

**OF PATENTS AND GENES****FLOWS OF KNOWLEDGE AND INTELLECTUAL PROPERTY RIGHTS**

## Abstract

On the basis of results from the endogenous growth theory and of the economic analysis of intellectual property rights, the paper considers the advisability of patenting elements of the human body, like genes and proteins. These appear as «essential facilities» for further research in molecular biology and for the furtherance of public health goals ; hence, no broad patents should be granted over them, and, in certain circumstances, no patents at all. As, nevertheless, broad patents have actually been granted, their usage should be liable to public regulation, as are, in an increasing number of countries, natural monopolies on which public utilities rely. Some consequences for the implementation of TRIPS in developing countries are considered.

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## **1. IMPACTS OF INTELLECTUAL PROPERTY RIGHTS ON GENES : THREE EXAMPLES**

### **1.1. Genes BRCA<sub>1</sub> and BRCA<sub>2</sub> as indicators of susceptibility to breast cancer**

The first example involves the biotechnology firm Myriad Genetics (Salt Lake City, Utah, USA), which owns since 1977 the rights attached to patents granted by the US Patent and Trademark Office (USPTO) on genes BRCA<sub>1</sub> and BRCA<sub>2</sub> ; these genes indicate susceptibility to breast cancer, i.e. mutations of these genes reveal a greater risk of developing breast cancer. The patents also cover diagnostic tests for detecting mutations. On this basis, Myriad Genetics claims the rights to all diagnostic tests involving the BRCA genes ; this is in line with the broad reach that the USPTO and the American courts generally grant to patents on genes.

In order to enforce its rights, Myriad Genetics notified to all laboratories engaged in independent research or clinical trials of diagnostic tests involving the two BRCA genes, that they should cease these activities. Among the most concerned laboratories was the service of clinical genetics at the University of Pennsylvania ; they were rather advanced in testing for susceptibility to breast cancer, and had a significant number of persons at risk under observation ; nevertheless, the lawyers advising the University recommended to cease all these activities, for fear of litigation by Myriad Genetics for infringement of its patents. In Canada, the public Health Service has been more reluctant to comply with the requests from Myriad Genetics (it was also much less exposed to a judicial action) : they were not prepared to pay Myriad Genetics \$2800 per test, whereas the cost in Canada was only \$300.

In Europe, the European Patent Office (EPO), following the lead of the USPTO, has also granted patents to Myriad Genetics. However, within a certain period after it has been granted by the EPO, a patent may be opposed by any person or organization who has reasons to think that the patent has been inappropriately granted. In this case, the Institute Curie in France, along with other Belgian, Danish and French institutions, has filed an opposition. The outcome of the procedure, that is conducted by a kind of appellate body within the EPO, is awaited with great interest.

## **1.2. Protein CCR5 and new medicines to combat AIDS**

In 1995, another US biotechnology firm, Human Genome Sciences (HGS), filed for a patent on a gene coding for a protein, CCR5, that, according to HGS, might be involved in inflammatory disorders ; in fact, no precise function was claimed to support the requested patent. While USPTO was examining the claim, scientists at the National Institutes of Health (NIH, the large American network of public laboratories working in life sciences) and at the Free University of Brussels, whose work didn't depend in any respect from HGS s' claims, discovered that CCR5, when on the surface of a cell, might function as a gate for the entry of the HIV virus into the cell. On that basis, new medicines were subsequently developed that essentially shut the gate.

As if ignoring this independent discovery, USPTO granted HGS a patent which asserted rights over the gene that codes for CCR5, hence over all functions of that gene and all the applications derived from those functions. From a juridical point of view, therapies for AIDS derived from the role played by CCR5 might not be marketed without licenses granted by HGS, although their development didn't scientifically rely on anything HGS had done. HGS agreed to several licenses, for a significant portion of the profits made from the new medicines.

This is an emblematic case that illustrates the oddity of patenting a gene as if it merely were a "material compound", i.e. as a synthetic chemical molecule, the invention of which patent law and jurisprudence usually reward by rights over all possible applications.

## **1.3. Genes coding for growth factors**

What does it mean that a gene codes for a growth factor ? It means that the gene controls the production of a protein the function of which is to bind with a receptor situated on the surface of a cell, and then stimulate cell division ; this effect may contribute to the repair or replacement of damaged or diseased tissues. The growth factor is the protein ; but to be effective, it needs to bind with a receptor on the surface of a cell that is consequently stimulated to reproduce itself.

What is at stake in the lawsuit considered in this section, are the rights over the genes coding for heparin-binding growth factors (HBGFs), heparin being a receptor on the surface of many cells. Thomas Deuel (Harvard Medical School) has purified and sequenced some among these genes, and on that basis had petitioned for patents. In November 1993, the appellate body of USPTO had backed the decision made by the examiners of the Office to reject Deuel's petition for obviousness, taking into account the scientific and technical knowledge available at the time.

Deuel lodged an appeal with the Court of Appeals for the Federal Circuit (i.e. the federal court that is specialized in intellectual property disputes), which in 1995 reversed the decision made by USPTO. The Court accepted that the scientific and technical literature, to which Deuel had access at the time his work was in progress, suggested how to proceed, and offered an application to another line of molecules ; however that was not a sufficient reason to deny Deuel a patent. This is not an unreasonable conclusion, as long as it is recognized that Deuel's results are neither pioneering nor specially broad. That, the Court refused to recognize, by granting a patent not only over the genes that Deuel had purified and sequenced, but also over all genes coding for HBGFs ; how many of those genes there are, nobody knows, but it is clear that the number is high. The Court's decision is all the most paradoxical as in their «discussion», the judges write : «claims 4 and 6 are thus tantamount to the general idea of all genes encoding the protein, all solutions to the problem»<sup>1</sup>.

This example illustrates a characteristic drift : to treat as if it was pioneering an invention which is merely marginal in itself, but which is closely related to discoveries or inventions that are of much greater significance and are available freely. The marginal invention which gets a broad patent positions itself on the border between what D. Foray (2003) respectively calls «IPR science»<sup>2</sup> and «open science»<sup>3</sup>. Deuel sought the protections of IPR science, and the Court of Appeal for the Federal Circuit granted him protections so broad that it is as if he deserved all the credit for the open science on which he has relied.

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<sup>1</sup> Claims 4 and 6 are the claims with the broadest reach made by Deuel. The complete «discussion» presented by the Court is reproduced in R. P. Merges (1997), pp. 595-598.

<sup>2</sup> IPR for «intellectual property rights».

<sup>3</sup> In Deuel's case, it is a discovery rather than an invention. According to a strict interpretation of the patent laws, a discovery is not patentable, only an invention is. However, since twenty years or so, this distinction has been ignored by the main patent offices and by the courts.

## 2. ECONOMIC FACTORS CONDUCTIVE TO INNOVATION

In order to properly assess the economic significance of the three cases discussed in the previous section, and more generally to assess the positive and negative contributions of patent protections to innovation in biotechnologies, it is necessary to first recall the main lessons drawn from the microeconomic analysis of innovation and intellectual property.

Endogenous growth theory provides solid foundations for investigating the economic factors conducive to innovation. Indeed, as P. Aghion and P. Howitt put it : «The economic growth involves a two-way interaction between technology and economic life : technological progress transforms the very economic system that creates it»<sup>4</sup>.

In this framework, it has been shown, both theoretically and empirically, that the following four factors are conducive to innovation :

- (1) Competition for realizing innovations ; in its extreme form, it is Schumpeter's «creative destruction».
- (2) Ex-ante competition on the product markets : firms try to escape «neck-and-neck» competition by innovating<sup>5</sup>.
- (3) The diffusion, as large as possible, of knowledge, created by previous innovations : knowledge is a public good and, as such, ideally should be freely available<sup>6</sup>.
- (4) Limitation of ex-post competition on the markets for the products that derive from the innovative effort : the prospect of a protected market is more attractive for the innovator than the prospect of a competitive one.

As ex-post competition after one round of innovation is ex-ante competition before the next round, factors (2) and (4) are colliding. This is not directly the case between (1) and (3) on

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<sup>4</sup> Aghion, P. and P. Howitt (1998), p. 1.

<sup>5</sup> The effects of «neck-and-neck» competition on innovation are analyzed in Aghion, P., C. Harris, P. Howitt and J. Vickers (2001).

<sup>6</sup> «The invention makes it possible for other researchers to begin working on the next innovation» (Aghion, P. and P. Howitt (1988), p. 54). In the same spirit, S. Scotchmer, using a famous expression coined by I. Newton,

one side, and (4) on the other side ; however, indirectly, it becomes the case, as soon as the limitation in (4) is implemented through instruments of protection of intellectual property like patents. Schumpeter was very much in favour of the limitation of ex-post competition, to the point of recommending monopoly powers in favour of the innovators ; but he meant powers on products, i.e. on private goods, emanating from new knowledge, not powers on knowledge itself, which is a public good. Having also in mind the fact that any monopoly is detrimental, at least directly, to the consumers' interest, it appears that granting patents to innovators is a seriously imperfect way of creating incentives to innovation, and of financing the necessary investments ; it should thus be used only under the condition of carefully balancing its benefits and its costs, and of taking into account other incentives and other sources of finance<sup>7</sup>.

In particular, making knowledge available as largely and as freely as possible is of paramount importance, as P. David argues : «Legal and other institutional arrangements may be imposing high costs on research intensive firms, and society more generally, by restricting access to some elements in the streams of creative thought, and thereby making it less likely that the elements will be rapidly rearranged and recombined in new and fruitful ways»<sup>8</sup>.

The extent of the monopoly power embedded in a patent is characterized by the patent's length and breadth. The length is, at 20 years, more and more uniform around the world ; for products, like pharmaceuticals, that are subject to long regulatory delays, it may be up to 25 years. These are legal lengths. The actual lengths are often shorter, as new competing products are developed without infringing to the existing patents.

A patent's breadth can often be characterized by the minimum differentiation degree – be it vertical, horizontal, or in terms of reduced production costs – that a new product must entail with respect to the product covered by the patent, in order to avoid infringing to the patent. There is thus a protection zone out of which competitors must keep in their efforts to innovate

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entitles her review paper in the *Journal of Economic Perspectives* : «Standing on the shoulders of giants : cumulative research and the patent law» (Scotchmer, S. (1991)).

<sup>7</sup> Academic competition, and the partly symbolic retributions it entails, provide powerful incentives to discover and invent ; but it requires public or charitable funds for its financing. In a world of perfect information, that would not create distortions, in a world where imperfect information prevails it does, and we are again with an imperfect instrument. In *Intellectual property : when it is the best incentive system ?*, N. Gallini and S. Scotchmer (2002) assess the merits and the imperfections of various systems of creating incentives to and providing finance for innovation. In *R. and D. cooperation and competition*, M. L. Katz and J. A. Ordover (1990) mention for the USA rates of more that 40 % for public subsidizing of private research (universities not included).

<sup>8</sup> David, P. (1993), p. 29.

in their turn. They might be helped in these efforts by the information that must be disclosed when a patent is granted, information that would not be available if, in the absence of a system of protection of intellectual property, innovations were kept secret.

However, if its breadth is excessive, what a patent blocks weighs more than what it allows : the benefits are superseded by the losses in terms of factors (1), (2) and (3) above, and in terms of direct consumers' surplus. The losses in terms of (3), i.e. the lost opportunities of large and free use of knowledge as public good, may be specially significant, as R. P. Merges and R. R. Nelson recall : «When a broad patent is granted, its scope diminishes incentives for others to stay in the invention game, compared with a patent whose claims are trimmed more closely to the inventor's actual results»<sup>9</sup>.

### **3. APPROPRIATE PATENTS' BREADTHS : GENERAL RESULTS AND APPLICATION TO BIOLOGY AND BIOTECHNOLOGIES**

From section 2, it appears that the choice of an appropriate breadth for a patent is decisive in terms of the role that this patent plays in the innovation process : if the breadth is too narrow, factor (4) loses much of its incentive effect ; if it is too large, factors (1), (2) and (3) are damped down. How to determine an "appropriate" breadth ?

Many contributions<sup>10</sup> in the economic literature specializing in the subject provide elements of answers to that fundamental question. From these elements the following results emerge : a patent on an invention (or a discovery, see note (3) in section 1.3.) should be the narrower,

- the less there are substitutes for the products developed from the invention, or the more difficult it is to by-pass the invention (or, more often, the discovery) in subsequent research ;
- the less the invention is costly to complete by the inventor ;
- the more there are non-monetary incentives (e.g. "academic rewards") available to motivate the inventor.

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<sup>9</sup> Merges, R. P. and R. R. Nelson (1990), p. 916.

The first condition implies that it is not appropriate to grant a broad patent to an invention (and, a fortiori, a discovery) that commands important applications or lines of research that cannot be pursued without the results covered by the patents ; in such circumstances, the invention (or discovery) is an «essential facility», essential for developing these applications or for working on further research. We here reach a junction between the protection of intellectual property and the protection of competition, including the competition for innovation and the access to knowledge, as argued by W. K. Tom and J. A. Newberg, both members of the US Federal Trade Commission, in *US Enforcement approaches to the antitrust-intellectual property interface* : «If market power in an antitrust sense is not to be presumed, then, as with any other form of property, the existence of such power must be determined by evaluating the availability of close substitutes»<sup>11</sup>.

When an element in the body (gene, protein, ...) plays roles for which it cannot be replaced by any other element, we are at an extreme case of the situation discussed above : any substitute is lacking, not only close ones. Regarding such elements, which incidentally are discovered and not invented, even the caution urged by R. P. Merges and R. R. Nelson (see quotation in section 2) might not be sufficient : from the point of view of economic efficiency, it might be required to reduce a patent's breadth below what would coincide with «the inventor's actual results».

The case of genes is of special interest. Many play essential roles for which there are no substitutes. In antitrust terms, they are «essential facilities». Moreover, they are no longer costly to isolate, sequence and characterize. For all these reasons – and the first one is paramount – no broad patent should be granted on a gene.

The problem then is that, because patent offices and courts deal with a gene as if it were a synthetic chemical molecule (referred to as a «material compound»<sup>12</sup>), the patents they grant

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<sup>10</sup> Among the most significant ones are : Merges, R. P., and R. R. Nelson (1990), Chang, H. F. (1995), Scotchmer, S. (1999), Gallini, N. and S. Scotchmer (2002), Denicolo, V. (2002).

<sup>11</sup> Tom, W. K. and J. A. Newberg (1998), p. 346. That «market power is not to be presumed» means that not all patents automatically create problems from the point of view of competition protection ; however problems, possibly serious ones, derive from the absence of close substitutes, and then need remedies. See also Barton, J. H. (1995).

<sup>12</sup> Obviously, genes are molecular systems. But, as far as the functioning of a living organism is concerned, they are above all information systems that code complex, diversified and essential biological activities.



are «product patents» that cover all the gene's functions and all applications of those functions ; they cannot but be broad. The only logical conclusion is that, for the sake of economic efficiency, genes should not be patented at all.

#### 4. REGULATING THE ACCESS TO ESSENTIAL FACILITIES WITH LICENSES

In effect, tens of thousands of claims on human genes have been granted by USPTO or are being examined there ; to mention only two among the numerous firms involved, Incyte Pharmaceuticals and Human Genome Sciences respectively have 4500 claims (organized in 570 patents) and 3400 claims (450 patents) ; this is a race towards the confiscation of genes. EPO is some distance behind, but is following suit. There are also patents on DNA subsequences and on proteins. That situation is a serious obstacle to further research and to a large diffusion of essential therapies. Increasing transaction and litigation costs considerably increase the time and resources necessary to complete a research project. That has for example been the case for the *Malaria Vaccine Initiative*<sup>13</sup>, an international nonprofit project the promoters of which discovered that they were dependent on more than 20 patents, some ill-defined or even overlapping (nobody had very much cared for patents to which no clear perspective of profitability was attached) ; it took years to disentangle this web ; it could have been even more difficult if hundreds of patents had been involved<sup>14</sup>.

In such circumstances, it is no surprise that much dissatisfaction with the functioning of the patent system was expressed in the answers to a survey conducted in 1998 by the NIH with the US biotechnology firms. They didn't repudiate the patent system, but they complained at length of the proliferation of upstream patents that blocked or kindered their own research efforts : and, year after year, the situation was worsening. Transaction and litigation costs were exploding. Even convenient arrangements between firms like cross-licensing or establishing patent pools were becoming insufficient to stem the tide, to «navigate the patent thickets»<sup>15</sup>.

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<sup>13</sup> See Nuffield Council on Bioethics (2002).

<sup>14</sup> As is the case when pharmaceutical companies screen molecules as candidates for medicines, or when tests are made with DNA chips («If DNA chip development lives up to its promises, it will enable clinicians or even patients themselves to quickly and inexpensively test for up to 20 000 to 30 000 genetic properties from a drop of blood or hair sample». Ontario Draft Report to Premiers (2002), p. 11). For a wealth of examples, see also NHI (1998).

<sup>15</sup> As shown in Shapiro, C. (2000) ; see also Tirole, J. (2003).

The number of patents granted by USPTO is not the only parameter explaining the difficulty and the cost of negotiating intellectual property rights. The uncertain validity of many patents, insufficiently investigated by USPTO, is also a problem. And so is the behaviour – well documented in the survey – of the participants in the market for intellectual property rights, in so far as the sellers tend systematically to overestimate what they have to offer, and the buyers tend systematically to underestimate what they are offered<sup>16</sup>. The transactions become even more difficult, and somewhat perverse as far as the subsequent diffusion of knowledge is concerned, when the seller requests property rights on the inventions or discoveries that the buyer might make with the help of the knowledge handed over by the seller. University researchers find such requests specially difficult to handle. Many among them had enthusiastically endorsed the opportunities created by the Bayh-Dole Act<sup>17</sup> ; they subsequently had to put up with the inconveniences of the new regime of «IPR science». Under the previous regime of «open science», they were often granted by firms specific or tacit exemptions from effects of intellectual property rights. That was over : finding that the university researchers had become tough players on the IPR market, the firms became equally tough with them ; they often requested rights over results obtained in university laboratories ; interesting other firms to the same line of research, or attracting sponsors, was then very difficult. The mechanisms of IPR science, as they work in reality, are apt to breed serious obstacles against the course of innovation.

All these problems need not emerge when patents play their basic role as supports of efficient transactions in knowledge. That has been the case with the Boyer-Cohen patent that covers a basic technique in genetic engineering : it has been the support of a large number of non exclusive licenses sold at reasonable prices ; moreover, free use of the technique for nonprofit researches has always been possible<sup>18</sup>. But more often, in order to maximize their profits, patent holders either exploit their patents themselves (like Myriad Genetics), or sell exclusive licenses. It may even happen that, in order to protect existing productions techniques,

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<sup>16</sup> Then, otherwise advantageous transactions are not realized ; see Gresik, T. and M. Satterthwaite (1989).

<sup>17</sup> Named after his proponents, representative Bayh and senator Dole, this Act was passed by Congress in 1980 ; it authorizes and even incites scientists working on federal funds to patent their inventions or discoveries ; they may keep for themselves the bulk of the ensuing financial returns.

<sup>18</sup> Other major discoveries or inventions in biology and biochemistry were not patented at all, and their use is completely free. It is for example the case of the Kohler-Milstein method for the in vitro production of monoclonal antibodies ; the work has been entirely funded by the Laboratory of Molecular Biology, Cambridge (U. K.) ; G. Kohler and C. Milstein were granted the Nobel prize in medicine ; see Kohler, G. and C. Milstein (1975).

they block the use of patents they own<sup>19</sup>. So there are many circumstances in which licenses are not offered to anybody needing them and prepared to pay reasonable prices.

Public utilities (electricity, rail, telecommunications, ...) depend on essential infrastructures (grid, track, local networks, ...). Without access to these natural monopolies at fair prices, firms are excluded from the corresponding businesses. Regulating access, and price of access, by specialized public authorities (the regulators) is now the almost universal approach to the problem<sup>20</sup>.

Genes, proteins, and other elements of the body, constitute an essential infrastructure of critical importance to further research and to public health. If owners of patents don't offer licenses at reasonable prices, when some research or public health imperative would require it, then it is no less economically justified to regulate them than it is to regulate the owners of electricity, rail or telecommunications networks. Compulsory licenses may be used as regulation tool. Canada and the USA have a long experience with compulsory licenses, to deal mainly with health requirements in Canada, and as antitrust remedies<sup>21</sup> in the USA, where they have also been used in defence procurement to overcome deadlocks between private firms (in aeronautics, and in electronics) deemed detrimental to the national interest.

There are familiar objections against compulsory licenses. They weaken the incentives to innovation brought by the corresponding patents. In network utilities, the parallel concern is that capped prices for the access to essential infrastructures lead to underinvestment in these infrastructures. More generally, the asymmetry of information between regulator and regulated firms makes it impossible for the regulator to set appropriate access conditions (to essential patents here, to essential infrastructures there). These problems are serious, and deserve serious consideration, which is precisely what they got in the regulation of network utilities. In particular, both academic research and regulators' learning-by-doing have produced procedures converging to the setting of access conditions in such a way that information useful to the regulator is revealed during the course of the procedure and thanks to in - built incentive

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<sup>19</sup> This is known as the *Arrow effect*, introduced in Arrow, K. (1962).

<sup>20</sup> See Henry, C. and M. Matheu (2001).

<sup>21</sup> See Barton, J. H. (1995) and Scherer, F. M. (1998). Interestingly, from the large set of data he has gathered, F. M. Scherer concludes that, statistically, to impose compulsory licenses on the firms considered had no effect on their subsequent propensity to innovate.

devices<sup>22</sup>. What has been possible for network utilities regulation does not seem unattainable for intellectual property regulation.

## 5. CONCLUSION

«While patent protection provides an incentive for R and D, the patenting of intermediate technologies (particularly gene-based ones) required in the research process may actually create disincentives for researchers in terms of accessing, or unwittingly infringing patents on technologies they need. This is an area where patent practices in the developed world can impinge directly on what research is done for people in the developing world, and there are implications for the type of patent regimes that developing countries adopt<sup>23</sup>».

John Barton and the Commission he chaired, on behalf of the UK Department for International Development, were looking for means of *Integrating intellectual property rights and development policy*. What they say here, in carefully chosen words, is that such integration is made all the more difficult by the disease of the patent system that started and developed in the USA, and then reached Europe : unwarranted patents, unduly broad patents, less than rigorous examinations by the patent offices, propatent zeal of the courts specialized in intellectual property disputes, explosion of transaction and litigation costs, to the point of hindering rather than promoting research and innovation.

If this is the system that the WTO, by implementing the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), is meant to spread all over the planet, the doubts, that one might already have concerning the uniformisation of intellectual property protection resulting from the TRIPS, are seriously reinforced, and the difficulties of integrating intellectual property rights and development policy are increased. At least the option of regulating essential patents remains available to the developing countries : even this is in doubt, as they are under pressure from developed countries to formally renounce the faculty of imposing compulsory licenses.

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<sup>22</sup> See Henry, C. and M. Matheu (2001) and Armstrong, M., S. Cowan and J. Vickers (1994).

<sup>23</sup> Commission on Intellectual Property Rights (2002), p. 34.

It seems clear that the drift characteristic of the patent systems in the developed countries will considerably complicate the adoption by the developing countries of intellectual property regimes that suit their needs.

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