ANNEX 1: Comments of the EPO

"Trilateral Project WM4":

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

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.

Answer: a computer model is not considered to be a patentable invention; it merely presents the atomic coordinates of a single protein molecule in space *as such*, without any direct technical character (it is non-technical by not solving a **technical** problem, and it does not have a technical effect in itself).

The subject-matter is not directed to patent eligible subject-matter. According to Article 52(2)(d) of the EPC presentations of information shall not be regarded as inventions which are susceptible of industrial application and which are new and which involve an inventive step.

A search of this claim will not be carried out according to Rule 45 EPC.
It is therefore also not relevant to patentability that a search of the prior art did not identify any references that teach or suggest protein P.

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.

Answer: no difference in patentable subject-matter under the EPC can be seen between the subject-matter of claims 1 and 2; a data array is a presentation of information.

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

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

Answer: such a storage medium is not considered to be a patentable invention; it merely specifies the atomic coordinates of a single protein molecule in space, without any direct technical character; the data merely encode cognitive content in a standard manner. Thus, the subject-matter referring to the presentation of information is not directed to patent eligible subject-matter according to Article 52(2)(d) of the EPC

It is noted that in a particular circumstance a "Technical Board of Appeal" has decided (**T1173/97**, OJ 1999, 609) that the information encoded on a computer-readable storage medium can be patentable, ie can be regarded as an invention which is susceptible of industrial application and which is new and which involves an inventive step. The data encoded on the medium concerned a computer program considered in this special case to have a technical character by having a further technical effect (EPO Guidelines Part C Chapter IV.2).

Cases 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

Case 3 answer: The claim is not directed to subject-matter excluded under Article 52(2) EPC: in addition, the claimed subject-matter may satisfy the requirements of industrial applicability and clarity, enablement, support (the description gives experimental data and explains that the protein, when active, lowers blood pressure). It is assumed that the description also specifies the purification of the protein necessary to perform NMR at 0.2nm resolution.

Novelty/inventive step: No
The prior art teaches a protein from the same source organism having the same specific function and approximately the same molecular weight. It would be the starting position of the EPO to raise an objection for lack of novelty over the cited prior art document.

If the applicant provides evidence for the novelty over the prior art protein, novelty and inventive step can be accepted (it is noted that it is presently considered that the structural data at high resolution fully define the protein, including the deducible primary sequence).

Case 4: Crystals of known proteins

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

Answer: The claim is directed to patentable subject-matter under Article 52(1) EPC: in addition, the claimed subject-matter may satisfy the requirements of clarity, enablement, and support (the description gives experimental data how to make the crystals and explains that the protein, when active, lowers blood pressure).

Novelty/Inventive step/industrial application: yes.
The prior art did not disclose crystals of protein P and also did not teach how to obtain crystals of protein P. Although protein P in crystalline form is said to be inactive (but by which assay is it possible to determine that the **crystallised** protein P is inactive? such an assay appears only to be possible for a protein in solution) it may advantageous to produce the protein in eg a stable form (and high purity) and also to use the crystals for determination of the 3-D structure, the atomic coordinates useful in *in silico* screening methods and rational drug design.

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 acids 223, 224, 227, 295, 343, 366, 370, 378 and 384 according to Figure 1.

Answer: With respect to the wording "An isolated and purified molecule" it is noted that the word "molecule" is probably not desired, and should be replaced by "polypeptide" or compound. If indeed a "molecule" is claimed then this claim would not be sufficiently disclosed as a molecule as such has not been enabled.
If reference is made to "polypeptide" then the claim is not directed to subject-matter excluded under Article 52(2) EPC: in addition, the claimed subject-matter may satisfy the requirements of industrial applicability and clarity, enablement, support (the description gives experimental data and explains that the protein lowers blood pressure).

Novelty/inventive step: No
The prior art teaches protein P; this known protein/polypeptide comprises the binding pocket and the natural polypeptide is therefore prejudicial to the novelty of the claimed subject-matter.

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.

Answer: the claim refers to patentable subject-matter under Article 52(1) EPC: in addition, the claimed subject-matter satisfies the requirements of clarity, enablement, and support (it is assumed that the description gives sufficient detail to accept that the variable ends of the polypeptide portion are not relevant to the blood pressure lowering activity of the claimed portion).

Novelty/Inventive step/industrial application: yes.
The prior art did not disclose the specified portion of protein P and also did not teach or suggest to make this portion having a non-obvious higher signaling activity compared to the whole 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 shown in Fig. 1; 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.

Answer:

An in silico screening method is considered to be a patentable invention under Article 52(2) and 52(3) of the EPC; it refers to a method having a link to a technical contribution by the use of technical data. With respect to the sufficiency of disclosure it is noted that, although the applicant may file as support further technical information with examples providing evidence for the correctness of the prediction of the position of the pocket, the method as claimed (in the absence of eg further information on the candidate compounds) is not fully enabled in the absence of any working examples.

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) ...

Answer: an *in silico* screening method with this wording is considered to be a patentable invention (it is assumed that the 3-D molecular model shown in Fig.5 presents the complete structure of protein P). It refers to a method having a link to a technical contribution characterised by technical feature(s). This activity is not regarded as a presentation of information or as a pure mathematical method, excluded by Article 52(2)(d) or (a) of the EPC, respectively, but to the use of the structural data.

Thus, the subject-matter is directed to patent eligible subject-matter. In addition, the claimed subject-matter may satisfy the requirements clarity, enablement and support (the description gives experimental data including identified compounds).

Novelty/Inventive step/industrial application: yes.
The prior art did not disclose or suggest the 3-D coordinates of protein P. The claimed method applying the use of the coordinates is therefore considered to be new, non-obvious and industrial applicable.

Claim 2: A compound identified by the method of claim 1.

Answer: the claimed subject-matter refers to identified compounds and therefore can be considered to present patent eligible subject-matter. However, it would appear that a lack of sufficiency of disclosure and/or lack of support should be raised, as the claimed compound has not been enabled over all the whole range of claimed embodiments (Reach-through claim; see answer for claim 2 of case 8; reference can also be made to the earlier trilateral project B3b report with theme: comparative study on "reach-through claims").

An incomplete search will be carried out for this reach-through claim, limited to the example of the description.

With respect to novelty, it would be the starting position in examination that the natural ligand already in the state of the art is prejudicial to novelty.

Claim 3: A database encoded with data comprising names and structures of compounds identified (by) the method of claim 1.

Answer: a database is not considered to be a patentable invention; it merely presents the stored data without any direct link to a technical contribution.

The subject-matter is not directed to patent eligible subject-matter. According to Article 52(2)(d) of the EPC presentations of information shall not be regarded as inventions which are susceptible of industrial application and which are new and which involve an inventive step.

A search of this claim will not be carried out according to Rule 45 EPC.

Case 8: Pharmacophores and pharmacophore - defined compounds

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.

Answer: such a pharmacophore is not considered to be a patentable invention; it merely presents the spatial arrangement of some further characterised atoms within a molecule and is not directed to patent eligible subject-matter according to Article 52(2)(d) of the EPC as it is a mere presentation of information. It is not regarded as an invention which is susceptible of industrial application and which is new and which involves an inventive step.

A search of this claim will not be carried out according to Rule 45 EPC.

In addition, the use of the distances between the atoms as parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is impossible to compare these parameters with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Claim 2: An isolated compound or its salt defined by the pharmacophore in claim 1.

Answer: in the present wording of claim 2, "compound **defined** by the pharmacophore", one cannot make a real distinction between the subject-matter of claim 1 and claim 2. If one reads "comprises" in stead of "defined" the following is noted:
the claimed subject-matter concerns a compound and therefore represents patent eligible subject-matter. However, it would appear that a lack of sufficiency of disclosure should be raised (Article 83 EPC). The application must contain sufficient information to enable the person skilled in the art, using his common general knowledge, to perform the invention over the whole are claimed without undue burden and without needing inventive skill (EPO Guidelines C-II, 4.9). The application is not sufficiently enabled, taking into account the scope of the claim embracing an excessively large number of compounds and the fact that the description refers to one novel ligand designed on the basis of the phar-

macophore. A lack of support should also be raised according to Article 84 EPC in the light of the EPO **Guidelines C-III, 6.3**: In order to comply with the requirements of Art.84, there must be sufficient support of **technical** character in the description that allows to extend the particular teaching of the description to the whole field claimed. In the case of the pharmacophore it is unclear how far the scope extends: the features of the compound concerning the spatial arrangement of the 3 atoms do not support sufficiently the characterisation of the compound (a meaningful comparison with the prior art cannot be made (**Guidelines C-III, 4.7a**).
It is furthermore noted that the natural agonist of protein P will fulfil the structural requirements of the pharmacophore, and therefore would be prejudicial to novelty (and in fact should result also in an objection for lack of unity of invention).

An incomplete search will be carried out for this reach-through claim, limited to the example of the description.

Afterword:

The legal positions in the USA and Japan differ greatly from that under the EPC: only the EPC contains an exclusion such as that in Art.52(2) and (3) EPC (IBM decision T1173/97; OJ 1999, 609, Reasons 2).

Mathematical methods and presentations of information are in the EPC excluded from patentability (Article 52(2)). On the other hand, those methods and presentations are only excluded **as such** (Article 52(3) EPC). If a further **technical effect** results from the claimed subject-matter (a technical process in which the method is used; VICOM decision T 0208/84) then it is possible to recognise patentability.

In the case of a model of a protein it is considered that the model is a presentation of information as such. In the case of an *in silico* screening method using the model of a protein (obtained in a non-obvious way) to identify ligands the method is considered to be linked to a further technical effect.

There is no case law yet with respect to 3-D structures/models in relation to patentability under Article 52(2)(3) EPC.