Chadwick, R., Levitt, M. and Shickle, D. (1997) *The Right to Know and the Right not to Know*. Avebury Press, Aldershot, UK.

Lewin, T. (July 21, 2000) Genetic testing brings tough new choice in families. *The New York Times*.

Lichtenstein, P., Holm, N.V., Verkasalo, P.K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A. and Hemminki, K. (2000) Environmental and heritable factors in the causation of cancer—analysis of cohorts of twins from Sweden, Denmark, and Finland. *N. Engl. J. Med.*, **343**, 78–85.

MacDonald, A.S. (1997) How will improved forecasts of individual lifetimes affect underwriting? *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **352**, 1067–1075.

McGleenan, T., Wiesing, U. and Ewald, F. (1999) *Genetics and Insurance*. Springer Verlag, New York, NY.

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Rewarding true innovation

Experimental use exemption and the trends in gene patenting • by Luca Falciola

In 1980, the US Supreme Court decision in *Diamond v. Chakrabarty* not only helped considerably the development of the biotech industry, but also affected practices in the intellectual property area. After the rejection of the US Patent Office's claim that living organisms *per se* cannot be patented, companies now were able to seek a wider protection for products created using DNA recombinant technologies, while patent offices were given the opportunity to expand their activities into this area.

The speed at which genetic information is accumulated by far exceeds the speed at which patent offices can examine applications thoroughly

During the 1980s, recombinant proteins were mostly developed for the treatment of pathologies such as diabetes, anemia, growth disorders and infertility. The properties of these molecules were well characterized *in vivo*, so patent offices were able to apply the well established principles of patent law—utility, inventiveness, novelty and unity—in a satisfactory way.

But in the last decade, technological advances in sequencing and bioinformatics have allowed biotech companies to identify, massively and at low cost, novel

gene sequences for which they are seeking patent protection (Figure 1; Table I). The speed at which genetic information is now accumulated and submitted to patent offices by far exceeds the speed at which genes can be even roughly characterized, and that at which patent offices can examine applications thoroughly to decide on their patentability (Figures 2 and 3).

Due to this trend, a hard-to-calculate, but enormous and increasing bulk of genetic information has become *de facto* a research tool (Ducor, 1999). As had been made clear in articles and discussions in journals like *Nature* and *Science*, many scientists regard this as a major deterrent to research, and hold the patent system responsible for this distortion of law practice. However, before labeling the whole patent system as faulty, the actual impact of this patenting frenzy on the activities of research laboratories should be evaluated, taking into account some of the concepts of patent law, as well as some consequences of the current situation.

Apart from the basic requirements for obtaining a patent, the patent system also assigns a fundamental importance to the concept of experimental use exemption to patent infringement (Ducor, 1999). This institution stems directly from the original goal of the patent system to promote innovation by granting, in exchange for public disclosure of the invention, a time-limited exclusivity for commercial exploitation.

Patent infringement takes place if a product or a method covered by a patent is produced, used, imported or sold without permission or license from the patentee. A researcher working on a patented matter to improve it cannot be sued for patent infringement as the experimental use exemption applies to his work.

A researcher working on a patented matter to improve it or for non-commercial research cannot be sued for patent infringement

Patent literature makes available to the public a large body of knowledge in terms of DNA/protein sequences, biological materials deposited in public collections such as the American Type Culture Collection, and experimental results, which is not always, or only later, disclosed in other form. This information is published in a format compliant with Patent Offices procedures of analysis, which are different from those of the scientific peer-reviewing system, but scientists can find and make use of relevant first-hand data for the purpose of their research.

Some attention should be taken in considering the possibility that some research activities may not fall under the experimental use exemption. In non-corporate

Fig. 1. Biosequences disclosed in patents. Elaborated on data extracted from DGENE/GENESEQ, a database produced by Derwent.

Table I. Origin of biosequences disclosed in patents. Elaborated on data extracted from DGENE, a database produced by Derwent

Origin	Nucleic acid sequences		Protein sequences	
	1990	1999	1990	1999
<i>Homo sapiens</i>	487	66 668	699	32 861
Synthetic	913	33 147	1459	13 269
<i>Saccharomyces</i>	13	936	10	267
<i>Neisseria</i>	32	3291	33	2243
<i>Mus, Rattus</i>	124	6508	116	2865
<i>Staphylococcus</i>	7	745	6	489
<i>Chlamydia</i>	2	10 496	1	2629
Mycobacteria	16	1219	14	870
Hepatitis viruses	27	3313	8	1263
<i>Bacillus</i>	50	913	48	823
<i>Escherichia coli</i>	10	401	10	282
<i>Haemophilus</i>	12	128	10	268
<i>Arabidopsis</i>	2	752	2	261
<i>Equus, Sus, Bos</i>	48	590	43	502
<i>Caenorhabditis</i>	0	362	0	127
<i>Oryza, Zea</i>	22	358	20	377

environments, it is becoming increasingly important to produce results that can lead not only to scientific publications, but also to patent applications, and thus eventually to a commercial exploitation. As has often been pointed out, licenses and royalties on products are becoming more and more important resources to finance research institutions (Mulligan and Steele, 2000). On the other hand, non-corporate

research has an important role. The massive investments in the life sciences made by governments are still a driving force in generating the knowledge base for the biotech industry (Kroll *et al.*, 1998). Therefore, suing public research institutions could be an indelicate move, damaging to the image of a company and to its relationship with the scientific community. Thus, the applicability of the

experimental use exemption can become a matter of interpretation and, eventually, negotiation.

An interesting situation is represented by the use of DNA microarrays as research tools. The companies that assemble and sell such products are actually facing a large problem as they may be obliged to obtain multiple licenses when using DNA sequences covered by patents. As these

Fig. 2. Published patents containing DNA or protein sequences. Elaborated on data from the patent databases of the Delphion Intellectual Property Network (<http://www.patents.ibm.com>).

Fig. 3. Published patents containing novel protein sequences and claiming therapeutic application. Elaborated on data extracted from the patent databases of the Delphion Intellectual Property Network.

chips are on the market for basic research as well as for commercial purposes such as drug development, it is clear that experimental use exemption does not always apply. Therefore, the company owning the granted patent on a useful DNA sequence should get a share of the profits made by selling the chips. Such a situation can lead to potentially enormous negotiation problems, with hundreds of

licenses necessary for a single type of array. Lacking a widely accepted policy on these issues, most DNA chip manufacturers immobilize only DNA sequences that are in the public domain. Evidently, this represents a limitation of the DNA chips' potential, and can hamper research efforts. This example shows clearly that uncertainties and the fragmentation of patent rights can deter research programs that

are necessary to confer a real value to this knowledge.

Another interesting case is represented by the trend in patenting activities related to single nucleotide polymorphisms (SNPs). While many patents disclose alternative methods to identify SNPs, some others disclose hundreds of SNP-related probes with very limited evidence of their utility, and therefore their patent-

ability can be questioned. Only a minority of patent applications characterize SNPs that are clearly related to a disease or a gene function.

It is evident that there will be problems of dependency and license negotiations on those SNPs with commercial potential. To prevent this outcome, some pharmaceutical companies and governmental institutions formed the SNP consortium, a time-limited cooperation of academia and companies to share the results of their SNP discovery programs. The consortium makes the information available to the scientific community as a database, but it also files provisional patent applications to establish discovery dates. The applications will be relinquished afterwards to avoid dependency on the SNPs as such, once their actual effect is demonstrated.

Licenses and royalties are becoming more and more important resources to finance research institutions

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The trend in patenting of SNPs illustrates that it is becoming more and more difficult to assess the real enforceability of patent applications based on long sequence listings. Since unity of the invention is a basic criterion for patentability, patent offices will force applicants to split the original application into several separate ones, each covering SNPs with shared features. Fees and work-hours for the applicant consequently increase during the prosecution of such patent applications—maintaining a single patent only in the major countries can cost hundreds of thousands of US dollars. It is, therefore, a more reasonable and efficient way to file applications where only SNPs with medical utility are disclosed in order to obtain really enforceable patent rights. A company must also take into account that the value of a SNP disclosed in a patent application may be dramatically affected if an alternative method becomes available for population screening. This

holds true for expressed sequence tags (ESTs) as well: obtaining the protein without using the patented EST may not require a license, depending on the claim wording in the granted patent. Another aspect of this field is that public-private initiatives such as the Merck Gene Index project are promoting the unrestricted exchange of genetic data.

Nowadays, patent offices and practitioners are facing major procedural and organization problems since dictionary-sized applications disclosing thousands of sequences challenge not only the criteria for granting a patent, but also established practises in examining, archiving and publishing. From the legal point of view, patent offices have to deal first with the basic rules contained in patent conventions and treaties. Even if the adaptation of the examination guidelines and the outcome of patent lawsuits—events already going on or expected to come in a few years—may have an impact on patent law, the basic criteria for granting a patent will hardly be affected.

The patent community is concerned that the patent system might lose credibility if the protection offered were perceived as limiting economic advances

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In addition, international documents such as the agreement on Trade-Related aspects of Intellectual Property rights (TRIPs), the conventions on biodiversity and on the protection of plant varieties, as well as EC directives established general rules for the implementation of intellectual property rights. Any important or unilateral change of gene patenting policies must take into account the principles defined by these documents that were directed to harmonize patenting practices not only in different countries but also for any economic activity. There is large consensus in governments and industries on the fact that standardizing of patent poli-

cies is very important to create economic, scientific and social value around the identification of the 'functional' genetic information (Brown, 2000). This has become a challenge not only for companies, but also for the scientific community as a whole, given that the public and shareholders have great expectations for the development of new drugs and treatments, and do not wish to see resources wasted on endless legal battles.

Many people, not only in academia but also in industry, would therefore like to see gene patenting restricted to sequences that clearly define a function or a disease (Thomas, 1999). The patent community largely agrees as it is also concerned that the patent system might lose credibility if the protection offered were perceived as limiting rather than promoting economic advance and diffusion of knowledge. The risk of 'over-patenting' can exist, but in most of the situations the application of existing laws can moderate most of the excesses and, in the end, help to reward real creativity by granting patent protection that is fair and sensible. The adoption of a collaborative attitude amongst the various actors when it comes to facing patenting problems would help eliminate the remaining uncertainties.

Brown, K. (2000) The human genome business today. *Sci. Am.*, **283**, 40–45.

Ducor, P. (1999) Research tool patents and the experimental use exemption—a no win situation? *Nature Biotechnol.*, **17**, 1027–1028.

Kroll, P., Ault, G. and Narin, F. (1998) Tracing the influence of basic scientific research on biotechnology patents. *Patent World*, **106**, 38–46.

Mulligan, L. and Steele, P. (2000) Innovation from non-industrial sources. *Expert Opin. Ther. Patents*, **10**, 17–24.

Thomas, S.T. (1999) Genomics and intellectual property rights. *Drug Discov. Today*, **4**, 134–138.

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