The aim of this study was to provide a comparative assessment of legal issues at the nexus between intellectual property rights and a central area of modern biotechnology, proteomics. Specifically, the study discusses the patentability of proteomic patent claims, and the scope of protection of biotechnological inventions in the post-genomic, or proteomic, era. The major findings of the analysis can be categorized accordingly, i.e., into findings related to patentability, and into results in the area of the scope of protection. Moreover, the study of proteomics as an issue for intellectual property rights protection yields some more general results. These will conclude this section.

A. Patentability of Proteomic Patent Claims

As to the patentability of proteomic inventions, a first set of results is related to proteins defined by structural properties *per se*. As shown in Chapter 3 B II, both the EPO and the USPTO share similar views regarding proteomic claims directed to the polypeptide as such. Provided that the polypeptide occurs in various folding types, 3-D structures can establish unambiguous parameter constellations despite previous disclosure of the related amino acid. Consequently, novelty can be established according to classical doctrines originating in the field of chemical compounds, such as the principle of unambiguous parameter. In this respect, it is important to note that the legal treatment of chemical patents does specifically refer to 3-D structures. This can be seen in the legal treatment of stereochemistry inventions. Here, novelty can only be established through the description of the specific 3-D *enantiomere*. The sole inclusion of *racemate mixtures* in the patent description does not suffice. Hence, 3-D information or data can serve as important parameter during the typical application process.

In the area of crystalline proteins, it is again a principle from the field of chemistry that helps to distinguish between novel proteomic compounds and the prior art. Novelty is established by the new physical characteristics of protein crystals. In a similar way, claims to selected structural features (such as binding pockets/epitops) achieve novelty according to principles developed for selection inventions. In particular, the selected sub-field must be narrow and sufficiently far removed from the known range illustrated by working examples. Moreover, it must not merely be randomly selected, but should be the result of a more tightly focused selection. Finally, the selected area should not provide a mere embodiment of the prior art description, but, rather, another invention.

A second set of results concerns the area of bioinformatics. In this respect, Chapter 3 B III 1 illustrated the controversial issue of the patentability of so-called *in-silico* screening methods. The European patent system acknowledges patentability and accepts the claim under the requirements for patentable subject matter.[1171] In contrast, the American patent system rejected related claims, finding that merely non-functional, descriptive data was provided, which renders the research results obvious. Surprisingly, the U.S. applies stricter standards for patentability than Europe, even though many critics of intellectual property rights claim that the U.S. system sets looser standards.[1172]

Based on the application of various general principles, the EPO's solution proves to be more coherent. By contrast, the USPTO's findings are subject to criticism, since they do not consider the patent as a whole, but only its computer-related aspects. Such an approach fails to consider the relationship between biological function and the computerized method. The major question is *not* whether a known algorithm is fed with new data, but whether the effect of the *in vivo* biological process that is simulated with this algorithm is non-obvious. [1173] While the EPO's result is consistent with general principles, the reasoning behind it requires some substantial modifications. In particular, the "further technical effect" required by the EPO should not only be derived from software-related aspects, but from the biological function the protein performs *in vivo*.[1174]

In sum, the analysis of bioinformatics claims shows that both offices derive their solutions from the application of principles that were originally used in the area of computer-implemented inventions. However, the nature of proteomic bioinformatics requires a more comprehensive analysis of the invention as such that goes beyond the aspects of computer implementation. Since the protein's functions define the characteristics of the biological binding process, the former must be considered a crucial element of the *in-silico* method. The computer-based visualization of a biological function translates and transfers a biological mechanism into virtual space, where the (*in vivo*) technical effect is reproduced *in silicio*. The patentability requirement of "technical feature" must therefore be derived from the protein's function. Such an approach, in turn, is also consistent with what is interpreted as a further technical effect by the European Board of Appeals.[1175]

A third set of results – demonstrated in Chapter 3 B III 2 - are those involving protein data. Like *in-silico* methods, they are treated under the principles developed for computer-implemented inventions. The application of these rules shows that claims to mere data lack a further technical effect under the European patent system. Similarly, the U.S. patent system considers the claims as abstract ideas, finding that

1171 Chapter 3 B III 1 a) cc) ii.
1172 Chapter 3 B III 1 a) cc) iii.
1173 Chapter 3 B III 1 a) cc) iii.
1174 Chapter 3 B III 1 a) cc) ii.
1175 Chapter 3 B III 1 a) cc) ii.

they establish mere non-functional descriptive material.[1176] Both views consistently apply well-established principles, and should not be disputed on legal grounds. Nevertheless, scientists could argue that the patent offices do not sufficiently take biophysical concepts into account and act in a discriminatory manner. Patent offices allow patents on standard chemical formulae which are, in fact, merely 2-D coordinates of molecules combined together with some standard rules of chemical connectivity. The 3-D coordinates of proteins, by contrast, are not deemed to be patentable, although they too demonstrate standard rules of chemical connectivity between atoms. From a legal perspective, the offices correctly distinguish between computer storable data and the established chemical practice of determining compounds by means of chemical formula. From a scientist's perspective, however, it appears that distinctions are made regarding the patentability of a molecule depending on the dimension in which the coordinates are represented.[1177]

A final group of claims – demonstrated in Chapter 3 B III 3 - deals with the potentially large number of innovations that will be directed to *identified compounds* obtained by *in-silico* screening methods. Patent applicants may seek to cover these compounds by drafting reach-through claims. The claim language is specified in a way that is broad enough to dominate future compound discoveries that can be used for rational drug design. Both offices adopt a similar approach regarding the strategy of reach-through claiming. Claims are treated under strict standards and typically fail due to a lack of enablement. Hence, inventors should handle the method with caution. With strict conditions for both the written description/sufficient disclosure requirement and the enablement factor, it may be advisable to use other approaches such as milestone payments or reach-through licensing methods. [1178]

To meet the patentability requirements of written description/sufficient disclosure and enablement, it is advisable for applicants to disclose theoretical information about the size and shape of binding sites of the computerized method and of corresponding compounds. Claims that define identified compounds by size and shape are not considered as reach-through claims and are generally allowed by patent offices. Inventors, however, must take into account that such claims pose a high risk of being rendered invalid. If only one prior art ligand has the shape and size demonstrated by the claim and therefore would respond to the *in-silico* protein, the claim lacks novelty. With many molecules being reported in prior art, but not defined by size and shape, the concrete risk of annihilation of novelty is difficult to foresee.[1179]

1176 Chapter 3 B III 2 b).
1177 Chapter 3 B III 3 III 2 c).
1178 Chapter 3 B III 3 c) bb).
1179 Chapter 3 B III 3 c) aa), Chapter 3 B IV.

Long before the term proteomics began to dominate biotechnological research, the question of whether the scope of protection of DNA patents would provoke infringements by yet unrealized inventions was discussed extensively. In particular, some observers raised concerns regarding whether the design of new gene-based pharmaceuticals would be hindered by patented gene sequences. When it became clear that the direct applicability of genetic information to medical conditions was indeed somewhat limited, these concerns experienced a revival.[1180] In what form and to what extent do issues of *dependency* between existing patents on gene sequences and other biotechnological inventions arise? What can be said about the likelihood of *infringement* when it comes to gene patents involving the encoded (or recombinantly produced) protein? And how are problems of *competitive use* dealt with? Since proteomics is one of the most important research area in today's biotechnology environment, these questions particularly apply to proteomic inventions. Part C. of Chapter IV. therefore analyzes issues related to patent dependency and infringement - between gene patents and claims related to the 3-D protein structure, and between different protein-related claims.

The results of this analysis can be summarized as follows. First, the *use of naturally purified and naturally obtained crystalline proteins* does not constitute any infringement.[1181] This stands in sharp contrast to *recombinantly produced proteins*, whose 3-D structure inherently falls within the scope of gene patents that declare the encoded protein as its function.[1182] This discrepancy between recombinant production and natural purification/crystallization results from the fact that the patent system rewards the inventors of recombinant technologies for their contributions to the highly efficient production of large quantities of proteins. Naturally occurring proteins are encoded from non-isolated genes and are not related to the patent covering the isolated gene sequence. As long as available purification and separation techniques fail to provide sufficient amounts of high quality proteins, inventors are forced to rely upon recombinant technologies. Therefore, issues of patent dependency cannot be avoided. The temporary limitation of gene patents, however, will pro-

1180 One example is the issue of gene therapy. Gene therapy is a technique for correcting defective genes causing disease development. In most gene therapy treatments, a normal gene is inserted into the genome to replace a disease, causing gene. Despite great promises and high expectations, the approach has yet not proven succesful in clinical trials. In 1999, gene therapy suffered a major setback with the death of 18-year-old Jesse Gelsinger. This patient died shortly after starting the therapy. In 2003, a second child treated in France developed a leukemia-like condition. As a consequence, the FDA placed a temporary halt on all gene therapy trials using retroviral vectors in blood stem cells; see Human Genome Project Information, available at http://www.ornl.gov/sci/techresources/Hu man_Genome/medicine/ genetherapy.shtml; last checked on January 21, 2008. As for the several approaches that may be used for correcting genes, see Straus, Joseph, Patenting Human Genes in Europe - Past Developments and Prospects for the Future, 26 IIC 920 (1995).

1181 Chapter 4 C I; Chapter 4 C III.

1182 Chapter 4 C II.