surrounding this area of the law, the inventor should, to the extent possible, seek broad literal coverage rather then rely upon the doctrine of equivalents.[1095]

V. U.S. Patent No. 5,835,382 "Small Molecule Mimetics of Erythropoietin"[1096]: A characteristic proteomic patent

A number of cases involving the filing of patents involving protein crystal structure determination have been described. Furthermore, the case study illustrated further claims related to proteomic research, among them claims to 3-D structural data directed towards the use of structural data in rational drug design. To substantiate the results of these concrete claims, it is useful to consider another patent. Specifically, the legal treatment of a patent directed to the screening of erythropoietin (''Epo'') mimetics will be reviewed, since it encompasses a number of characteristics typical of proteomic inventions.[1097] In particular, it demonstrates an indirect way to claim a protein defined by its folding type and may also involve screened sequence-dissimilar proteins consisting of the same folding type as the ''Epo'' molecule. The invention involves a computer-assisted method for identifying molecules that are able to bind to the ''Epo'' receptor. Due to their structural similarity these ''Epo'' 'mimetics'[1098] act in the same fashion as ''Epo''. In particular, they are capable of binding to the ''Epo'' receptor. Since they display the response usually found in ''Epo'', the identified compounds emulate the important functions that are otherwise performed by the ''Epo'' molecule, acting as agonists of the ''Epo'' receptor. The claimed method is conducted on grounds of precise structural information obtained from x-ray crystallographic methods of the extracellular domain of ''Epo'' receptor linked to a binding peptide (which acts as an ''Epo'' mimetic). This crystallographic data enables the identification of atoms in the peptide mimetic that are significant

1095 Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claiming genuses of related protein sequences, Holman, Christopher M., Protein similarity score: a simplified version of the blast score as a superior alternative to percent identity for claimng genuses of related protein sequences, 21 Santa Clara Computer & High Tech. L.J. 2004, 55, 61 who recommends not relying on the doctrine in order to expand the claim coverage on protein variants.

1096 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1097 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998, see also Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951.

1098 The term "Mimetics" refers to selected chemical structures similar to the three-dimensional structure of the subset of atoms of the the 'EPO' peptide, see Meyers, T. C./Turano, T. A./Greenhalgh, D. A./Waller, P. R., Patent protection for protein structures and databases, 7 Suppl Nature Structural Biology 2000, 950, 951.

for ‘‘Epo’’ receptor binding. This data includes a 3-D array of the important contact atoms.[1099]

The written description reveals the tertiary structure of the ‘‘Epo’’ receptor and discloses the binding properties of potential ‘‘Epo’’ mimetics. It determines that other molecules including a portion in which the atoms have a 3-D structure similar to some or all of the ‘‘Epo’’ contact atoms are likely to be capable of acting as an ‘‘Epo’’ mimetic. The description further discloses that a peptide considerably smaller than the natural ‘‘Epo’’ can act as an agonist and induce an adequate biological response. Thereby, it is assumed that the binding peptide forms a substantially smaller contact interface than the natural ‘‘Epo’’ with the receptor. The description also concludes that the identification of the most crucial residues and functional key interactions provides a practical target for drug design.[1100]

To get a better sense of what is exactly claimed, it is useful to reproduce excerpts of the actual specification. It reads as follows:

1. A computer-assisted method for identifying potential mimetics of erythropoietin, using a programmed computer comprising a processor, a data storage system, an input device, and an output device, comprising the steps of:
   (a) to ... (d)
2. A computer-assisted method for identifying potential mimetics of erythropoietin, using a programmed computer comprising a processor, a data storage system, an input device, and an output device, comprising the steps of:
   (a) to ... (c)
3. A compound having a chemical structure selected using the method of claim 1, said compound being an ‘Epo’ mimetic.
4. ...[1101]
5. The compound of claim 3 wherein said compound is a peptide.
6. The compound of claim 5 wherein said peptide has 15 of fewer amino acids.[1102]

The patent includes various aspects that are remarkable in light of the discussion above. With regard to the demonstrated invention involving a natural ‘‘Epo’’ product, it must be distinguished, because it is not directed to the purification of natural ‘‘Epo’’, but rather to its replacement through a different protein. The underlying motivation of the inventors, however, might be similar; both methods may enable drug design independent of recombinantly obtained ‘‘Epo’’ molecules. The former method obtains the ‘‘Epo’’ molecule from urine, plasma or other substances; the latter

1099 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1100 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

1101 Claim 4 referred to non-peptide molecules that are not subject of this analysis.

1102 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998.

is directed to the identification of 'Epo' mimetics that equally perform the natural ''Epo'' functions.[1103]

As to the question of dependency, it is relevant that the computerized data related to the ''Epo'' receptor has been obtained on grounds of recombinant technologies and associated crystallizing methods not encoding ''Epo'' itself, but rather the membrane receptor protein to which ''Epo'' binds. High relevance is established with regard to the question of whether dissimilar proteins bearing structural similarities and function infringe earlier issued patents. From the perspective of inventors holding patents to the original ''Epo'', the claimed ''Epo'' mimetics might represent a case of sequence-dissimilar proteins having equal/similar folding features and functions as the native ''Epo''. It is also worth noting that the question of 'reach-through claiming' is not raised. Potentially screened ''Epo'' mimetics are precisely defined by size and shape. The patent description thus provides sufficient information for matching the enablement requirement.

In terms of scope of protection issues, it is clear that anyone who uses the coordinates to identify structures similar to the specified peptide may be an infringer and consequently may be liable for damages and prohibited from using this method to find ''Epo'' mimetics. As for patent dependency and infringement of other patents, the following rules can be established. First, the computerized method stimulates the ''Epo'' receptor rather than the ''Epo'' molecule itself. Hence, no patent dependency exists with regard to inventions involving the natural or the recombinantly obtained ''Epo''. Second, the structural data referring to the ''Epo'' receptor relies on recombinantly produced molecules and crystallographic analysis. Therefore, patent dependency with regard to potential patents covering these crystallizations methods is established. Additionally, patents involving the recombinant production of ''Epo'' receptors are infringed. Patents for recombinantly obtained ''Epo'' molecules are not infringed unless the patent owner includes structural knowledge as to the crucial binding residues and core interaction features, i.e., atoms. In this event, the patent is extended to the ''Epo'' mimetic molecule determined by this information pursuant to the doctrine of equivalents.

The patent demonstrates the great significance of the above conducted discussion on infringement through the use of sequence-dissimilar proteins or other non-patented molecules. In order to 'invent around' existing patents, inventors search for proteins that are not yet patented but able to perform similar biological functions. Attempts to find alternatives for patented compound occur also in the field of prion research. For example, U.S. Patent 5,773,572, entitled "Fragments of prion proteins", concerns synthetic polypeptides that emulate the 3-D structures of proteins involved in mental prion disorders.[1104]

1103 Wilson; Ian A./Livnah; Oded/Stura; Enrico A./Johnson; Dana L./Jolliffe; Linda K., Small molecule mimetics of erythropoietin, La Jolla 1998

1104 U.S. Patent 5,773,572 "Fragments of prion proteins" by Fishleigh, Robert Vincent/Robson, Barry/Mee, Roger Paul, Macclesfield 1998.

VI. Use of selective 3-D protein structure parts (Selection inventions)

1. Relationship to patents covering the entire protein

With regard to a selection invention, it is primarily the dependency on the patent that covers the entire protein that has to be considered. Hence, the patent to the genetic sequence is only involved if the entire protein is part of a patented recombinant process. A potential claim to a selective part of a protein has already been analyzed in the case study above,[1105] but shall be introduced again, reading as follows:

> 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.[1106]

As introduced above, "selection inventions" claim a narrow range within a broad scope disclosed by the prior art. [1107]Besides determining the "obviousness" of a claim to a selective field of a broader invention, the question of patent dependency is a decisive element of selection inventions. For classification of the problem, the same principles are applied as those used for the treatment of "improvement inventions". Developments of improved versions of drugs are not necessarily directed to a selective part of the earlier invention, but can also cover additional aspects or the broadening of the earlier version. Generally the term "improvement" is used as an "umbrella term" and also includes the cases in which one "invents around" an existing invention, e.g. attempts to advance the existing technique by using different compounds or facilities without touching the scope of the existing patent.[1108] With the high standard of the "obviousness" factor developed in the field of "selection inventions", the inventive step requirement, however, always includes an improvement over the earlier invention, and the prior art, respectively. Thus, even though not all improvements of a drug produce selectivity, each selective invention can be considered as improvement. The same protein can be used in an improved manner due to the disclosure made with regard to the binding pockets. Generally, patent law does not vest in the original patent holder any right to improvements or derivative inventions and new patents can be granted for the selective part if all other requirements are met. In most cases, the selective patent is "blocked" by the original patent holder, meaning that the selection invention cannot be used without a license from the original patent holder whose technology has been incorporated into the improved

1105 Chapter 3 B II 2 a).

1106 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.

1107 Chapter 3 B II 2 d).

1108 Dow, Kenneth J./Quigley, Traci Dreher, Improvements for handling improvement clauses in IP licenses: an analytical framework, 20 Santa Clara Computer & High Tech. L.J. 2004, 577, 580-581.