

# Patent Prosecution in Proteomics

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## Abstract:

This paper presents a brief overview of intellectual property rights and the various areas in proteomics to which IP rights may be applicable. Technology transfer, including licensing and business agreements, are not covered in this paper. Instead, issues and complications related to national and overseas patent prosecution in this relatively new field will be discussed.

## Intellectual Property Overview

Some find the concept of intellectual property hard to grasp, often because it's hard to determine the monetary worth of ideas. One simple example of the value of intellectual property is the common occurrence of expensive and high-stakes infringement lawsuits. One of the costliest examples is the decades long case of Eastman Kodak vs. Polaroid, which resulted in the destruction of Kodak's instant photography business, as well as more than \$3 billion dollars in infringement damages, compensation and legal fees, and research and manufacturing costs.<sup>[1]</sup> Even lawsuits that result in settlements, such as that filed by the University of California against Genentech for the company's manufacture and sale of the growth hormone product Protropin<sup>R</sup>, can be severe (\$200 million in the case of UC vs. Genentech) punishments for the defendants.<sup>[2]</sup> That is not to mention the hundreds of thousands of dollars lost by both sides on legal and courtroom fees and on time spent by employees and management embroiled in the suit.

Although successful suits filed by small companies can result in large settlements or infringement damages from industry juggernauts, companies without the proverbial 'deep pockets' typically do not have the time and money to spend on lengthy, costly litigation. The price of resolving patent disputes can sometimes cripple a business, compared with the modest cost of building an effective IP portfolio. Thus, successful companies stand to benefit more from a strong IP portfolio to accompany equally strong and innovative research and development. Besides, with sound and

successful innovation, a company can avoid being mired in litigation over a technology that it has long since improved upon.

From a different angle, those still questioning the value of intellectual property can look at the value derived from successful licensing of IP. The well-known Cohen-Boyer recombinant DNA patents, often credited as key catalysts of today's biotech industry, were reported to have earned \$37.3 million in licensing royalties in 1997 alone.<sup>[3]</sup>

While U.S. legislation such as the Bayh-Dole Act allowed for transfer of ownership of many government funded inventions from the U.S. government to the universities<sup>[4]</sup>, resulting in successful licensing of almost half of university-born inventions<sup>[5][6]</sup>, the fact is that an estimated 3% of all patents are actually licensed.<sup>[7]</sup> Thus an effective IP prosecution strategy should take note of the competing demands for licensing revenue and defense from litigious competitors. On one hand well-written patents are needed to defend the core technologies a company builds upon, and on the other hand an aggressive patenting strategy is needed to map the course a company sees itself undertaking. The latter can result in licensing deals, or serve as a useful method for sidestepping unwanted litigation, by keeping far ahead of the competition.

This paper presents a brief overview of intellectual property rights and the various areas in proteomics to which IP rights may be applicable. The perfection of an IP portfolio is of interest to startups and their investors, whereas licensing agreements are of interest to manufacturers and customers. Technology transfer, including licensing and business agreements, are not covered in this paper. Instead, issues and complications related to national and overseas patent prosecution in this relatively new field will be discussed.

## Patents

United States patents offer protection for any process, machine, manufacture, or composition of matter, or any improvement thereof, that are novel, useful, and non-obvious.<sup>[8]</sup> The Agreement in Trade-

Related Aspects of Intellectual Property Rights (TRIPS Agreements) in 1994, a multilateral concord proposed by the council administering the WTO's intellectual property agreement<sup>[9]</sup>, defines patentable matter as any invention that involves an innovative step and has a potential industrial application.<sup>[10]</sup>

In theory, the purpose of intellectual property is to foster intellectual and economic growth. Patents spur innovation through the disclosure and teaching of the details of an invention to the public, and in exchange, the inventor or owner is rewarded the legal rights of ownership. The legal rights give the owner exclusive rights to capitalize on the invention, by excluding others from making or using the invention, importing the invention into the U.S., or offering the invention for sale. These ownership rights are granted for a period of 17-20 years, depending on the date of filing of the patent.

Patents are obtained through a lengthy process that can sometimes turn out to be quite costly. In high-tech fields such as proteomics, the time between filing a patent and a first response from the U.S. patent office is typically a year and a half. This is due in part to the large volume of patent applications in these fields, and to the lack of expertise in the patent examiner corps. In Europe, Japan, and the Pacific, the "first to file" system applies. On the other hand, in the U.S. the "first-to-invent" system applies, but patent applications must be filed within one year of the first offer for sale of the product or the patent filing will be void. Thus it is important to keep an accurate record of dates of invention as well as offers for sale or other public disclosures.

## Copyrights

Copyrights protect the original expression of an idea. By offering protection, copyright encourages the expression of original, artistic ideas into a tangible medium. Legal protection is effected instantly, when the original copyrightable subject matter is fixed into a tangible medium, e.g. on paper or in a digital storage form.

Copyrights are free and do not require months of paperwork as do patents, and they are valid for the author's lifetime plus 50 years. A longer period of validity (75-100 years) applies if the work was created for hire, which is generally the case in a business such as the biotech industry.

## Trade Secrets

Trade secrets are any technical or business information that give a company a competitive advantage. There is no formal filing procedure to register trade secrets. The secret need not be completely novel or exclusive, it simply must have a

derived or potential economic value from being unknown. Additionally, reasonable efforts must be made to keep the information secret, e.g. through the inexpensive use of Non-Disclosure Agreements (NDA). Legal protection under trade secret no longer applies when the information is publicly disseminated.

## Trademarks

Trademarks refer to the distinctive signature mark that can be used to protect the company, product, service, name, or symbol. The trademark must not be descriptive or generic. Legal protection is not offered to the technology, rather to the company good will and quality associated with the use of the recognized name or symbol. Trademarks provide exclusive rights within a region or nation and as long as used commercially, and they may be renewed indefinitely. Compared to patents, they are obtained within a moderate time period (usually under two years) and typically at a cost under \$5K per registered mark.

## IP Strategy

The IP rights are protected under various federal and state laws. Without protection, intellectual property falls into the public domain and may be used by any party without license. A sound management strategy would be to systematically build a portfolio consisting of different IP rights, with the aim of protecting the various aspects of the company's technology and commercial interests.

IP rights protect the commercial interests of a company at the various stages of design, manufacturing, and product operation. At the design and development stage, copyrights and trade secrets can be immediately enforced. Novel apparatus and methods can then be patented, a process that takes about three years and requires the investment of some funds. Once a product or service is developed, issued patents and trademarks protect the technology and associated names and symbols.

While copyright and trade secret protection are obtained easily, patents, trademarks, and maskworks require applicant action and response within critical filing deadlines. Generally, the first to patent will have the best chance of winning the broadest patents.

## Proteomics

The term proteome is often used to describe the total set of proteins expressed during the lifetime of a cell.<sup>[11]</sup> Proteomics, a term coined to convey the largely informational nature of the problem of

categorizing the proteome, is sometimes associated with structural genomics, which is the study of how protein structure and function relate to genes. In practice, proteomics involves everything from structure determination, at the lowest level, to functional analysis, and finally to cell modeling.

At the most fundamental level, scientists attempt to determine the composition and structure of individual proteins. This difficult task necessitates discovery of primary structure (the chemical bonds and sequence of amino acids comprising the protein), the secondary structure (existence of typical forms such as  $\alpha$ -helices,  $\beta$ -sheets), tertiary structure (the way in which secondary structures fold in 3-dimensions, see Figure 1), and quaternary structure (organization of polypeptide chains) of the protein.

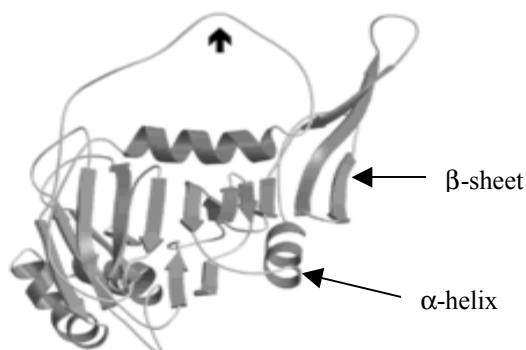


Figure 1: baculovirus P35<sup>[12]</sup>

With knowledge of protein structure, the function of a particular protein, whether for transport, storage, communication, etc..., can often be deduced. Still, knowledge of protein structure is not always enough to describe completely a protein's role in the cell. Comprehensive functional analysis must ultimately be performed by experimenting with gene mutations and environmental perturbations. With such a totality of information, predictive cell models may eventually be developed.

Protein structure determination, by far the most basic and essential task of proteomics, is estimated to cost upwards of \$100K per protein structure determined, not to mention a discovery time that can stretch from months to years.<sup>[13]</sup> For this reason the National Institutes of General Medical Science (NIGMS), a division associated with the National Institutes of Health (NIH) began a major funding effort in 2000 to build the tools and machinery needed to enhance research in this field. The goal is to reduce the cost of determining protein structure to \$10 to \$20K per protein by grouping them into structural families and solving structures of representative proteins from each family, thereby creating a skeleton model of a complete protein

inventory. By 2005, each research project is expected to solve 100 to 200 protein structures annually, with a total of about 10,000 structures solved over 10 years. The fund is managed by the Protein Structure Initiative (PSI), which was anticipated to distribute a total of \$150 million over the course of 2000-2005.<sup>[14]</sup> While European spending on proteomics research lags behind the U.S., several publicly funded research programs have recently been launched in accordance with the Sixth Framework Programme (FP6) of the European Commission, which has devoted an overall budget of approximately \$18 billion to the advancement of the European research community, of which proteomics research is a recent addition.<sup>[15]</sup>

As with many research trends, determination of protein structure is sometimes thought of as a panacea for everything from the environment to national security. In fact, proteomics and structural genomics research have already yielded valuable results in drug design. One example is the development of inhibitors for HIV reverse transcriptase (RT), an enzyme vital for the replication of the virus. With knowledge of crystal structures, scientists were able to identify optimal sites for disruption of RT function, resulting in successful non-nucleoside RT-inhibitors (NNRTIs).<sup>[16]</sup>

While it is clear that proteomics has valuable applications to human health, few large drug companies perform protein structure research or structure-based drug development because of high costs, relying instead on available structural information and trial-and-error to discover the compounds that activate or disable target proteins.<sup>[17]</sup> The huge cost of structure discovery is due in part to the lack of high-throughput tools and machines needed to accelerate present molecular structure discovery methods. X-ray crystallography, the most widely used method, requires gene cloning, protein expression, and protein purification and crystallization, all processes that, until very recently, still involved painstaking laboratory hours.<sup>[18]</sup> Thus, until the millions of government funding poured into national research centers results in the development of high-throughput devices and infrastructure for protein structure research, proteomics will remain mainly in the research stage, with most structure determination performed by funded research centers.

Currently there are numerous protein structure databases, with emphases on different aspects such as three-dimensional structure or protein families. The Protein Data Bank (PDB), a comprehensive depository of three dimensional structural data<sup>[19]</sup>, has around 19,000 protein structures archived. Although not even close to a comprehensive knowledge about the set of human

proteins, of which the human genome probably encodes about 300,000, the various databases and worldwide funding efforts recently implemented suggest that real proteomics applications are just around the corner.

## Protectable Applications in Proteomics

### Tools

The tools, methods, and infrastructure implemented to advance the state of protein structure research are excellent candidates for lucrative patents, because well-designed tools can become essential to the research process of the entire industry. The potential for licensing these “tollbooth” technologies is immense, as in the case of the Cohen-Boyer recombinant DNA patents, which, before they expired in 1997, could be said to be violated anytime anyone cloned DNA.

#### a. Software

Software for the collection, visualization, and prediction of protein structure data are all becoming important tools in the proteomics research process. This combination of informational science with cell biology is often referred to as bioinformatics, the study of high-throughput, automated information search and retrieval methods for the massive amounts of DNA, cell, and protein data accumulated each year by the scientific community. In proteomics, several public protein structure databases contain thousands of protein structures each, with more information being added each month. Data collection is also a vital element of proteomics, since efficient and adaptable methods are necessary to gather the continuous flow of data from various research facilities. Currently, to reduce the burden of data processing taken on by research centers, databases such as the PDB have created software for data annotation, translation, and input to automate the data deposit process.<sup>[20]</sup> The databases and accompanying automated data collection and search methods are protectable IP.

Software for protein structure prediction often involves matching a partial structure to known family representatives stored in a database. This type of prediction relies on sophisticated search algorithms, which can be patented in combination with the database that stores protein information. Types of prediction methods can range from sequence homology to methods as intricate as 3-D structure-based alignment. As more protein structures are solved, 3-D structure visualization becomes important not only for some prediction methods, but also as an educational tool. Software patents for structure prediction or 3-D visualization tools are similar to computer software patents.

#### b. Devices and Methods

A number of steps are involved in determining protein structure, and in proteomics in general. Protecting the devices and methods that assist the proteomics research process is a standard practice.

In proteomics research, proteins must be isolated in the step known as separation. There can be ten to twenty thousand different proteins expressed in a single cell, so refined identification and separation techniques are essential.<sup>[21]</sup> Mass spectroscopy, peptide mass fingerprinting, and liquid chromatography are commonly used techniques, with capillary electrophoresis emerging as a potentially powerful new method for protein separation. There are numerous devices on the research device market to automate separation. For example, the several varieties of capillary electrophoresis, all of which have their own advantages, also have their own machines and digitized systems. One trend is towards hybrid instruments, systems that use combinations of techniques (such as capillary electrophoresis and liquid chromatography) for wider scope of functions. Laboratory tools such as these, each of which improve upon a previous machine or method, are typical candidates for device and method patents. The trend towards lab-on-chip devices that combine electronics with the cell biology fundamental to proteomics makes for more complicated patents; indeed, few have the interdisciplinary training needed to write or examine patents in this relatively new, cross-technical discipline.

Cloning and expression of proteins is another bottleneck in proteomics research. Currently there is a need for high-throughput, high-yield methods for protein expression. Moreover, the production of properly folded proteins is another challenge to systematic magnification of purified proteins.

Finally, the primary method for protein structure research has been x-ray crystallography, with nuclear magnetic resonance (NMR) a close second. These processes, too, have a host of systems and methods to facilitate laboratory research. One bottleneck in x-ray crystallization is the production of crystallized proteins, which some companies have attempted to automate with robots.<sup>[22]</sup> Refinements in systems and methods for protein expression and structure determination will be reflected in the devices that are invented to automate the improvements.

### Diagnostics

Using protein markers to detect disease is one important application of proteomics to human health. Devices that check for elevated levels of certain proteins can serve as ultra-sensitive diagnostic tools for cancer and other hard to predict diseases.

For example, UC Berkeley researchers have been involved in the design of a micro-cantilever that detects the presence of prostate specific antigen (PSA), a prostate cancer marker found in the blood, at levels twenty times lower than the clinical threshold.<sup>[23]</sup> The micro-cantilever is an inventive device for the detection of a protein that is known to be associated with the disease. A more traditional device in the industry that will likely be used more frequently for protein marker detection is the protein array, a variation on the now standard DNA array. Use of protein markers can even extend from diagnostics and into methods for devising optimal treatment or for measuring progression or response to treatment. Speedy detection of protein markers can also be a means to accelerate clinical trials.

While a protein marker itself would not be patentable material unless isolated from nature, a novel device or method for detection of proteins, especially if such a detection has great therapeutic worth, would be valuable indeed. In some cases, however, it is necessary to claim both the detection method and the structure of the protein marker itself, in order to ensure successful prosecution of a protein marker patent.

### **Structure-Based Drug Design**

Structure-based drug design is still in its infancy in the pharmaceutical industry, making the practice breeding grounds for emerging industry standards. While combinatorial chemistry has been the method of choice in lead identification, understanding of protein structures lends itself nicely to screening of the molecules yielded from combinatorial chemistry. More commonly, protein structure data is used to optimize drug leads; for example, to modify molecules to achieve more potency.<sup>[24]</sup> In these cases, innovations in software and the accompanying databases of protein structure and ligand docking information will be the main drivers of the combination of structure-based and combinatorial chemistry drug design.

Of course, it is also customary to patent the drugs themselves. Generally, molecular structures and functions involved in the therapeutic process should be described in the specification. Further, unless the drug can be shown to have the alleged effect in humans, or the desired species, the drug in question often will not pass either the utility or the enablement requirement needed to prove patentability. Although it is of strategic importance to patent potential drugs that seem likely to pass human clinical trials, it is advisable to detail specific physical and chemical functions in order to avoid forced amendments that might limit the scope of the patent.

Another issue involved in the drug patent process is the fact that obtaining FDA approval for a drug often takes substantially longer than patent prosecution, effectively reducing the term of the patent once issued. One patent term extension is available, however, under the U.S. code, for products that were subject to regulatory review.<sup>[25]</sup>

## **Challenges to Patent Prosecution in Proteomics**

As already touched upon, there exist some challenges that are specific to the proteomics patent process. For example, while it is important to claim the function, or “mechanism,” of particular molecules in order to provide enabling description of certain drugs, general claims based purely on the mechanism may prove to be too generic as well. Very general mechanism claims to support Pfizer’s Viagra drug, for instance, “a method of treating erectile dysfunction in a male human, comprising orally administering to a male human in need of such treatment an effective amount of a selective cGMP PDEv inhibitor, or a pharmaceutically acceptable salt thereof, of a pharmaceutical composition containing either entity,” will soon be tested in upcoming court battles. Because the claim is so general, describing only the type of inhibitor and its function, the patent has the potential to include selective cGMP PDEv inhibitor compounds that achieve the desired function, which have yet to be discovered. Some feel that mechanism claims will be contested and found invalid during litigation because, for instance, they do not meet the requirement that genus claims disclose a representative number of species in order to show possession of the genus (in this case a method for treating erectile dysfunction using a specific inhibitor).<sup>[26]</sup>

Another type of proteomics-related claim construction in question is the ‘reach through’ claim, “which attempts to claim compounds which may be identified by a screening procedure, without having to specifically identify any specific compound”.<sup>[27]</sup> For example, a claim listing “an isolated receptor agonist wherein said receptor agonist is identified by the method of Claim X” that does not contain support in the specs, in particular detailing the structure or function of the claimed receptor agonist, is likely to be rejected. In the European Patent Office (EPO), no search will be performed for compounds only defined by the method for their identification. In the US Patent Office, on the other hand, the rejection might be overcome if it can be shown that one of ordinary

skill in the art would be expected to know that a particularly disclosed receptor agonist is representative of a family of molecules that can be identified by the claimed method.<sup>[28]</sup> Of course, the rejection can also be overcome by limiting the scope of the claim to specifically disclosed receptor agonists, if such agonists were in fact disclosed.

The EPO also has specific laws pertaining to biotechnology patents, described in the EU Biotechnology Directive of July 1998, and the European Patent Convention (EPC) of 1999. For instance, Article 53(a) of the EPC states that “European patents shall not be granted in respect of... inventions the publication or exploitation of which would be contrary to ‘ordre public’ or morality”<sup>[29]</sup>, and Rule 23d(d) excludes “processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes”.<sup>[30]</sup> Thus, patents that cover genetically modified animals, for example, that do not specify or imply medical benefits can be rejected by the EPO or challenged in an Opposition, a procedure in which any person may oppose a granted European patent within nine months from publication.

Finally, the notable rule pertaining specifically to biotechnology patents in both the US and Europe is that of utility. Under amended guidelines issued in January 2001, patentable subject matter is that which has specific, substantial, and credible utility. The addition of the substantiality requirement means that patent claims that require considerable research by a person of ordinary skill in the art in order to determine the function of a molecule are likely to be rejected. The motivation for the requirement is to reduce claims that expand the scope of the invention beyond the functions and utility described in the specifications. In its most simplified interpretation, the utility rule demands that each claim pertain to products that have a clear use and benefit to human society.

The challenges to proteomics patents are still evolving. Because of their direct application to biological life on earth, proteomics and genomics patents are subject to intense scrutiny by the various patent offices. As the technology develops, however, one impediment to the biotech patent process, namely the need for more cross-technically educated patent examiners and counsel, will eventually become less of a burden. Knowledge of the challenges to the proteomics patent process will lead to more skillful prosecution and more rapid innovation overall.

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