The Human Genome Project revealed that the human organism contains far fewer genes than proteins. The fact that approximately 33,000 genes encode more than 200,000 proteins invalidated the long-held assumption that one gene encodes a single protein.[1] In addition, the discrepancy between the number of genes and the number of proteins refocused attention on the latter.[2] The pharmaceutical and economic interest in protein analysis was further stimulated when studies demonstrated that even small structural variations – such as posttranslational or interactive modifications – could have an enormous impact on the physiology of the entire cell.[3]

The importance of these modifications can be illustrated using as an example the family of brain diseases known as "transmissible spongiform encephalopathies", or TSEs.[4] Among these, the Creutzfeld-Jakob Disease (CJD) and the Bovine Spongiform Encephalopathies (BSE) have alarmed scientists, politicians and the public worldwide, after an unusually large number of cases arose in Great Britain. CJD and its most important variant, vCJD, lead to strong personality changes, problems with balance and coordination and finally coma and death, just months after patients have developed the first symptoms. Until the early 1980s, there was no clear understanding of the causes of the disease. Consequently, medical treatments could not be developed. Most scientists conjectured that a virus was the most probable cause of the infection. This changed when Stanley Prusiner, a researcher at the University of California at San Francisco, suggested that JCD was not caused by a known pathogen, but by a protein characterized by a peculiar three-dimensional structure. While the hypothesis was harshly criticized initially, the idea that misfolded proteins

1 The number of different protein molecules expressed by the human genome is probably closer to a million than to the 200,000 generally estimated by genome scientists. The actual amount of proteins in the human organism is still unknown, but some researchers believe that there exist as many as two million, see Service, Robert F., Gene and Protein Patents Get Ready to Go Head to Head, 294 Science 2001, 2082, 2082. The number of genes of the human organism is barely higher than the number of genes characterizing the roundworm Caenorhabditis elegans. The fact that the human genome is able to produce such a high degree of complexity with only a few genes is generally attributed to the phenomenon of alternative splicing. Alternative splicing is explained in Pennisi, Elizabeth, Why Do Humans Have So Few Genes?, 309 Science 2005, 80 and Jollès, Pierre/Jörnvall, Hans, Proteomics in Functional Genomics, Protein Structure Analysis, Basel et al. 2002, XI. See also Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f.

2 Bohrer, Robert A., Proteomics: The Next Phase in the Biotechnology Revolution and the Next Challenge for Biotechnology Law, 22 Biotechnology Law Report 2003, 263, states that "[t]he massive trove of genetic information has produced more questions than answers".

3 Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f.

4 The term TSE is derived from the spongy holes that are present in infected brains.

(called prions, or proteinaceous infectious parts) were responsible for CJD is now widely accepted.[5] Prusiner received the Nobel Prize[6] in 1997, and prions can be considered the first 3-D proteomic structures that penetrated the consciousness of the wider public.[7]

The human genome project and subsequent "post-genomic"[8] studies clearly demonstrated that these 3-D structures are of prime importance.[9] More importantly, they revealed that molecular biology could only be understood as a dynamic system, which uses a wide range of regulatory mechanisms to control its activities.[10] The dynamic changes in proteins, such as their seemingly endless modifications and interactions, their binding activity or self-regulatory adjustments, can be considered their crucial element. This acknowledgement was the starting point for the so-called "post-genomic" era, where proteomics – the science of the proteome as defined below – begins.[11]

5 See Prusiner, Stanley B./Scott, Michael R., Genetics of Prions, 31 Annual Revue of Genetics 1997, 139. A major advancement in the study of prions and prion-based diseases was the discovery and purification of a protein characterized as prion protein ("PrP"). A leading theory is that prion diseases are caused by the modification of PrP from PrP.sup.C into PrP.sup.Sc. The precise biological function of PrP.sup.C is still unknown.

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

7 Neurodegenerative diseases like Alzheimer's provide another example of the importance of protein folding, with even larger social and economic implications, see Whitford, David, Proteins: Structure and Function, Hoboken, NJ 2005, 468-470.

8 The term "post-genomic" refers to research techniques that became relevant after the disclosure of genetic sequences; see Barton, John H., United States Law of Genomic and Post-Genomic Patents, 33 IIC 779, 786 (2002).

9 Thus, life science research moved from a genome-based level that emphasized the study of the gene to a 'post-genomic' level focusing on information regarding proteins; Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84-95, 84. Many scientist hold the view that proteomics involves complexities that scholars of genomics do not encounter. "If genomics resembles the Matterhorn, proteomics is like the Mount Everest", see Gwynne, Peter/Heebner, Gary, Drug Discovery and Biotechnology Trends – Proteomics I: In Pursuit of Proteins, Science 2003, 665, 665.

10 Straus, Joseph, Produktpatente auf DNA-Sequenzen – eine aktuelle Herausforderung des Patentrechts, GRUR 2001, 1016, 1019f. The disclosure of the human genome also showed that systems of DNA regulation have a much stronger impact than expected.

11 Barton, John H., United States Law of Genomic and Post-Genomic Patens, 33 IIC 779 (2002); Peltonen, Leena/McKusick, Victor A., Dissecting Human Disease in the Postgenomic Era, 291 Science 2001, 1224. In many cases, a better picture of the molecular biology of a cell is only achieved by the study of proteins, as emphasized in Russell, Robert B., Genomics, Proteomics and Bioinformatics: All in the Same Boat, 3 Genome Biology 2002, REPORTS 4034. Nevertheless, the Human Genome Project provides powerful insights into human diseases. It thus has been "worth the effort", as stated by Daiger, Stephen P., Was the Human Genome Project Worth the Effort? 308 Science 2005, 362, 364. The new proteomic view of a dynamic molecular biology inspired the further development of "genomic tools", such as 'Genome Fingerprint Scanning', which is usually combined with the proteomics technology of mass spectrometry, see Sender, Aaron J., Decoding Recorders for Protein ID, Genome Technology 2003, 26, 27.

One of the key promises of proteomics is that of drug design, because most drugs act through the modification of a specific protein. Proteomic technologies may speed up the screening of new pharmaceutical compounds and thus lower time and money consuming investments.[12] If a pharmaceutical company is able to market a drug only one year earlier, this could amount to $500 million additional profits.[13] Another promising and accelerating field is biomarker development. The term 'biomarker' refers to biochemical molecules that are used to measure the progression of disease or the effects of pharmaceutical treatment. Biomarkers are increasingly important in the progress of drug design, because they provide novel and specific means for early detection and diagnosis of diseases such as cancer, HIV or hepatitis.[14]

The era of proteomics thus offers a wide range of opportunities and challenges for research and development. At the same time, however, it creates new challenges for the individuals and institutions constituting the biotechnological research complex, including patent law as its central legal institution. Here, the main question is whether and how traditional standards must be readjusted in order to cope with the nature of this dynamic scenario envisioned by many. To answer this question, however, it is of paramount importance to answer yet another question: How do patent law institutions, in particular patent offices, currently treat proteomic inventions, and how would they treat the range of inventions that can be expected to materialize in the not so distant future? Due to the novelty and broad scope of the subject, a systematic description of current practices is still lacking, and the analysis below attempts to provide first steps towards a comprehensive summary of existing practices.

More generally, this study provides a comparative analysis of patentability issues related to proteomics inventions with the following two main objectives: to clarify current views and practices and to derive legal policy conclusions related to proteomic patents. It aims at identifying the issues that the major players in the field (research units, companies, lawyers, patent offices, courts and legislature) will be con-

12 The scientific community frequently emphasizes that the efficiency of drug design is significantly enhanced by proteomics. It is held that genomic information had little effect on drug discovery. In the long run, however, the advanced understanding of the roles genes and proteins play in the organism does promise new approaches to the comprehension of diseases; Hall, Stephan S., Revitalizing drug discovery, Technology Review October 2003, 39, 39

13 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, 104. Bioinformatics may also speed up discovery by screening precise drug targets at an early stage. See also Howard, Ken, The Bioinformatics Gold Rush, Scientific Am. 58, 58 (July 2000).

14 Kleist, Peter, Biomarker und Surrogat-Endpunkte: Garanten für eine schnellere Zulassung von neuen Arzneimitteln? 83 Schweizerische Ärztezeitung 2002, 2347, 2347; as for recent discoveries in the field of biomarkers, see Zucht, Hans-Dieter, Biomarker Discovery, Transkript 2004, 48; Deutsche Gesellschaft für Proteomforschung, Biomarker Discovery and Imaging Proteomics,Transkript 2004, 57; the search for disease biomarkers using proteomics is also referred to as "disease proteomics"; Hanash, Sam, Disease proteomics, 422 Nature 2003, 226, 229.

fronted with in the years to come. By discussing alternative approaches to deal with these problems, the study also contributes to the further development of legal standards. In the course of this analysis, it will become clear that proteomics touches yet another important policy issue. When the first DNA patents were granted, many observers expressed the concern that they would constitute the basis for permanent and harmful monopoly positions, with adverse effects on price setting behavior and research dynamics. In particular, it was hypothesized that gene patents would provide disincentives to invest in research and development activities that would lead to the pharmaceutical innovations originally envisioned. As will become clear below, proteomics is an important test field in this regard. It can provide some first indications as to whether the original fears were legitimate.

To summarize, the proteomic era confronts legal experts with a set of important and exciting questions. To answer these questions, chapter II introduces the reader to the scientific background of proteomics. This includes a discussion of different protein structural folding levels. Moreover, the relative importance of primary, secondary and tertiary protein structure is discussed with regard to biological functions, demonstrating why the tertiary stage is typically the major focus of pharmaceutical research. Furthermore, an overview of basic proteomic analysis techniques, as well as an illustration of major proteomic organizations and networks, will be provided. Chapter III looks at the patentability of proteomic inventions, and starts with an overview of general patentability requirements in both the European and the U.S. patent law system. The statutory background and the decisive case law are presented, with the focus set on applications related to proteomics. In a next step, the second part of Chapter III will go through a case study that illustrates how claims directed to typical proteomic features such as complex protein structures or bioinformatics research tools are likely going to be approached from the legal point of view. Among other things, the discussion will emphasize differences in the legal criteria and practices being applied in the U.S. and Europe in the course of the examination process.

The remainder of the study is devoted to the question of adequate scope of protection for proteomic inventions (chapter IV). Chapter IV first discusses claim construction issues related to the scope of protection. With patent infringement being treated under German law, particularly the German perspective will be taken into account. In a second step, a concrete claim analysis under both German and U.S. law will be carried out. Using a broad spectrum of claims from the field of 3-D protein structure, the scope of protection of DNA and protein patents is analyzed. Chapter V summarizes the major findings of the study regarding patentability and scope of protection and derives a set of core conclusions with respect to the broader policy implications of these findings.