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C. R. Biologies 326 (2003) 1115–1120
COMPTES RENDUS BIOLOGIES

Molecular biology and genetics

Patenting genome research tools and the law

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Received 16 September 2003; accepted 23 September 2003

Presented by François Gros

Abstract

Patenting genes encoding therapeutic proteins was relatively uncontroversial in the early days of biotechnology. Controversy arose in the era of high-throughput DNA sequencing, when gene patents started to look less like patents on drugs and more like patents on scientific information. Evolving scientific and business strategies for exploiting genomic information raised concerns that patents might slow subsequent research. The trend towards stricter enforcement of the utility and disclosure requirements by the patent offices should help clarify the current confusion. ***To cite this article: R. Eisenberg, C. R. Biologies 326 (2003).***

Résumé

Prise de brevet des outils de la recherche génomique et la loi. La prise de brevet des gènes codants des protéines thérapeutiques était relativement peu controversée aux débuts de la biotechnologie. La controverse est née à l'ère du séquençage à haut débit, lorsque les brevets sur les gènes ont commencé à ressembler moins à des brevets sur des médicaments et plus à des brevets sur l'information scientifique. Des stratégies scientifiques et industrielles évolutives pour l'exploitation de l'information génomique ont suscité des sujets de préoccupation, à savoir que les brevets ne ralentissent la recherche en aval. La tendance plus stricte des offices des brevets concernant les exigences d'utilité et de description devrait aider à clarifier la confusion actuelle. ***Pour citer cet article : R. Eisenberg, C. R. Biologies 326 (2003).***

Keywords: gene; information; intellectual property; patent; scope of protection

Mots-clés : brevet ; étendue de la protection ; gène ; information ; propriété intellectuelle

1. Introduction

Intellectual property issues have been surprisingly prominent in recent discourse about the genome project, both in the scientific community and throughout society. What makes this surprising is that patenting DNA sequences is not a new practice – it has been going on for years. It began with little fanfare and little controversy, in contrast to other extension of patents which have been much more controversial. For example, in the US considerable public controversy followed the allowance of patents on microorganisms [1], animals [2], computer software [3], and business methods [4]. The issuance of patents in each of these areas promptly provoked outspoken opposi-

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1631-0691/$ – see front matter
doi:10.1016/j.crvi.2003.10.001

tion along with media commentaries [5]. In recent years we have seen similar attention focused on the practice of patenting genes, but nothing like that happened when people first started patenting genes in the early days of the biotechnology industry in the 1980s. The practice of patenting genes was thus quite well established before it provoked any significant public controversy.

The first significant controversy over the patenting of DNA sequences arose in the early 1990s over patent applications filed by the National Institutes of Health (NIH) on the first few thousands ESTs that came out of the laboratory of Dr. Craig Venter when he was at NIH [6]. These filings not only provoked opposition from the usual anti-biotechnology groups (who had previously paid little attention to gene patenting), but also triggered a storm of controversy within the scientific community, and even some signs of concern within the pharmaceutical industry. More recently the patenting of genes has figured prominently in media coverage of the human genome project [7], with some newspaper stories devoted entirely to the subject.

2. Controversy about gene patenting

Why was the patenting of genes so uncontroversial in the early days, and why has it become so controversial since then? In the early days, patenting genes looked like patenting drugs; now, it looks more like patenting scientific information. We have a clear story (although some would dispute it) about why we want to issue patents on drugs. It is a lot less clear whether we want to issue patents on scientific information.

The first generation of patents on DNA sequences from the 1980s was directed towards genes encoding therapeutically significant proteins. The patents on these genes typically claimed isolated and purified DNA sequences encoding these proteins (generally cDNA molecules created by reverse transcription), a recombinant vector that includes the DNA sequences, and transformed host cells that include the vectors. Each of these claims covered tangible materials used to make pharmaceutical products. The effect was similar to a patent on a drug, although the gene patent was directed to the starting materials used in production of the protein rather than to the protein product itself. A patent on the recombinant DNA starting materials provided an effective commercial monopoly in the recombinant proteins encoded by the DNA sequences. The US Patent and Trademark Office (USPTO) and the courts treated these patents the same way they treated patents on new chemical compounds. The analogy may never have been perfect, but it worked in the sense of motivating investments in the biotechnology industry and in the development of new products.

This was important because the biopharmaceutical industry is an area where the patent system does real work. That is not so in every industry. Although most countries have unitary patent systems that purport to apply the same set of rules across all fields of technology, and the TRIPS agreement now prohibits discrimination in the provision of patent protection on the basis of field of technology [8], the empirical evidence suggests that patents play very different roles in different fields of technology [9]. In some industries, firms say that patents are not very important to their research and development (R&D) decisions. Other things are much more important in determining the profitability of investments in innovation, such as being first in the market, for example. By contrast, people in the pharmaceutical industry report that patents are crucially important to their R&D decisions, and that they would be unwilling to invest in development of a product that is not protected by patents.

What accounts for this difference? The standard account from the pharmaceutical industry is that the development of new drugs is a costly and risky business, and that there are many costly failures for each successful product. If generic competitors could enter the market (and thereby drive down prices on) the successful products without incurring all the R&D costs on the full range of successful and unsuccessful candidates, they would drive the research firms out of business. The early biotechnology firms that developed therapeutic protein products saw themselves as high-technology pharmaceutical firms, and they too wanted patents to prevent free riders from destroying their profits. Patents on genes promised to provide that protection and allowed these new firms to raise capital, and sometimes to get pharmaceutical firms to collaborate with them, to develop new products.

Some biotechnology firms still follow this model, looking to identify and bring to market new therapeutic proteins, either on their own or with pharmaceutical

partners. But the biotechnology and genomics industries have become much more diverse in their business and research strategies in recent years. The human genome may still contain sequences encoding therapeutic proteins that have not yet been identified. But most of the genome – and even most of the transcriptome – will have its primary value as a resource for future research. Some of this research will ultimately lead to the development of products that are far removed from the genomic information that helped researchers along the path to discovery. It is not obvious how to use patents on genes to capture the value that genomic information contributes to these future discoveries.

The different perspectives of different participants in the biopharmaceutical industry lead, not surprisingly, to different outlooks on the role of patents. Pharmaceutical firms, for example, although generally strong supporters of the patent system, are somewhat skeptical about genomic patents. They do not lobby against them because the pharmaceutical industry is loath to raise political opposition to patents in any form. They fear that any constraint on the patent system would prove to be the first step down the slippery slope toward compulsory licensing of all drug patents, which would be a disaster for them. But although pharmaceutical firms do not overtly oppose genomic patents, in recent years we have seen some of these firms investing in research to put genomic information in the public domain before genomics firms can appropriate it as their intellectual property. An example is the SNP consortium [10], which candidly proclaims a goal of preventing the issuance of patents on SNPs. The existence of such an initiative provides an important reality check on the economic impact of the patent system. Patents do not just give out wealth; they also take wealth away. Usually the wealth taken away by patents comes from disaggregated consumers of end products. Patent holders might argue that otherwise consumers would never have the benefit of these products, and whether or not this is true, consumers are not ordinarily well organized to dispute the claim. In the biopharmaceutical industry, patents on the many discoveries that are made on the road to drug development take wealth out of the pocket of future innovators, some of whom are quite savvy and guard their pockets closely. Pharmaceutical firms see the biotechnology firms and universities that hold patents on these upstream research inputs as so many tax collectors, threatening to dilute their anticipated profits on potential new products. These firms are well organized politically; they have a clear business model, and they tell a clear story about the role of patents in that business model.

The biotechnology industry is also somewhat organized, but they are less clear about their business models and about the role of patents in these models. They patent what they can and hope that some of their patents will someday help them to make a profit, perhaps by allowing them to capture a share of the profits on future drugs. But they have no clear predictions about the nexus between their current patents and potential future profits, and this confusion leads to overclaiming. This may explain the otherwise puzzling reaction in the financial markets a few years ago to the joint announcement from US President Bill Clinton and British Prime Minister Tony Blair approving of the policy of the public human genome project to put DNA sequence information promptly in public databases: "*To realize the full promise of this research, raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere*" [11]. This statement did not announce any change in law or policy, and even emphasized the importance of appropriate intellectual property protection. The negative reaction in the financial market suggests fundamental confusion about what business models would lead from genomic information to future profits, leading investors to gyrate between undue optimism and undue pessimism.

Although the statutes that provide for patent protection have changed little in the past 200 years, the application of these laws to new inventions is often indeterminate. Paradoxically, a legal system that is designed to promote technological change is slow to respond to changes in the technological landscape. The USPTO is still working through patent applications from the 1990s, and looks to even older decisions, based on older technologies, for guidance in evaluating these patent applications.

3. Patentability requirements in a changing environment

The US patent statute includes a number of doctrinal levels for determining what may be patented that constrain how the patent system responds to new technologies. Genomics challenges some of the traditional tools for sorting through these patent claims. Although this may seem surprising, after some twenty years of accumulating precedent in biotechnology patent matters, the landscape of discovery has shifted in ways that limit the guidance provided by older cases.

3.1. Eligibility requirement

A threshold requirement for patent protection is the existence of patent-eligible subject matter. Many people are surprised and puzzled to learn that it is possible to patent DNA sequences. The patent statute says that you can patent any new and useful process, machine, manufacture or composition of matter. Although DNA sequences might seem like they should fail the test of novelty because they are found in nature, patent applicants avoid this obstacle by claiming DNA sequences in forms that only exist through human intervention, such as isolated and purified cDNA molecules, recombinant vectors, and transformed host cells that contain recombinant vectors. Such patents are not infringed by the DNA in the cells of our bodies, and therefore the DNA in our cells does not defeat the novelty of these claims.

So far in the US, DNA sequences have been patented as compositions of matter, a characterization that highlights their material existence as molecules. But in the modern area of high-throughput DNA sequencing, much of the value of newly identified DNA sequences resides in databases of information rather than in tangible molecules. It is not clear how to draft patent claims that will permit patent owners capture of the value of this information. One strategy that some patent applicants have tried is to claim the DNA sequences stored in machine-readable form. This is a very interesting development, and raises questions that have not been resolved by the established practice of allowing patents on DNA molecules. Can patents be used to protect data? Just a few years ago the answer to this question would have been an easy "no". Today, following judicial expansions in the patent system to accommodate information technology, it is not so clear. Some decisions involving patents for software and other computer-implemented inventions arguably open the door to patents claiming data in machine-readable form, although I hope that the USPTO and the courts will reject these claims. They may well decide that pending claims on DNA sequence stored in computer-readable medium simply prove too much. One paradox that these claims raise is that the USPTO posts the text of issued patents on a website, as do other patent offices [12]; that website would arguably infringe patent claims on DNA sequences stored in machine-readable medium, suggesting a need to rethink this issue.

Patent rights are not well adapted to protecting information, particularly information about the natural world. Given that independent discovery of such information is quite likely to happen without the efforts of any particular patent holder, excessive protection of such information as intellectual property may slow down subsequent research more than it promotes the original data collection.

3.2. Utility requirement

The legal category that is doing the most work right now in determining which DNA sequences may be patented is utility. In order to be patentable, a new invention must be useful. This requirement is written into the US constitution, which authorizes Congress to issue patents to promote progress in the useful arts [13], as well as in the patent statute: "*Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter. . . may obtain a patent therefore. . .* " [14], but it is not entirely clear what this limitation means, or what function it serves in limiting what may be patented. The courts have sometimes treated utility as a subject matter limitation that restricts the patent system to applied technology, as opposed to abstract knowledge, or to "the world of commerce" rather than "the realm of philosophy" [15], although that distinction is ambiguous in this setting. The utility requirement is also embedded in disclosure requirements that compel patent applicants to teach the public not only how to make their inventions, but also how to use them: the US Code requires that a patent application include a disclosure that provides "*a written description of the invention, and of the*

manner and process of making and using it" in terms that "*enable any person skilled in the art... to make and use the same*" [16]. Another possible way of understanding the function of the utility requirement is that it serves as a timing device that determines whether an invention is ripe for patent protection, and when it would be better left outside the patent system until more work is done to understand it.

The meaning of the utility requirement has been much disputed in biotechnology and chemistry, where structures are typically discovered or built before their functions are well understood. At what point is such a discovery ripe for patent protection? The USPTO seems to vacillate between very strict enforcement of this requirement and very lax enforcement, with no clear policy basis for choosing one approach over another. The current trend in the USPTO is toward a relatively strict standard, at least as applied to DNA sequences [17], but it is not clear whether the courts will back them up if patent applicants appeal from rejections of their patent claims.

3.3. Disclosure requirement

Disclosure requirements have had growing importance in US patent law as applied to genomics discoveries. In order to get a patent an inventor must provide a written description of the invention, an enabling disclosure of how to make and use the invention, and disclosure of the best mode contemplated by the inventor of practicing the invention [16]. An applicant may not update this disclosure after filing a patent application, but must get it right the first time or else lose the benefit of original filing date (or even risk invalidation of an issued patent). Apart from informing the public, patent disclosures also demonstrate what it is that the applicant has done that justifies issuing a patent. The Court of Appeals for the Federal Circuit, which is the primary appellate court in patent matters in the US, has used the disclosure requirements in recent years to limit the scope of rights available to those who identify new DNA sequences [18]. Indeed, as a general matter, that court has been generous with patent applicants in matters pertaining to patent validity, but very strict with patent owners in determining the scope of patent rights. Some US practitioners summarize these positions in the aphorism that the Federal Circuit will not rest until it has held every US patent valid, but not infringed.

The disclosure requirement constrains the timing of patent applications: one cannot get a patent until one discloses the sequence. At an earlier point in the history of gene patenting, the effect was to deny patents to inventors who had an enabling methodology and a viable strategy for cloning a gene, but had not yet actually done so and therefore could not disclose the DNA sequence [19]. This approach also constrains the scope of claims and prevents patent applicants from getting broad patents that cover many variations on a sequence on the basis of a disclosure that does not explain how to sort through those possible many variations and determine which ones will work [20]. This is an interesting area to monitor in genomics and it is a limitation that is better grounded in recent appellate case law than utility.

3.4. Non-obviousness requirement

A final requirement for patent protection that should play a larger role in genomics than it has done so far is the non-obviousness requirement, or "inventive step" as it is known in European law. In order to be patentable, an invention must be non-obvious to a person of ordinary skill in the field, in view of the prior art or a previously disclosed knowledge in the field [21]. The meaning of that standard is much contested in the patent system. In a formulation that resonated with the courts in the past, the non-obviousness standard distinguishes the unpatentable work of the ordinary mechanic from the patentable advances of more insightful inventors. One way of understanding this distinction is that you do not need patents to bring about mundane advances that are within easy reach of the average person working in the field, but only for the non-obvious advances that require something beyond routine work. But the drafters of the current version of the US patent statute, who were uncomfortable with past judicial efforts to distinguish between patentable and unpatentable work in terms of the nature of the inventive work, added to the definition of non-obviousness, a sentence that discourages inquiries into how the inventor went about making the invention: "Patentability shall not be negativated by the manner in which the invention was made" [21]. Instead of asking how the invention was made, one should look at the results, and

ask whether the invention itself is non-obvious in light of the prior art.

This approach has arguably led to the patenting of trivial work in genomics. In the era of high-throughput DNA sequencing, the discovery of new DNA sequences has become highly routine and mechanical. But the fact that new DNA sequences are identified through the work of robots and computers that could be put to work by people of ordinary skill in this highly accomplished field does not seem to preclude them from being patented. For now, the Federal Circuit seems to think that the language of the statute precludes consideration of the routineness of the sequencing method in determining whether a sequence may be patented. Perhaps as the PTO sorts through patent applications that are currently pending, the law will start to shift toward a more robust non-obviousness standard in the future.

4. Conclusion

For the first generation of recombinant DNA products, patents on genes looked more or less like patents on drugs. Today, patents on genes look more like patents on scientific information. In contrast to patenting end products, patenting the information base for future R&D raises serious questions as to whether, on balance, it is more likely to promote progress or to retard it. As new business models evolve for translating DNA sequence information into profitable products, it is not yet clear what role the patent system will play.

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