ver, various attempts to isolate erythropoietin from urine resulted in unstable and biologically inactive preparations of the hormones.[899]

II. Use of 3-D structure from recombinant proteins

Recombinant techniques are presently more successful for the production of therapeutically effective amounts of proteins.[900] In this context, the first question that emerges is whether the use of the recombinantly produced protein 3-D structures infringes the patent involving the gene sequence. This query is easily solved if the sequence identical protein is used. The patent to the gene sequence that encodes for such a protein is literally infringed under Section § 271(a) U.S.C./Section 139 (1) GPA. It is irrelevant as to whether the protein is used specifically with regard to its 3-D structure. Although the claim to the gene sequence and the encoded protein does not include the structural coordinates as claimed, the structural coordinates are an inherent property of the claimed protein in a particular state. As illustrated in Part II, proteins automatically fold into their final folding stage after they are encoded by the underlying nucleotides.[901] The folding process is initiated as soon as the RNA translates the genetic information. Hence, the use of these proteins includes the tertiary or quaternary structure of the protein and not merely the amino acid sequence in its primary folding stage. Recombinant processes encode the protein as a whole, e.g., in its entire tertiary structure. Thus, a patent to the recombinantly produced tertiary structure automatically covers the recombinantly produced primary structure, the amino acid sequence. Accordingly, any patent to the recombinantly produced 3-D protein structure automatically depends on the earlier issued patent to the recombinantly produced amino acid sequences. In other words, in using the subject matter of the 3-D structure patent, the patentee will need to infringe the exclusive rights belonging to the patentee of the amino acids sequences.[902] This reasoning further complies with Art. 9 of Directive 98/44/EC stating that the scope of biotechnological inventions extends to "all material in which the product [consisting of genetic information] is incorporated". The term "incorporated" must be interpreted as referring to genetic information that "is inserted by means of a technical process".[903] A recombi-

899 As stated in U.S. Patent 5,441,868 "Production of recombinant erythropoietin" to Linn, F.K (Thousands Oaks 1995): "Prior attempts to obtain erythropoietin in good yield from plasma or urine have proven relatively unsuccessful. Complicated and sophisticated laboratory techniques are necessary and generally result in the collection of very small amounts of impure and unstable extracts containing erythropoietin."

900 See, for example, U.S. Patent 5,441,868 "Production of recombinant erythropoietin" to Linn, F.K (Thousands Oaks 1995).

901 Chapter B II.

902 Unless the experimental use exception applies.

903 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 267.

nant protein contains genetic information that was inserted by a recombinant technology.

Legal questions arise if known recombinant technologies are improved or modified in order to enable proteomic research.[904] With recombinant technologies frequently involving problems in 3-D protein structure determination, this issue typically occurs in the field of proteomic research tools. Most proteomic studies must recognize that the proteome changes constantly. Modifications and interactions, binding activity, and self-regulatory adjustments all ensure that the proteome sensitively reacts to the environment. In this context, European patent No. 0636183 "Compositions and Methods For Protein Structural Determinations" is of particular interest.[905] It focuses on the improvement of a recombinant method in order to enable NMR spectroscopy, which otherwise had not been possible. More specifically, the patent involves a new composition and method for the determination of 3-D structures of proteins expressed in cultures of mammalians or insects cells by NMR spectroscopy.[906] It takes into account that most mammalian proteins contain significant post-translational modifications that cannot be effected in bacterial or yeast systems. Existing studies on mammalian and insect cell produced proteins have also been unsatisfactory. Therefore, the patented invention provides a novel method for creating a mammalian or insect cell culture which is capable of producing the protein of interest in a nutrient medium containing all amino acids that are essential for the growth of the cell - in a configuration that permits NMR spectroscopy. The patent is specifically directed to proteins that cannot be analyzed by x-ray crystallography, such as mammalian cell proteins.[907] Claim 1 of European Patent No. 0636183 to "Compositions and Methods For Protein Structural Determinations" reads as follows:

> „A method for determining three-dimensional structural information of a protein, which comprises the steps of (a) growing, under protein-producing conditions, a mammalian or insect cell culture which is capable of producing the protein of interest in a nutrient medium which contains all amino acids that are essential for growth of the cells and which contains assimilable sources of carbohydrate, essential minerals and growth factors, wherein the amino acids and any other substrate used by the cells for protein synthesis in such nutrient medium are substantially isotopically labeled; (b) isolating the labeled form and (c) subjecting the protein to NMR spectroscopic analysis to determine information about its three-dimensional structure. [908]"

The question must be asked of whether the use of the above invention infringes patents involving similar recombinant technologies for the production of the same amino acid sequences. On the one hand, different recombinant technologies produc-

904 Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 310.

905 European Patent No. 0636183 "Compositions and Methods for Protein Structural Determinations" by Brown, Jonathan M., Columbia 1994.

906 Id.

907 Id.

908 European Patent No. 636183 "Compositions and Methods for Protein Structural Determinations, by Brown, Jonathan M., Columbia 1994.

ing the same amino acid sequences typically use the same gene sequences, which is why infringement should be constituted. On the other hand, Claim 1 is directed to a recombinant technology that for the first time provides a sufficient basis for any conduct of NMR spectroscopy. The question thus is whether it follows that infringement is not established. The new NMR approach, however, still relies on already patented recombinant technology. In conclusion, the method claimed in Claim 1 must be considered an improvement of earlier invented and patented mammalian expression systems. Consequently, Claim 1 depends on any earlier issued patents directed to recombinant technologies being used in the new NMR-related approach and infringement of those patents is constituted.[909]

III. Use of 3-D structure from crystallized proteins

An alternative to obtaining protein 3-D structures from natural or recombinant sources is to crystallize them.[910] Protein crystals are not only used for the determination of structural properties, but have a number of other applications. Lately, studies have shown that they are useful as a means of achieving controlled drug administration. With most drugs being rapidly cleared by the organism following medication, stabilizing a desired drug level in the organism is considered a major challenge. Protein crystals provide significant benefits in the controlled delivery of protein drugs such as insulin or interferon. To ascertain the prescription of correct dosages, uniform sizes must be produced.[911]

A patent on protein crystals can be directed either to the crystallization of the protein *via* a particular procedure, or to the obtained crystals themselves. To establish a comprehensive understanding of related claims, it is useful to consider a number of examples, both from the U.S. and Europe. A second step then focuses on the question of infringement. The following illustrates a U.S. patent claim to the crystals themselves:

> A crystal of a protein-ligand complex comprising a protein-ligand complex of an N-terminal truncated IF4E and a ligand, wherein the crystal effectively diffracts X-rays for the determination of the atomic coordinates of the protein-ligand complex a resolution of greater 5.0 Angstroms; wherein …"[912]

909 The development of the new method might, however, be covered by the research exemption, as for the German case (§ 11 No. 2 GPA), see Straus, Joseph, Zur Zulässigkeit klinischer Untersuchungen am Gegenstand abhängiger Verbesserungserfindungen, GRUR 1993, 308, 310.

910 Chapter 2 E II 2 a).

911 Basu, Sujit K./Govardhan, Chandrika P./Jung, Chu W./Margolin, Alexey L., Protein crystals for the delivery of biopharmaceuticals, 4 Expert Opinion on Biological Therapy 2004, 301, 301.

912 US Patent No. 5,872,011"Crystal of protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof", by Burley, Stephan K./Nahum, Sonnenberg/Marcotrigiano, Joseph/Gingras, Anne-Claude, New York 1999.