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.

The claim has been filed by Rockefeller University, which obtained U.S. patent No. 5,872,011 entitled "Crystal of a protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof."[913] The invention involves a form of the messenger RNA 5' cap-binding protein that can be crystallized with a ligand to form a crystal with sufficient quality to allow detailed crystallographic data to be obtained. Furthermore, the invention comprises the crystals and the three-dimensional structural information, and includes procedures for related structural based drug design using the obtained crystallographic data. As a preferred method, sitting-drop vapor diffusion is utilized to grow the crystal.

By comparison, a claim directed to the crystallization of the protein via a particular procedure can be expressed as in the following claim of US Patent No. 5,872,011:

> A method for determining the three-dimensional structure of a co-complex of [the specified protein] ... which comprises (a) x-ray diffraction data for crystals of the co-complex, and (b) utilizing a set of atomic coordinates selected from the group consisting of [the protein]; a portion thereof; and coordinates having a room mean square deviation therefrom with respect to conserved protein backbone atoms of not more than 0.65 ANG to define the three-dimensional structure of the co-complex. [914]

The claim is directed to the design of an immunosuppressive agent for the treatment of patients suffering from autoimmune disorders and for recipients of transplanted organs. Research efforts have led to the identification of a protein, tyrosine kinase, as a crucial element for immune responses. It was found that blocking the biological function of ZAP-70 leads to immunosuppression. The invention therefore proposes the design of a 3-D structure-based inhibitor of the ZAP-70 protein. It includes the cloning, expression and purification of the ZAP-70, its crystallization, the determination of its tertiary structure and the design of the suitable inhibitor. Using recombinant techniques, the patent depends on any existing patents with regard to such techniques.[915]

913 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.

914 US Patent 5,872,011 "Three dimensional structure of a ZAP tyrosine protein kinase fragment and modeling methods" by Hatada, Marcos H./Lu, Xiaode/Laird, Ellen R./Karas, Jennifer L./Zoller, Mark J./Holt, Dennis A., Cambridge, MA 2001. The term ZAP-70 refers to 'Zeta-chain-associated protein kinase 70'. It is a member of the protein tyrosine kinase family and is normally expressed in T cells and natural killer cells. It plays a critical role in the initiation of T-cell signaling. ZAP-70 is expressed in T cells and tumors of T-cell lineage. A high level of ZAP-70 expression appears restricted to a subgroup of chronic lymphocytic leukemia (CLL). The ZAP-70 gene is in chromosome 2q12, see: http://www.medterms.com /script/main/art.asp?Art.key=23234, last checked on January 21, 2008. Protein kinases are targets for treatment of several diseases. For a description, see Noble, Martin E. M./Endicott, Jane A./Johnson, Louise N., Protein kinase inhibitors: insights into drug design from structure, 303 Science 2004, 1800-1805.

915 Id.

Besides these two characteristic claims, it is useful to consider two further examples of patents granted by the EPO, to show the potential variations inherent in claims directed to crystallization. First, the European patent EP1518925 issued in 2005 covers an invention involving a novel crystal of a glucokinase protein and a drug design method using the 3-D structure coordinates obtained using this crystal. The glucokinase protein is crystallized and its 3-D structure thereof analyzed. In a second step, a binding compound for glucokinase is designed on the basis of the coordinate for the resulting three-dimensional structure.[916] Second, European Patent EP1212365, issued in 2002, covers the crystal structures of domains of the receptor protein tyrosine kinase (RPTK) and their ligands. Determination and use of the RPTK and their ligands are included. Further, the patent discloses the following information: one amino acid group of the receptor includes a 3-D structure of an extracellular domain of RPTKs. The 3-D structure of RPTKs can facilitate the design and identification of modulators of RPTK function. Other such structures can include RPTK ligands, such as stem cell factor or a fragment thereof. Modulators of RPTK function can be used to treat disease mediated by inappropriate RPTK activity.[917]

Having reviewed several representative claims, one has to ask whether the use of 3-D protein structure obtained from a protein crystal infringes the patent to the recombinantly produced amino acid sequence. At first glance, it seems that a protein-crystal-invention does not involve any information which could establish dependency from an underlying gene patent. The process of crystallization as such does not make any use of gene-related information necessary. Protein crystals are obtained from saturated protein solutions.[918] Their production is only possible if sufficient purified proteins are available. Accurate crystallization requires a method capable of producing large amounts of proteins with correct functional characteristics. So far, attempts to obtain proteins from natural sources have proven relatively unsuccessful, which is why most inventions related to drug design or pharmaceutical products prefer the use of recombinant proteins. Recombinant technologies provide the necessary amount and the purification state required for stable end products. Thus, most inventions, such as the one discussed above for the ZAP-70 protein, tend to the use of recombinant proteins.[919]

916 European Patent No. 1518925 “Crystal of Glucokinase Proteins, and method for drug design using the crystal” by Kamata, Kenji/Nagata, Yasufumi/Toshiharu, Iwana, Tokyo 2003.

917 European Patent No. 1212365 “Crystal Structures of Domains of Receptor Protein Tyrosine Kinase and Their Ligands” by Schlessinger, Joseph/Hubbard Stevan/Mohammadi, Moosa/Plotnikov, Alexander/Zhang, Zhongtao/Kong, Xiang-Peng, New York 2002.

918 The term protein solution refers to proteins in aqueous form, see Whitford, David, Proteins: Structure and Function, Chichester, West Sussex, U.K., 358.

919 US Patent No. 5,872,011 “Three dimensional structure of a ZAP tyrosine protein kinase fragment and modeling methods” by Hatada, Marcos H./Lu, Xiaode/Laird, Ellen R./Karas, Jennifer L./Zoller, Mark J./Holt, Dennis A., Cambridge, MA 2001. The patent specification determines a ‘naturally occurring’ gene encoding the protein being used in the invention.

As for infringement, both patent law systems, i.e. 35 U.S.C. Section 271(a) and § 139(a) GPA require, among others, that a product "is used." Hence, the patent to the 3D crystal may be infringed under the following circumstances. First, anyone who uses the crystallographic data may be liable for damages. Second, anyone who reconstructs and uses the coordinates of the structural features, even with some deliberate errors, may be liable for damages, provided that the existing errors are not essential.[920] The patent to the recombinant production of a certain protein is infringed if the process of obtaining a protein crystal includes the use of patented recombinant processes for the production of such protein. If crystals are obtained without any involvement of patented recombinant techniques, no infringement is constituted. These rules are applicable to both, 35 U.S.C. Section 271(a) and § 139(a) GPA.

From a licensee perspective, the use of protein crystals also appears to be cost-effective. Nevertheless, existing difficulties with crystallization techniques have resulted in the issuance of a relatively small number of patents related to crystalline forms.[921] With crystallizing techniques constantly improving, this might change in the near future. Large firms are addressing the challenge of optimizing protein crystallization. With high quality crystals being largely dependent on a suitable environment, a main focus is the optimization of crystallization conditions.[922] Experience shows that crystallization in a microgravity environment produces crystals having improved properties over crystals prepared under the normal gravity on earth.[923] Hence, scientists use the International Space Station, which provides access to such an environment, for conducting intensive experimental projects. Meanwhile, national agencies, such as the National Aeronautics and Space Administration (NASA)[924] have become leading federal institutions in promoting and funding protein crystallization research. Improved crystallization conditions will help to optimize the properties of obtained crystals, resulting in more accurate 3-D protein structures and advances in drug design.

IV. Use of new proteomics technologies: An example using sequence-dissimilar proteins sharing common 3-D fold

The issue of whether patent claims should be interpreted broadly enough to encompass later-arising technologies that were unknown at the priority date has

920 Barton, John H., United States Law of Genomic and Post-Genomic Patens, 33 IIC 779, 788 (2002).

921 See USPTO and EPO databases. As stated in Burley, Stephan K./Nahum, Sonnenberg/Marcotrigiano, Joseph/Gingras, Anne-Claude, Crystal of protein-ligand complex containing an N-terminal truncated eIF4E, and methods of use thereof, New York, NY 1999, Only few protein crystals have been produced with sufficient quality.

922 See Chapter 2 E II 2 a.

923 http://liftoff.msfc.nasa.gov/shuttle/msl/science/pcg.html, last checked on January 21, 2008.

924 http://www.nasa.gov/, last checked on January 21, 2008. .