functionality to be present. *See Arrhythmia Research Tech. v. Corazonix Corp*., 958 F.2d 1053, 1057, 22 USPQ2d 1033, 1036 (Fed. Cir. 1992). This is an inquiry distinct from the test for "utility" as discussed in A2 below. Here, the method steps are applicable to a set of structural parameters and the result set provides a number of lead compounds with an increased probability of binding to the protein whose structure was input. Thus, the method provides a useful, concrete and tangible result that can be used to guide further screening. Irrespective of the recitation of specific structural coordinates, the claims are directed to *in silico* screening methods that have a practical application, and therefore the methods are statutory subject matter under the *State Street* rationale.

A2: The utility of the claimed methods depends on the utility of the candidate compounds identified as a result of the screening methods. The specification teaches that protein P, when active, lowers blood pressure, however there is no indication whether there is a correlation between binding activity and activation. The claims comply with the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be accepted as a specific, substantial, and credible utility. However, in the absence of a known or disclosed correlation between binding and activation, identifying compounds which can bind to protein P is not a specific, substantial, and credible utility.

A3: Enablement in this case depends first on choosing, with only general guidance from the specification, one or more programs to identify the binding pocket of protein P, then on demonstrating that the identification of the binding pocket is correct, and finally on the expectation of success in identifying compounds that bind to protein P and the amount and nature of experimentation required to determine which of the candidate compounds would be useful. Unless the binding pocket identification programs were known to be highly predictive, it is likely that the amount of experimentation required to identify and confirm the binding pocket would be considered undue because the programs would yield multiple possible binding pockets and the skilled artisan would have to choose the most likely predicted bind-

ing pocket(s) to test in order to determine the actual pocket. If the binding pocket is not confirmed prior to screening for potential binding compounds, the sets of possible binding compounds could be completely devoid of compounds that bind protein P. Furthermore, even if the claimed methods identified compounds that bind to protein P, the specification does not appear to teach how to use such compounds without undue experimentation.

The claimed methods of identifying compounds that bind to protein P comply with the written description requirement of 35 U.S.C. 112, first paragraph. The specification describes prior art programs that can be used to identify the binding pocket and to screen for candidate binding compounds. The specification also describes the structural coordinates of protein P, which are required by the pocket prediction and screening programs. Therefore, the specification describes the elements that are necessary to carry out the claimed method such that one skilled in the art would have recognized that applicant was in possession of the claimed invention.

Note that claim 2 fails to comply with the definiteness requirement of 35 U.S.C. 112, second paragraph because it attempts to claim a process without setting forth any steps involved in the process.

A4: The claims are novel because the 3-D coordinates are not found in the prior art. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that can potentially bind protein P is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become nonobvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. See *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983) (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability); *Ex parte Carver*, 227 USPQ 465, 470 (Bd. Pat. App. & Int. 1985)(Messenheimer and Nusbaum, Examiners-in-Chief, concurring)(Recorded signals are accorded patentable weight in determining obviousness where signals are used to actuate and control sound recording responsive device structure to produce appellant's disclosed acoustic phenomena because the

signals define a functional relationship of the type referred to in *Gulack*.).

## 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 information is taught by the prior art.

**USPTO ANALYSIS:**

**Claim 1:**

A1: See analysis of Case 6.

A2: See analysis of Case 6.

A3: The specification adequately describes and enables one skilled in the art to make the claimed method of screening by virtue of working examples that identified compounds that bind to protein P. The working examples provide sufficient guidance regarding the screening program, and demonstrate the effectiveness of the screening program in using the disclosed 3-D coordinates of protein P to identify ligands that bind with sufficient affinity that a biological effect would be expected by one skilled in the art. With respect to the how-to-use prong of the enablement requirement, the specification teaches that protein P, when active, lowers blood pressure, however there is no indication whether there is a correlation be-

tween binding activity and modulation of blood pressure. If compounds that bound protein P could be used to modulate blood pressure without undue experimentation, the claimed method would comply with the enablement requirement of 35 U.S.C. § 112.

A4: Claim 1 is novel because the 3-D molecular model of Fig. 5 is not found in the prior art. The key factor in analyzing the obviousness of these claims over the prior art is the determination of whether the claimed data processing method used to identify compounds that can potentially bind protein P, i.e., steps (1) through (n), would have been obvious to one skilled in the art. See the analysis of Case 6, A4. In this case, the fact pattern suggests that the claimed method would have been *prima facie* obvious over the prior art because steps (1) through (n) appear in the prior art methods.
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**Claim 2:**

A1: Claim 2 is directed to statutory subject matter (a compound).

A2: See analysis of Case 6, A2. The claim complies with the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure.

A3: The claim does not comply with the enablement and written description requirements. The claimed invention is drawn to a compound identified by the method of claim 2. However, no structural or specific functional characteristics of such a compound is provided. This situation is analogous to that of *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Because one skilled in the art would conclude that the inventors were not in possession of the claimed invention, the claim fails to comply with the written description requirement.

This claim also fails to meet the enablement requirement for the “how to make” prong of 35 U.S.C. § 112, first paragraph. The fact pattern fails to disclose any particular structure for the claimed compound. The specification does not provide any guidance or any working examples in this unpredictable art, and thus the artisan would have been unable to make the claimed compound without undue experimentation. An assay for finding a product is not equivalent to a positive recitation of how to make such a product. Further, while the claimed compound meets the utility requirement of 35 U.S.C. § 101, the claimed invention may not comply with the “how to use” prong of 35 U.S.C. § 112, first paragraph. The specification

does not teach how to administer the claimed compound so as to effect a viable blood pressure treatment regimen. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the subject or patient. In the absence of additional information the skilled artisan would not have been able to use the undisclosed compound(s) for treatment without undue experimentation.

A4: If a search of the prior art yielded one of the compounds tested experimentally in the specification, Claim 2 would be rejected as anticipated by the prior art compound. If the prior art teaches agonists or antagonists of protein P, and the examiner can provide evidence or reasoning supporting a conclusion that the prior art compound inherently falls within the scope of the claim, the claim would be rejected as being anticipated or rendered *prima facie* obvious by the prior art. See the analysis in Case 3, A4.

A5: The claimed invention is drawn to a genus of compounds identified by the method of claim 2 and the specification discloses at least some examples of the structure of compounds within the scope of what is claimed. However, there is no evidence that there is any *per se* structure/function relationship between the disclosed compounds and any others that might be found using the claimed method. Structural identifying characteristics of the genus members are not disclosed. Therefore, as noted in A3 above, the claimed invention is not supported by an adequate written description. The rejection might be overcome with a showing of objective evidence that supports the proposition that the particularly disclosed compound were representative of the structure of the group of molecules that would be detected or identified by the claimed method.

**Claim 3:**

A1: The claim is nonstatutory under 35 U.S.C. § 101 because it is an abstract idea not tangibly embodied and is a mere collection of data. *See, e.g., In re Warmerdam*, 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1760 (Fed. Cir. 1994) (descriptive material *per se* is not patent eligible subject matter).

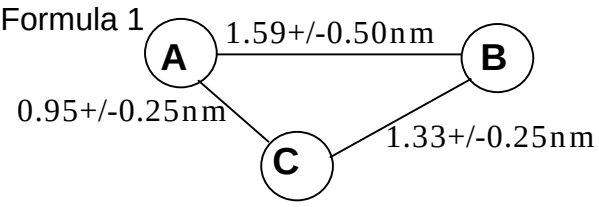
A5: If the specification provided the necessary support, the claim could be drafted as a statutory data structure having some functional relationship information built into the database, e.g. for indexing, storage or retrieval. However, the novelty or nonobviousness of any data structure so claimed would be determinative of patentability over the prior art, rather than the novelty or nonobviousness of the data within the data structure. *See In re Lowry*, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994).

## 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:

Formula 1




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 discloses 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.

**USPTO ANALYSIS:**

**Claim 1:**

A1. The pharmacophore is merely a generalized concept and not a compound or article of manufacture (see Case 1). As such the pharmacophore is an abstract idea and is not patent eligible subject matter under 35 U.S.C. § 101. *See In re Warmerdam*, 33 F.3d 1354, 1360, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994).

**Claim 2:**

A1: Claim 2, directed to any compound defined by the pharmacophore, is patent eligible subject matter under 35 U.S.C. § 101.

A2: The specification teaches that protein P, when active, lowers blood pressure, however there is no indication whether there is a correlation between binding activity and activation. The claim complies with the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be accepted as a specific, substantial, and credible utility.

A3: Claim 2, directed to any compound defined by the pharmacophore, would be rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement. With respect to the how-to-make prong of the enablement requirement, the specification only enables the compound that was actually made and tested, since there is no evidence that the specification provides sufficient guidance regarding how to choose an array of specific atom groups that could form compounds that would fit the general formula, and how to test the compounds such that making and testing would not constitute undue experimentation. With respect to the how-to-use prong of the enablement requirement, even if the claimed compound meets the utility requirement of 35 U.S.C. § 101, the specification does not teach how to administer the claimed compound so as to effect a viable blood pressure treatment regimen. Treatment and administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the subject or patient. In

the absence of additional information the skilled artisan would not have been able to use the claimed compound(s) for treatment without undue experimentation.

Claim 2 would also be rejected under the written description requirement of 35 U.S.C. § 112, first paragraph. A large number of possible compounds may fit the pharmacophore formula. However the specification does not set forth a representative number of structures that would allow the person of ordinary skill in the art to conclude that the inventor had possession of the broad scope of the genus invention at the time the application was filed.

Claim 2 would also be rejected as failing to comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph because a pharmacophore, which is an abstract concept, does not define a compound.

A4: With respect to the prior art, the example states that an agonist of protein P was found in a prior art search. The claimed pharmacophore, and any generic claim to compounds defined by the pharmacophore, would be rejected as being anticipated by, or obvious over, the prior art if the examiner could provide evidence or sound scientific reasoning that it is more likely than not that the prior art agonist binds to the ligand binding pocket of protein P and would therefore fall within the formula of the pharmacophore. See the analysis in Case 3.