2. Major fields of 3-D protein structure inventions

The number of inventions in the field of proteomics has significantly increased after the disclosure of the human genome. First of all, certainly the improved knowledge in genetics pushed forward the further disclosure of protein structures. Scientists, however, also started to focus intensely on protein research and increased investment. 3-D protein structure inventions play an important role in a number of fields. The following attempts to provide an examination of claims related to protein structural properties *per se*, including an analysis of claims to 3-D structure defined by structural coordinates and claims to protein crystals. The next chapter will then focus on proteomics and bioinformatics, including the assessment of claims to *in-silico* screening methods related to tertiary protein structure and identified compounds. Finally, claims directed to data related to structural features will be examined.[487]

II. Proteomics and protein structural properties *per se*

1. Structure defined by structural coordinates and protein crystals

a) Claims

As a first step, claims directed to the polypeptide *per se* are examined. The first group of cases consists of a claim related to a protein having the structure defined by structural coordinates and of another claim that refers to the crystalline form of a protein. The structure definition is based on NMR spectroscopy. With regard to the claim directed to the crystalline protein structure, one must consider that protein crystallization is only possible with a very low percentage of all existing polypeptides. Particularly, hydrophic, (for example membrane proteins) are not available in crystalline form, and it is generally possible to achieve crystalline forms of only 5 % of proteins.[488] Thus, the advantages of this particular claim do not reduce general difficulties of protein patenting.

The actual claims read as follows:

> Claim 1:
>
> An isolated and purified protein having the structure defined by structural coordinates as shown in a specific figure.

487 A number of articles focuses on the Trilateral Study conducted by the patent offices, see for example Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95; Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191-209.

488 Peters, Linde, Postgenomik, http://home.t-online.de/home/linde.peters/intro.htm#postgen0, Part IV, 3.

Claim 2:

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

b) Background

The claim description of Claim 1 reports 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. Additionally, it provides experimental data and illustrates that the protein, when active, lowers blood pressure. The structural coordinates were derived from a solution phase protein by NMR at O.2nm resolution. The prior art does not include any references that reveal the 3-D structure of the protein. However, it demonstrates a protein from the same source organism having the same specific function and approximately the same molecular weight.[489] With regard to the claim related to the crystalline protein form, a nucleotide sequence encoding the amino acid sequence of protein P is known in the art. The description explains that the administration of protein P was previously shown to lower blood pressure. The inventor alleged the novel production of a stable crystalline form of protein P. The crystalline form of protein P was inactive. The description provides experimental data of how to synthesize the crystals and demonstrates that the protein, when active, lowers blood pressure. Related prior art methods used in protein P crystallization have all been unsuccessful, so that there existed clear technical difficulty in reproducing the claimed crystalline form of protein P.[490]

c) Solutions proposed by the EPO and the USPTO

Regarding the claim directed to the *isolated and purified protein* (Claim 1), the EPO maintained that the claim would not be directed to a subject matter excluded under Art. 52(2) EPC.[491] The claimed subject matter complies with the requirements of

489 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 1-79, 7ff.

490 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

491 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Busi-

industrial application, clarity, enablement and support. The claim, however, fails the novelty requirement, since the prior art already contains a protein from the same source organism with approximately the same characteristics. The EPO stresses, however, that novelty and inventive step can be accepted if the applicant provides the evidence of novelty over the prior art protein. The structural data fully defines the protein, including the deducible primary sequence.[492]

As to claim 2, which refers to a *crystalline form* of a protein, the EPO states that the claim is directed to a patentable subject matter according to Art. 52(1) EPC. Additionally, the claimed subject matter complies with the requirements of clarity, enablement and support. The requirements of novelty, inventive step and industrial application are given, since the prior art does not include crystals of protein P and also did not illustrate the synthesis of protein P crystals. The EPO suggested, however, to produce the protein in a stable form. The crystals should be used for determination of the 3 D structure and those atomic coordinates, which are useful in *in silicio* screening methods and rational drug design.[493]

The USPTO maintains that an *isolated and purified protein* (Claim 1) may be considered either a composition of matter or a manufactured product and therefore can be considered as statutory subject matter according to 35 U.S.C. § 101.[494] 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 satisfies the utility requirement of 35 U.S.C. § 101. Based on the information that is provided by the specification, a person of ordinary skill in the art is able to synthesize the claimed protein. With respect to the "how-to-use prong"[495] of the enablement requirement, the claimed isolated and purified protein P must, so ruled the USPTO, be effective in modulating blood pressure without undue experimentation. Under this circumstances, the claimed method complies with the enablement requirement of 35 U.S.C. § 101.

The USPTO further states that the patentee provides sufficient structural information such that one skilled in the art recognizes that the inventor is in possession of the invention as claimed. Thus, the written description requirement is fulfilled.

ness Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35.

492 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

493 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35f.

494 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

495 "The how-to-use-prong of section 112 incorporates, as a matter of law, the requirement of 35 U.S.C. § 101 that the specification discloses a practical utility for the invention… if the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112," see In re Ziegler, 992 F.2d 1197, 1200-01, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993).

Moreover, the USPTO applies its general practice to the case. Pursuant to this, the examiner rejects the claims as anticipated by, or alternatively as obvious when compared with the reference under the following circumstances: An inventor claims a synthesis in terms of a property or characteristic. The synthesis existing in the prior art appears to be the same as that of the claimed composition, but the particular property or characteristic was not explicitly disclosed by the reference. The rejection is thus supported by evidence or reasoning supporting the indifference over the reference.

An initial search therefore is limited to a conventional prior art search. The patent examiner does a text search with initial search terms referring to the genus and/or species of organism from which the claimed protein was prepared along with an approximate molecular weight. Evidence of impact on blood pressure associated with any proteins found in this search is also considered. A search for an appropriate protein and nucleic acid is also to be made provided the 3-D structure is sufficient to derive amino acid sequence information.[496]

In the case at issue, the prior art demonstrates a protein originating from the same source organism, having the same specific function and approximately the same molecular weight. Although the prior art does not include the atomic coordinates as claimed, the atomic coordinates are an inherent property or characteristic of the claimed protein in a particular state. Lacking evidence that the state defined by the coordinates represents a form distinguishable from that for the protein present in the prior art, the claim must be rejected according to 35 U.S.C. § 102 as being anticipated by, or alternatively, as obvious when compared with the prior art protein (35 U.S.C. § 103). This situation corresponds to the situation in which a claimed protein is characterized by amino acid sequence, but is otherwise identical to a prior art protein that has yet to be sequenced. The Patentee may overcome the rejection by submitting evidence proving that the prior art protein is not the same as, or an obvious variant of, the protein described in the prior art. [497]

As for the *protein crystal* (Claim 2), the USPTO held that it refers to a composition of matter and is therefore patent-eligible subject matter. Assuming that (1.) it is well established in the art that a crystalline form of a protein can generally be reconstituted in an active form, and (2.) there is no evidence that the utility of lowering blood pressure by administering a reconstituted active form of protein P lacks credibility, the claim form has a specific substantial and credible utility as an intermediate in preparing the active form of Protein P. This result persists, even though the claimed crystalline form of protein P is inactive. As to the enablement require-

496 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 65.

497 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64-66.

ment, the specification demonstrates the synthesis of the claimed crystals. With regard to the "how-to-use prong" of the enablement requirement it must be assumed that the claims comply with the utility requirement of 35 U.S.C § 101. Additionally, 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 satisfy the enablement requirement of 35 U.S.C. § 112. Since the structure of protein P is provided, the claim complies with the written description requirement. The novelty requirement is met, since the prior art teaches that a crystal of protein P differs from known forms of protein P. As to obviousness under 35 U.S.C. § 103, there is no prior art reference demonstrating or suggesting a crystal of protein P or related proteins. Although a general desire to obtain the crystal structure of any given protein exists, the methodology of doing so is highly unpredictable and specific to each individual protein. Without this expertise in the art of protein crystallization, the synthesis of a specific known protein in crystalline form is nonobvious.[498]

d) Discussion

As for novelty of the *isolated and purified protein* (Claim 1), the EPO applies principles that have been developed by a German court for the patentability of chemical substances. As established in the *Trioxane* decision of the German Federal Supreme Court[499], a chemical substance can be described sufficiently and unambiguously by different parameters. A parameter existing in prior art is novelty-destroying, if it is specific enough to unambiguously identify a substance. Thus, one must closely examine the value of a given parameter by determining its capacity to individualize a particular substance.[500] If a protein is already unambiguously identified by its primary structure, the creation of novelty due to 3-D structural data is anticipated. The USPTO reaches, on distinct but similar grounds, the same solution.

Prima facie, the patent offices' rejection of Claim 1 might give rise to the notion that the establishment of novelty for proteins defined by structural coordinates will, more generally, face substantive hurdles. To put this impression into perspective (and to shed further light on the novelty requirement in cases in which the prior art includes the primary structure), it is useful to compare Claim 1 with claims in which

498 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191-209.

499 BGH, 3 IIC 226 (1972) –Trioxane.

500 Bostyn, Sven J.R., Enabling Biotechnological Inventions in Europe and the United States: A Study of the Patentability of Proteins and DNA Sequences with Special Emphasis on the Disclosure Requirement, Munich 2001, 81.

the three-dimensional structure does play a more prominent role, such as in the case of prion proteins.

As explained earlier[501] the long-held hypothesis that the amino acids in all cases code for a single unique tertiary structure cannot be held anymore. The prion protein (PrP) occurs in two different folding types. The normal, cellular PrP (PrP C) is converted into PrP Sc through a posttranslational process.[502] As detailed in Chapter II, this pathogenic prion form causes neurodegenerative disorders, such as bovine spongiform encephalopathy (BSE), its human equivalent Creutzfeld-Jakob disease (CJD), Kuru and Scrapie. In the case of prions, the 3-D protein structure consequently is a more reliable parameter than the amino acid sequence and must be sufficient to match the novelty requirement. Other neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease are not considered to be prion-based, rather are caused by misfolded 3-D protein structure. Even though the precise molecular structure has not yet been identified, it is already clear that these diseases are accompanied by amyloidal brain plaques.[503] Thus, the 3-D structure can be expected to be the key parameter in these cases as well.[504]

The European Patent Office had not yet dealt with novelty in prions. Cases related to stereochemistry, the study of the 3-D shape of molecules, however, involve similar issues. The major focus of stereochemistry is stereoisomers that are compounds consisting of the same atoms and bonds, but possessing different 3-D structures. The major kinds of stereoisomers are enantiomers, i.e. mirror image stereoisomers, and diastereomers which is simply any stereoisomer that is not an enantiomere.[505]

In T 12/81 the Technical Board of the European Patent office did yet not clearly determine that the spatial form of a stereoisomer suffices to establish novelty, finding that a prior art document anticipated a claim directed to diastereomers, even though it did not specify the exact spatial form of the diastereomers. [506] The Board explained that the prior art document that disclosed a chemical substance described by its structural formula failed to explicitly mention the particular stereospecific

501 See Chapter 1 and Chapter 2 B II 2.

502 Prusiner, Stanley B., Nobel Lecture, 95 PNAS 1998, 13363, 13363.

503 A protein called β-amyloid, discovered in 1984, was found to be the primary component of the brain's plaques. According to the amyloid hypothesis, the build-up of β amyloid causes Alzheimer's disease by destroying brain cells.Travis, John, Saving the Mind Faces High Hurdles, 309 Science 2005, 731, 732

504 Diagnostic methods that rely on 3-D information include 'positron emission tomography' (PET) 'fluorescent staining assay', 'immunoassay' and 'electron microscopic assay', see Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 89.

505 See Organic Chemistry Online (Published by Paul R. Young), Stereochemistry: Isomerism in Carbon Compounds, available http://www.chem.uic.edu/web1/OCOL-II/WIN/HOME.HTM, last checked January 21, 2008.

506 T 12/81, N. Publ., No. of the Reasons 17. The reaction of the literature on this decision of the Board of Appeals was moderately critical, see Hüni, Albrecht, Zur Neuheit bei chemischen Erzeugnissen in der Spruchpraxis des Europäischen Patentamts, GRUR 1986, 461, 462.

configuration. The Board concluded that nevertheless the document anticipates the particular stereospecific configuration, because the stereospecific configuration must be considered the inevitable result of one of a number of processes adequately described in the prior art document.[507]

The rule that the precise asymmetric form of a stereoisomer must be considered novel in comparison with disclosed racemates is set forth in T296/87.[508] In this case, the Technical Board of the European Patent Office had to decide upon the issue of whether novelty of Enantiomers was anticipated by the description of a racemic mixture, a mixture of equal amounts of left- and right-handed enantionmers.[509] The patent description determined racemates in the state of the art by means of expert interpretation of the structural formula and scientific terms.[510] The problematic issue with regard to novelty was that this did not sufficiently specify the precise configuration of the enantiomers at issue.[511] Due to the asymmetric carbon atom contained in the formula, enantiomers can occur in a plurality of conceivable spatial configurations. With the patent description only determining the racemic mixture, a more specific determination of the spatial enantiomers configuration was lacking. The EPO's Board of Appeal applied the principles developed in the German *Trioxan* decision stating that a chemical substance is held to be new if it is distinguishable from a known substance in an unambiguous parameter.[512] The Board concluded that this configuration is such a parameter. The Board explained that the specific racemates included in the prior art do not alone provide any information related to the configuration in individualized form. Consequently, the description of the racemate mixture bears insufficient information to unambiguously determine enantiomers lacking a reliable parameter.[513]

The principle of that an enantiomer is considered new with regard to a racemic mixture is affirmed and further developed in T 1048/92.[514] Here, the crucial prior art document referred to the enantiomer within an example. Further, it contained a 'Markush formula' that included the exemplified subject. With regard to this Markush formula, it was indicated that the formula includes "various optically active

507 T 12/81, N. Publ.No. of the Reasons 5-17. The Board concluded that "the concept of novelty must not be given such a narrow interpretation that only what has already been described in the same terms is prejudicial to it", see T 12/81, N. Publ., No. of the Reasons 5; also Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 146.

508 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206, 207.

509 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206. Separating different forms of enantiomers bears significant difficulties, because they have nearly identical properties, see Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 148.

510 "The situation is different if the state of the art includes enantiomers, howsoever designated (D, d, L, l or + or -), which are specifically named and can be produced", see T296/87 Enantionmers/HOECHST, OJ 1990, 195, 207.

511 D- and L-enantiomers

512 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 206-207.

513 T 296/87 Enantionmers/HOECHST, OJ 1990, 195, 207.

514 T 1048/92, N. Publ. (EPO 1994).

isomers" and that "the invention embraces such optically active isomers".[515] The Board of Appeal held that novelty was established. It reasoned that the applicant had chosen one of the two conceivable configurations of the subjects being exemplified in the prior art document. With regard to the indications concerning the occurrence of optical isomers made in the prior art document, the Board concluded that they did not refer to the individual substance distinguished by its steric form as disclosed by the patent applicant.[516]

With the 3-D protein structure determining the protein's function, it is the most unambiguous parameter. Hence, the tertiary folding type is comparable to the asymmetric configuration of enantiomers. In light of principles developed in the above-described decisions from the field of stereochemistry and in the landmark of *Trioxane*, the tertiary folding structure can suffice to match the novelty requirement.[517] The primary structure of a protein does not always contain sufficient information to unambiguously determine a substance. This is illustrated by the case of prions. The amino acid sequence does not provide sufficient information regarding folding of the prion protein at the tertiary level. The determination of the amino acid sequence lacks important information as to whether a normal, cellular prion (PrP C) or the diseased form (PrP Sc) is given. As a consequence, data related to the folding type of a protein can still establish novelty, even though the amino acid is completely known and publicized. This principle, however, is only applicable to proteins that occur in a plurality of 3-D structures. In cases in which the state of the art teaches that there typically exist only single folding stages, the amino acid sequence must be considered the most reliable parameter. [518]

The USPTO precisely determines with regard to *Claim 1* that a patent applicant must prove that the state defined by the coordinates represents a form distinguishable from that for the protein present in the prior art. The office thus applies its general practice regarding what is considered novel. As stated in *Fiers v. Sugano*, "a precise definition, such as structure, formula, chemical name or physical properties is necessary for providing sufficient identification".[519] This information is provided if the patent applicant offers evidence that the claimed compound is less ambiguous

515 T 1048/92, N. Publ., No. of the Reasons II. A 'Markush formula' is the most concise means of defining a class of chemical compounds in a claim, see T 1020/98, N. Publ., No. of the Reasons 3.1. (EPO 2003).

516 T 1048/92, N. Publ., No. of the Reasons 2.5. See also: Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 149.

517 For the Trioxane decision, see Hirsch, Fritjoff, Neuheit von chemischen Erfindungen, GRUR 1984, 243, 244.

518 As to the applicable principles, see: Rauh, Peter A./Jaenichen, Hans-Rainer, Neuheit und erfinderische Tätigkeit bei Erfindungen, deren Gegenstand Protein oder DNA-Sequenzen sind -- Volker Vossius zum 60. Geburtstag, GRUR 1987, 753, 755; also: Bostyn, Sven, A test too far? A critical analysis of the (non)-patentability of diagnostic methods and consequences for BRCA gene type patents in Europe, Bioscience Law Report 2001/2002, 111-121.

519 Fiers v. Sugano, 984 F. 2d 1164, 1172 (Fed. Cir. 1993).

than what is considered state of the art. Again, numerous U.S. patents granted in the field of stereochemistry are based on this assessment of novelty.[520]

As to *Claim 2* related to a *crystalline form* of a protein, the EPO applies established principles for the patenting of chemical inventions. Generally, chemical substances of the same chemical composition must be considered identical. However, it is not impossible that two substances with the same molecule structure can be viewed as being distinct. They must therefore be distinguishable through reliable parameters. The discrimination of chemical substances of a same chemical composition does not only depend on their form (polymorph) but also on their physical characteristics.[521] As stated in *Trioxan* and stated earlier, the crucial characteristic of a particular chemical compound for determining novelty does not necessarily need to be its chemical constitution. The chemical formula of a chemical substance is rather only one of a variety of existing criteria that can be used for classification.[522] The fact that a chemical formula is generally the most reliable definition of a substance does not mean that other definitions do not exist. It is comparable to the definition of substance based on its physical parameter. There is not just a single method of determining the novelty of a chemical compound, but rather a wide variety of methods.[523]

The EPO's statements regarding other patent requirement can be clearly followed. The solution of the technical problem to establish a crystalline form of protein P clearly involves an inventive step, because it cannot *a priori* be expected that the crystalline protein form consists of any advantages compared to the form that is reported in the prior art. Moreover, it would not have been obvious to a skilled person how to translate protein P into its crystalline form.[524] The claimed crystalline form of protein P is advantageous. The inactive form can be reconstituted into an active form, and administration of the reconstituted active form of protein P is known to result in the reduction of blood pressure. Such characteristics and the knowledge,

520 See for example U.S. Patent 7,211,580: McDonald, Andrew/Bergnes, Gustave/Feng, Bainian/Morgans, Jr., David J./Knight, Steven David/Newlander, Kenneth A./Dhanak, Dashyant/Brook, Christopher A., Compounds, compositions and methods, South San Francisco, CA; Philadelphia, PA 2007.

521 The coherency of polymorphs and particular features is widely known in the field of anorganic chemistry. For example, the polymorphic form of carbon can occur as carbon black, graphite or diamond, the polymorphic form of calcium carbonate as crayon or marble, and the polymorphic form of aluminium oxide in a- and g- modifications. Polymorphic characteristics also exist in organic chemistry. Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 264; see also Wachenfeld, Joachim, The Patenting of Protein Structures, http://www.vossiusandpartner.com/eng/publication/mip-yearbook.html 2002, Comment.

522 BGH, 3 IIC 226 (1972) – Trioxane.

523 Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 264; BGH, 3 IIC 226 (1972) – Trioxane.

524 Hirsch, Fritjoff, Die Bedeutung der Beschaffenheit chemischer Stoffe in der Patentrechtssprechung, GRUR 1978, 263, 265.

which this crystalline form provides about the three dimensional structure of protein P allow for the protein's use in drug design.

The USPTO applies *In re Bergstrom*[525] to Claim 2, finding that novelty exists due to the fact that the crystalline form of protein P differs from any known form of protein P. Claims directed to products having distinguishable physical forms comply with the novelty requirement, even where their utility is identical to that of the known product.[526] Consequently, novelty is accepted. With the methodology of obtaining protein crystals being highly unpredictable, it is also consequent that the Office accepts non-obviousness under 35 U.S.C. §103.

2. Protein Domains

As for the second group, the EPO had to examine an invention involving structural protein features as binding pockets and protein domains.[527] A binding pocket or so-called active center of a protein is responsible for the catalytic mode of function. It consists of polypeptides that are specifically folded. Due to the specific concave structure within the enzyme, the active center/binding pocket can bind to a suited substrate. In general, there exist six different types of enzymes, oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.[528] Of major importance are hydrolases that split a substrate under "hydrolytic" conditions.[529] Hydrolosys refers to the splitting of a chemical compound with adsorption of a water molecule.[530]

A protein domain is a discrete portion of a protein assumed to fold independent of the rest of the protein and possessing its own function. Thus, it is a region of a protein's amino acid sequence that has evolutionary, structural, and functional significance. Pharmaceutical researchers are most interested in protein domains because they determine the "active" or "binding" sites of molecules. The combination of domains in a single protein determines its overall function. Generating a set of structures representative of most of the possible folds for specific protein domains is the basis of interpreting the structures for new proteins based on known fold-structure

525 In re Bergstrom, 427 F. 2d 1394, 1401-1402 (C.C.P.A. 1970).

526 Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1380 (Fed. Cir. 2003)("[T]his court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs."); also In re Cofer, 354 F.2d 664, 666 (C.C.P.A. 1966).

527 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

528 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 191.

529 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 191.

530 Whitford, David, Proteins, Structure and Function, Chichester, West Sussex, U.K. 2005, 202.

relationships.[531] The particular protein domain shows a significantly higher signaling activity. The transduction of signals at the cellular level refers to the movement of signals from outside the cell to the inside and thus to the question of how membrane receptors transfer information from the environment into the cell's interior. Approximately half of the 25 largest protein families that are encoded by the human genome deal primarily with information processing. Signal movement can be simple. For example, some receptors constitute channels, which, upon ligand interaction, allow signals to be passed in the form of small ion movement either into or out of the cell. These ion movements lead to changes in the electrical potential of the cells that, in turn, propagates the signal along the cell. More complex signal transduction involves the coupling of ligand-receptor interactions to many intracellular events.[532]

a) Claims

The comparative study used the following claims to specify the rules suggested for the patenting of binding pockets and protein domains.

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

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.[533]

531 Available at http://www.genomicglossaries.com/content/proteomics.asp., last checked on January 21, 2008. Another arrangement of structural features and functional groups important for biological activity is a pharmacophore. A pharmacophore is an arrangement of structural features and functional groups important for biological activity. Thus, it refers to the atoms that are involved in the binding of a ligand binding pocket as a whole. If, for example, the binding pocket of a protein consists of 30 binding pockets out of which five are involved in the binding of a particular pharmacophore, those five create the pharmacophore of the mentioned ligand. The binding pockets of the protein and of the ligand must fit together. As for pharmaceutical drugs, a pharmacophore is the functionally relevant portion and it assists in determining a protein's entire 3-D structure, see Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95, 91.

532 Berg, Jeremy M./Tymoczko, John L./Stryer Lubert, , Biochemistry, New York, NY, 2002, 395-424.

533 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

b) Background

Protein P is a known protein whose amino acid sequence has been demonstrated. The patent description provided experimental data and explained that the protein lowers blood pressure. The patentees claimed that they had made a novel discovery, specifically that the active residues in the binding pocket of protein P consist of the above mentioned amino acids. The description specified 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. In addition, the description provided evidence regarding the above mentioned domain. It was explained that the domain showed a significantly higher signaling activity compared to the entire protein P when activated by a natural ligand of protein P. Neither is information available demonstrating the position of the binding pocket of protein P, nor reports suggesting a protein structure domain containing the described binding pocket.[534]

c) Solutions proposed by the EPO and the USPTO

The EPO, firstly, addressed the language of claim 1. The office suggested replacing the word "molecule" by "polypeptide" or compound. If a "molecule" were claimed, the claim would not be sufficiently disclosed, as a molecule as such was not enabled. A claim directed to "polypeptide" would not be directed to any subject matter excluded under Art. 52(2) EPC and comply with the requirements of industrial applicability, clarity, enablement and support.

The EPO rejects Claim 1 on the ground of novelty. Since prior art already includes protein P, the state of the art also comprises the binding pocket. Thus, the natural polypeptide would be prejudicial to the novelty of the claimed subject matter.[535]

With regard to Claim 2, the EPO finds that it is directed to a patentable subject matter according to Art. 52(1) EPC. The requirements of clarity, enablement and support are satisfied. The furnished description would provide sufficient detail regarding the variable ends of the polypeptide. The polypeptide should not be relevant to the blood pressure lowering activity of the claimed portion. The EPO also accepted the novelty, inventive step and industrial application requirements. It states

534 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 9.

535 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

that the specified portion of protein P was not disclosed in the prior art. Further, there was no demonstration or suggestion that this portion may exhibit a higher signaling activity compared to the complete protein P.[536]

The USPTO stressed that Claims 1 and 2 are patentable, eligible subject matter because they are each directed to a composition of matter (an isolated and purified molecule). Moreover, Claims 1 and 2 meet the utility requirement of 35 U.S.C. § 101 since polypeptides exhibiting the binding pocket as defined in the claim are shown to have a higher signaling activity than protein P when activated by a natural protein P ligand. Further, protein P is known to lower blood pressure when active. Lacking a written description and encompassing a broader scope than is enabled by the specification, Claim 1 is rejected under 35 U.S.C. § 112, first paragraph. The claim does not comply with the written description requirement, because it recites a "molecule" defined only by the "structure" of 9 amino acid residues from a source polypeptide of at least 161 residues. From the view of the USPTO, the recited structure is open-ended and only determines a portion of the claimed molecule. The molecule is defined as a polypeptide, but it might 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. They do not constitute a representative number of species of the claimed genus, which include polypeptide and non-polypeptide molecules, to allow one of skill in the art to envision all members of the genus. Therefore, they do not provide an adequate written description of the genus.

As to the enablement requirement, the specification enables the full-length protein P and the specifically disclosed fragment. However, 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. The total number of molecules encompassed by the claim is extremely large. This is due to the fact that there are a large number of residues within the pocket that can be changed to comprise any one of 20 amino acids. Additional unspecified moieties may be included on either end of the binding pocket thereby generating a vast number of molecules encompassed by the claim. Further, a lack of guidance exists regarding structural changes, which may be made in the amino acid sequence between and around the active residues in order that the resulting polypeptide retains its 3-D structure and activity at the binding pocket. Therefore, it requires undue experimentation to make and use the invention over the entire scope claimed in Claim 1.[537]

536 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

537 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 68f.

Claim 2, however, complies with the enablement and written description requirements. It is limited to fragments of protein P that contain the binding pocket described in the specification to retain binding activity and the signaling activity of protein P. The USPTO further stressed that Claim 1 recites open "comprising" language. Thus, the Claim encompasses natural protein P. Claim 1 is anticipated by protein P and therefore lacks novelty according to 35 U.S.C. § 102. Claim 4 is directed explicitly to fragments of protein P consisting of the amino acid residues comprising the binding pocket and retaining binding and signaling activity. These fragments are not included in the prior art and are not rendered obvious based on the known amino acid sequence of the entire protein P.[538]

d) Discussion

Considering the statements provided by the patent offices, it must be noted that the EPO provides only very brief conclusions, whereas the USPTO gives a more detailed description of its reasoning. The two offices adopted similar approaches in their assessment of Claims 1 and 2. They found that the patentable subject matter is easily satisfied. The criteria of description and enablement warranted more analysis. Both the EPO and the USPTO held that Claim 1 referring to a molecule does not satisfy the written description requirement. It is remarkable that the offices do not refer to the enablement factor in the context of comprising language, which they only examine with regard to novelty. The matter of "comprising language" has been the subject of a number of discussions.[539]

The USPTO referred to the character of "open comprising language" with regard to the patenting of DNA fragments (ESTs) in consideration of the "written description guidelines" of January 5, 2001.[540] In Footnote 13 of the official document, the office states:

> "A determination of what the claim as a whole covers may result in a conclusion that specific structures such as a promoter, a coding region, or other elements are included. Although all genes encompassed by this claim share the characteristic of comprising SEQ ID NO: 1, there may be insufficient description of those specific structures (e.g. promoters, enhancers, coding regions, and other regulatory elements) which are also included."

Moreover, the office specified its view in the "Synopsis of Application of Written Description Guidelines"[541]:

538 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 69.

539 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 281.

540 Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, P1, "Written Description" Requirement, 66 FR 1099 (January 5, 2001).

541 Synopsis of Application of Written Description Guidelines, available at

> "In the case of a partial cDNA sequence that is claimed with open language (comprising), the genus of, e.g., "A cDNA comprising [a partial sequence]," encompasses a variety of subgenera with widely varying attributes. For example, a cDNA's principle attribute would include its coding region. A partial cDNA that did not include a disclosure of any open reading frame (ORF) of which it would be a part, would not be representative of the genus of cDNAs because no information regarding the coding capacity of any cDNA molecule would be disclosed. Further, defining "the" cDNA in functional terms would not suffice in the absence of a disclosure of structural features or elements of a cDNA that would encode a protein having a stated function. (…)"[542]

In the course of the Synopsis, the USPTO referred to a specific claim which was rejected due to its comprising language. The USPTO in this case argued the following:

> "Here, the specification discloses only a single common structural feature shared by members of the claimed genus, i.e., SEQ ID NO: 16. Since the claimed genus encompasses genes yet to be discovered, DNA constructs that encode fusion proteins, etc., the disclosed structural feature does not "constitute a substantial portion" of the claimed genus. Therefore, the disclosure of SEQ ID NO: 16 does not provide an adequate description of the claimed genus. Weighing all factors, 1) partial structure of the DNAs that comprise SEQ ID NO: 16, 2) the breadth of the claim as reading on genes yet to be discovered in addition to numerous fusion constructs and cDNAs, 3) the lack of correlation between the structure and the function of the genes and/or fusion constructs; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of DNAs which comprise SEQ ID NO: 16. Conclusion: The written description requirement is not satisfied."[543]

Accordingly, the USPTO in the case of the synopsis rejected the DNA claim on the basis that the comprising language is too broad for sufficient enablement. The arguments outlined in the above cited example, however, do not equally apply to the proteomic case at issue. As to the synopsis, the USPTO alleges that the breadth of claim regarding genes yet to be discovered in addition to numerous fusion constructs and cDNAs leads to a lack of enablement. The case at issue, by contrast, involves a protein (P) that is already included in the prior art and thus disclosed. The breath of claim consequently only refers to features that are already state of the art. Thus, the use of comprising language does not lead to a lack of enablement. The term "comprise" is not rejected as failing the enablement factor in general, but only in the case where sufficient enablement is not provided by the given written description and/or by the prior art. This differentiated view of the phrase "comprise" complies with former statements provided by both patent offices. In the Trilateral report considering the patenting of ESTs, the USPTO stated that "comprising claim" indeed would

http://www.uspto.gov/web/menu/written.pdf, p. 31-32, last checked on January 21, 2008.

542 In this context the USPTO referred to the claim formulation of Regents of the University of California v. Eli Lilly & Co., 119 F3-D 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Here, a description of a genus of cDNAs had been achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

543 "Synopsis of Application of Written Description Guidelines available at: http://www.uspto.gov. /web/menu/written.pdf, 31, last checked on January 21, 2008.

be broader than the "consisting claim".[544] The crucial question, however, would be whether the invention could be carried out in light of the *In re Wands* factors, which serve to assess sufficient enablement.[545]

In *Ak Steel Corp. v. Sollac*, the Federal Circuit extensively commented on the interpretation of "comprising" and "consisting", holding that a "comprising claim" must be considered as "open-ended".[546] Accordingly, the court does generally accept "comprising language" under the written description requirement. The question of sufficient enablement rather has to be assessed by the analyses of the *In re Wands* factors and does not primarily depend on the question of what is included from a comprising claim. Moreover, the question must be decided on the grounds of each given case.[547]

The EPO also considered the interpretation of the terms "comprising"/ "consisting" on various occasions, that collectively mirror a differentiated approach. In the course of the Trilateral Project related to the patenting of DNA fragments the offices held that

> "We are not able to see any difference when judging invention activity with respect to the claim language "consisting of" or "comprising". [548]

As to the particular "comprising claim" directed to ESTs the office states that it does not include DNA with unlimited length, but rather lengths that are still suitable for the purpose of DNA micro array technologies. In T 759/91, the Board of Appeal of the EPO had already extensively analyzed the issue stating that

> "While in everyday language the word "comprise" may have both the meaning "include", "contain" or "comprehend" and "consist of", in drafting patent claims legal certainty normally requires it to be interpreted by the broader meaning "include", "contain" or "comprehend".[549]

Applying the principles set forth above to the claim at issues, it appears consequent that both offices reject claim one. The office applies its well established practice that a claim should only encompass as much as is contained in the description. Here, the description provides information exclusively regarding the polypeptide chain of the

544 Trilateral Project B3b Comparative study on biotechnology patent practices, Theme: Patentability of DNA fragments, available at: http://www.european-patent-office.org/tws/sr-3-b3b.htm.

545 In re Wands, 858 F.2d 731, 731 (Fed. Cir. 1988). (The enablement requirement must be determined in light of "a. The quantity of experimentation necessary to practice the claimed invention; b. The amount of direction or guidance presented in the specification; c. The presence or absence of working examples in the specification; " d. The nature of the invention; e. The state of the prior art; f. The relative skill of those of ordinary skill in the art; g. The predictability or unpredictability of the art; and; h. The breadth of the claims).

546 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1239, 1244-1245 (Fed. Cir. 2003). The court further explains that the phrase "consisting essentially of" in a patent claim represents a middle ground between the open-ended term "comprising" and the closed ended phrase "consisting of".

547 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1244-1245.

548 Ak Steel Corp. v. Sollac, 344 F.3d 1234, 1244-1245.

549 T 759/91, N. Publ., No. of the Reasons 2.2. (EPO 1993). See also T 711/90, N. Publ., No. of the Reasons 2.2. (EPO 1993).

protein. Yet, the entire molecule contains additional information not supported by the disclosed description. Therefore, the USPTO consequently applies its written description guidelines, stating that:

> "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art"[550]

It is also consequent that the two offices discuss the comprising language with regard to novelty. They both found that claim 1 does not satisfy the novelty requirement, whereas they concur that the novelty of Claim 2 is established. Notwithstanding the details provided by the USPTO, it is unclear as to how novelty of Claim 2 is derived. The EPO rejects the novelty of Claim 1 on the grounds of that the prior art already reported protein P, meaning that the state of the art also encompasses the binding pocket. Hence, the natural polypeptide is prejudicial to the novelty of the claimed subject matter.[551] The EPO found the novelty of Claim 2 to be given, stating that the prior art did not disclose the specified portion of protein P. The state of the art does not suggests this portion to exhibit an unexpected elevated signaling activity compared to the whole protein P.[552]The USPTO further stresses that Claim 1 is anticipated by protein P and therefore lacks novelty. Due to its open "comprising" language, the claim encompasses natural protein P. The office accepts the novelty of Claim 2 by reasoning that it is directed only to fragments of protein P that were not included in the prior art or were obvious. Hence, the "comprising language" does not only result in a lack of written description, but also in a lack of novelty. With "comprising" being understood in a broader sense than "consisting", Claim 1 encompasses the entire protein P, meaning that it overlaps with what is included in the prior art. According to the Board of Appeal of the EPO, such "overlapping claims" do not focus sufficiently on the specific part of the selection invention.[553] If a skilled person, however, is able to carry out the invention according to the description of the prior art that is used for the support of the new invention, the patent application does not match the standards of a selection invention. Therefore, Claim 1 fails to meet the novelty requirement. In accordance with statements of the patent offices set forth above, only the novelty of Claim 2 can be acknowledged.

550 Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement, 66 FR 1099 (January 5, 2001).

551 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

552 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 36.

553 T 279/89, N. Publ., 4.2 (EPO 1991), see also T 279/89, N. Publ., 4.2 (EPO 1991); T 666/89, OJ 1993, 495; T 255/91, OJ EPO 1993, 318; Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.

Could novelty be established, assuming that the claim used "consisting language" instead of "comprising language"? Novelty might be derived under the principles of the first and second medical indication pursuant to Art. 54(5) EPC. As mentioned in Chapter III, a case of a first medical use exists if the invention resides in the initial discovery that a certain substance can be used for medical treatment. In this event, a broad claim to a pharmaceutical composition containing the substance is allowed without restriction of the actually identified medical use. When a further medical use of a substance already known to be pharmaceutical useful is identified, the EPO allows so-called 'second medical use' claims in the Swiss-type format.[554] These claims relate to a new use of an already known substance. Although the principles of first and second medical indication are applicable to field of proteomics, the claim at issue does not meet the requirements of Art. 54(5) EPC. Lacking Swiss-type format, it is not directed to a further use of protein P. The claims merely refer to a new characteristic of protein P and thus cannot be considered novel under the principles of first and second medical indications.

Novelty might further exist under the principles developed for 'selection inventions.'[555] A selection invention refers to an invention in which the constituting elements are derived from the species conception of a generic invention.[556] Specifically, the compound as such has been reported by the prior art, but the more selective structure/pure form etc., remains undisclosed as it falls within the classification of the already known protein.[557] Accordingly, a selection invention refers to technical contents that are not explicitly disclosed by the generic invention.[558] In *Thiochchloroformates/HOECHST* that refers to a process of preparation of a chemical compound, the Board determined that a selection invention exists:

554 Busse/Keukenschrijver, PatG, § 5 No. 33; § 3 No. 201.

555 Guidelines for Examination in the EPO, Part C-IV, 911a explain that "the subject-matter of selection inventions differs from the closest prior art in that it represents selected sub-sets or sub-ranges. If this selection is connected to a particular technical effect, and if no hints leading the skilled person to the selection exist, then an inventive step is accepted (this technical effect occurring within the selected range may also be the same effect as attained with the broader known range, but to an unexpected degree). The criterion of 'seriously contemplating' mentioned in connection with the test for novelty of overlapping ranges should not be confused with the assessment of inventive step. For inventive step, it has to be considered whether the skilled person would have made the selection or would have chosen the overlapping range in the hope of solving the underlying technical problem or in expectation of some improvement or advantage. If the answer is negative, then the claimed matter involves an inventive step." See also Cornish, William/Llewelyn, David, Intellectual Property: Patents, Copyright, Trade Marks and Allied Rights, 6th ed., London 2007, 194.

556 See T 0012/90, N. Publ., No. of the Reasons 3.3.1 (EPO 1990); the patentee claimed novelty on the ground of selective group of chemical compounds. The board rejected, considering the selection as being too broad.

557 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345.

558 Turrini, Enrico, The Concept of Novelty – A Review of the Case Law of the Board of Appeal of the European Patent Office, 22 IIC 932, 938 (1991).

> "if the sub-range selected is narrow ... and sufficiently far removed from the known range illustrated by means of examples. The sub-range is novel not by virtue of an effect which occurs only within it; but this effect permits the inference that what is involved is not an arbitrarily chosen specimen from the prior art but another invention (purposive selection)."[559]

In other words, a) the selected sub-field is required to be narrow, b) the selected field is sufficiently far removed from the known range illustrated by working examples, c) the sub-field must not merely be randomly selected, but should be the result of a more tightly focused technical teaching and d) the selected area should not provide a mere embodiment of the prior art description, but another invention.[560]

These principles developed by the Board of Appeal of the European Patent Office for the field of chemistry[561] are also applicable to protein-related inventions. Like a chemical compound, a protein consists of distinct structural features, which can be compared to a variety of structural items. The composition of those structural items can be considered as being similar to the composition of chemical features. With regard to the claim at issue, the binding pocket/protein domain of Claims 1 and 2 are a narrow field of the disclosed protein P. Being excluded from any working examples known in the prior art, a) and b) are thus satisfied. The focus on the binding pocket structure is intensive and results in a specific selection, and thus complies with c). Consequently, the claim at issue meets the novelty requirement under the principles for selection inventions. Moreover, the involvement of an inventive step is required.[562] With respect to the selection invention a person skilled in the art should not be allowed to complete the technical problem.The selection invention[563] that is deemed to be nonobvious involves an outstanding effect, property, or use when compared with the compounds in the known generic invention.[564] It has been determined that the binding pocket exhibits higher signaling activity which can be defined as an outstanding effect. As to what has been included in the prior art, the elevated signaling activity must be considered an unexpected result and thus can be de-

559 T198/84 Thiochchloroformates/HOECHST, OJ 1985, 209.

560 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 345; T 279/89, N. Publ.; see also Domeij, Bengt, Pharmaceutical Patents in Europe, Stockholm 2000, 157-168, 164.

561 Further decisions of the Board of Appeals related to selection inventions are T247/91, N. Publ.(EPO 1982); T45/91, N.Publ. (EPO 1992); T198/84, OJ 1985, 209; T133/92, N. Publ.(EPO 1994). As for the German case law, see Hirsch, Fritjoff, Neuheit von chemischen Erfindungen, GRUR 1984, 243, 245 and the cited decisions therein.

562 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 348.

563 The principles of the selection invention thus do not fit under the typical "three-step-examination" of state of the art, novelty and inventive step. Since novelty already depends on the inventiveness, the third step, the "inventive step"m is inherent in the novelty analyses, see Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 348.

564 Blumer, Fritz, Formulierung und Änderung der Patentansprüche im europäischen Patentrecht, München 1998, 358.

fined as being nonobvious. Consequently, both claims meet the inventive step requirement.

The U.S. patent law system is also familiar with the principles related to selection inventions.[565] The taken approach resembles the European one. A "selection invention" refers to a species or subgeneric invention directed to a prior art reference (i) possessing novelty over the closest disclosed embodiment of that prior art reference; and (ii) being within the scope of that prior art reference. As under European patent law, the crucial element is the distance of the closest embodiment to the claimed inventions. The major question is whether that closest embodiment raises a *prima facie* case of obviousness.[566] The chemical case law is split in this respect.[567] *In re Susi,* the court found a chemical invention to be *prima facie* obvious where the broad prior art disclosure includes at least some of the compounds claimed by the applicant, and the prior art chemicals were of a class to be used for the same purpose as the compounds of the applicant.[568] Thus, any disclosure that includes the chemical materials claimed by the applicant would render the claimed materials obvious and require an applicant to rebut the *prima facie* case with evidence of nonobviousness.[569] The rational established in *Susi* was followed by several other decisions. In *Merck & Co. v. Biocraft Laboratories Inc.,* the applicant claimed solely one of 1200 embodiments disclosed by the prior art.[570] The court found that when the prior art teaches the skilled person that any of the 1200 embodiments could be used; a case of *prima facie* exists. The court held that this was especially true, because the claimed composition was used for the same purpose taught by the prior art.[571] A different line of determining obviousness was set forth with the decision of *In re*

565 A number of further decisions related to selection inventions are cited by Wegner, Harold, Patent Law in Biotechnology chemicals & Pharmaceuticals, New York 1994, 161 and 167. See also In re Petering, 301 F.2d 676, 133 USPQ 275 (C.C.P.A.), indicating that a prior genus could be an anticipation of alter species or Kalman v. Komberly Clark Corp., 713 F.2d 760, 771, 218 USPQ 781, 789. More recently, the CAFC decided in CFMT, Inc. v. Yieldup International Corp. 349 F.3d 1333 (Fed. Cir. 2003) that additional inventive work does not alone show enablement. Developments related to selection inventions do not cast doubt on enablement of the original invention, see also Eli Lilly v. Zenith Goldline, 364 F.Supp.2d 820 (S.D.Ind. 2005) ("Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability").

566 Wegner, Harold, Patent Law in Biotechnology Chemicals & Pharmaceuticals, New York 1994, 160-161.

567 The principle that it is allowed to claim a narrow range within a broad range disclosed by the prior art is also referred to as "the doctrine of selection inventions", see Varma, Anita/Abraham, David, DNA is different: legal obviousness and the balance between biotech inventors and the market, Harvard Journal of Law & Technology 1996, 53, 69.

568 In re Susi, 440 F.2d 442 (C.C.P.A. 1971).

569 In re Susi, 440 F.2d 442, 446.

570 Merck & Co. v. Biocraft Laboratories Inc., 874 F.2d 804 (Fed. Cir. 1989), cert. denied, 493 U.S. 975 (1989).

571 Merck & Co. v. Biocraft Laboratories Inc., 874 F.2d 804, 807.

Jones.[572] The Federal Circuit held that a *prima facie* obviousness based on structural similarity was not raised where the claimed chemical compound was a subspecies of a broad genus. The court concluded that "we decline to extract from *Merck* the rule that … regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it." The court distinguished *Merck* by stating that the claimed species was not specifically disclosed, but merely encompassed by the broad and general prior art teaching. This rational was approved and further developed by *In re Baird*.[573] The applicant's claim involving a bisphenol A[574] had been rejected as being *prima facie* obvious over prior art disclosure of a broad genus of diphenols.[575] The court accepted the claim, stating that there was nothing in the prior art suggesting that a skilled person should select bisphenol A from among more than 100 million diphenols included in the broad genus disclosed in the prior art. The court explained that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."[576] Finally, in *In re Bell*, the Federal Circuit addressed of what is understood as an inordinately large number of possibilities that faces one skilled in the art attempting to arrive at the claimed DNA sequence.[577] The Court followed the rational set forth in *re Jones*, stating that a *prima facie* case of obviousness requiring a person skilled in the art to select among a large number of choices is not properly decided.[578]

Although the cited case law is not unambiguous, the breadth of claims must be considered the crucial factor with regard to the obviousness requirement. As for the claim at issue, it follows that the claim meets the requirements of novelty and non-obviousness, provided that the patent applicant uses "consisting language" instead of open "comprising language".

572 In re Jones, 958 F.2d 347 (Fed. Cir. 1992).
573 In re Baird, 16 F.3d 380 (Fed. Cir. 1994).
574 Bisphenol A is a chemical substance (phenol) that is used to make polycarbonate plastic.
575 Phenols represents a group of chemical compounds consisting of a hydroxyl group (-OH) linked to an aromatic hydrocarbon group; such as phenol (C6H5OH).
576 In re Baird, 16 F.3d 380, 382.
577 In re Bell, 991 F.2d 781 (Fed. Cir. 1993).
578 In re Bell, 991 F.2d 781, 784; see also Varma, Anita/Abraham, David, DNA is different: legal obviousness and the balance between biotech inventors and the market, Harvard Journal of Law & Technology 1996, 53, 73, and cited case law. The authors also provide a detailed discussion of the In re Bell decision.

The following claims concern proteomic technologies involving *in-silico* screening methods and the identified compounds thereof, as well as inventions involving the 3-D structural data of proteins *per se.* All these inventions are part of the rapidly evolving area of bioinformatics. *In-silico* screening consists of computerized simulations of the three-dimensional structure of a given polypeptide and was already introduced in Chapter II. The current availability of new information technologies enables scientists to compare a gross amounts of structural data. Therefore, approaches such as *in-silico* screening are increasingly replacing earlier *in-vivo*[579] and *in-vitro* methods.

The major goal of *in-silico* methods is to identify compounds which can bind to a computerized protein. In addition to applications for new *methods*, patent offices are confronted with an increasing number of patent applications related to the *results* from *in-silicio* screening. Specifically, we have seen in recent years the filing of applications involving the identification of candidate compounds which would theoretically form the most stable complex with the computerized 3-D models of proteins. The latter, again, are the subject of an increasing number of applications filed in recent years. Through methods such as NMR structure determination, X-ray crystallography and protein homologous-comparison, the speed of 3-D structure identification has increased steadily. Claims are often directly directed to *in-silicio* screening methods, since applications argue that the findings they put forth are a necessary precondition for compound identification.

Combined with a number of other influences, these new forms of research have resulted in the development of bioinformatics. Bioinformatics, in turn, refers to 'the application of quantitative analytical techniques to the modeling of biological systems'.[580] More specifically, the term describes the development and employment of computer-implemented algorithms and data processing methods directed to data analysis and interpretation.[581] The latter are then used in the design of new pharma-

579 Within a living organism or body. For example testing conducted on whole animals, such as mice.

580 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA - The Journal of Law and Technology 2003, 93-131, 94. Bioinformatics draws researchers from the fields of biology, computer science, statistical mathematics, and linguistics.

581 Rimmer, Matthew, Beyond Blue Gene: Intellectual Property and Bioinformatics, 34 IIC 31, 31 (2003) defines "bioinformatics" as "the art and science of using computer systems to store, manage and analyse biological information that brings together the diverse disciplines of mathematics, statistics, engineering, and computer science to map and model genes and proteins". The purpose of bioinformatics changes in relation to the improved organization of vast amounts and numerous types of biological information, and the clarification of the biological or medical significance of such information through its analyses. See also Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 85.