"GENE" PATENTING (for The Scientist)

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There is no *a priori* reason to deny a patent or other legal protection to an intellectual product solely because it is a "gene" sequence: although genes, as DNA molecules, may be considered "immortal", thanks to their semi-conservative replication, a similar feature could probably be attributed to other biological structures such as cell membranes, and most likely to their molecular building blocks (and, if immortality is the issue, certainly to their constitutive atoms!). Thus it seems there is hardly anything sacred in genes, as some, not necessarily bioethicists, may believe (Nature 358: 272, 1992).

Similarly, there is no *a priori* reason to grant patents solely because the relevant inventions are (based on) genes. Certainly genes are important structures, arguably the most important in an organism, as carriers of the genetic information. But in order to be patentable, the relevant findings must be novel, useful and non obvious, as traditional and proper for patents. Genes are not Alladin's lamps for biotechnology, as many, not necessarily venture capitalists, seem to expect.

After laboriously gaining the approval of rigorous critics, and mollifying the opposition of stern antagonists, the complex but fragile creature known as the Human Genome Project, like a novel Saturn, is on the verge of being devoured by its own sons, maddened by the hubris that scientific power, when it is ly

fictitiously magnified. Making use of a more recent mythology its apprentices occasionally seem deranged as if blinded by the sight, or by the illusion, of the Holy Grail.

A brief chronicle of such a tragical plot is due.

The request of patent for several hundred "gene" sequences last summer, and a few thousand later on, was forwarded to the US Patent and Trade Office by the NIH. As it is known, these Institutes together with the US Department of Energy are responsible for coordinating the whole Project in the US, and thus essentially in the developed world. This role has been recognized to the NIH mainly thanks to the scientific authority and the political expedience, even if not always supported by an adequate diplomacy, of Nobelist Jim Watson, appointed director of the NIH-sponsored Project a couple of years ago. One of the strongest reasons for the preferential funding claimed by Watson for the Project was its highly beneficial impact on mankind's fight against diseases (J. D. Watson, Hospital Practice 26: 45-49, 1991).

The unexpected and controversial NIH request to the PTO for patents on "gene" sequences amounted to an opening to the privatisation of the Project: as such it would pose the Project exactly on a collision route with Watson's stated principles, or at least drastically anticipate a change expected only for a later phase. In addition to this social aspect, a few disturbing scientific flaws made the NIH request hardly defendable. The request concerned results obtained by Dr. J. Craig Venter, then a researcher of the National Institute of Neurological Disorder and Stroke, through an automated sequence analysis of pieces of cDNA

from a human cDNA library. The thrust of Dr. Venter's contribution has been essentially the subcloning of a commercially available cDNA library and the sequencing of random pieces of few hundred bases. These results have been made possible by routine procedures, albeit stretched to a hardly matchable limit: a reported impressive pace of 70,000 bp a day. But their accuracy should be checked, to avoid embarassing analogies with "dinosaur's" DNA possibly represented by plasmid vector sequences (Nature 358: 271, 1992).

In an extensive coverage by the generally reliable Science section of the New York Times (July 28), the merits of Dr. Venter have been implicitally equated to the other epochal fulminations, such as that which hit Saul on his way to Damascus, or that which almost sank Archimedes while buoying in the warm waters of the Sicily sea, or, disguised as a famous apple, fell on Newton's head. So science historians and future generations are informed that "Dr. Venter, like hundreds of other scientists, frustrated by the snail's pace at which he was able to decipher the human genetic material, one day, on a plane from Tokyo had an inspiration and suddenly realized that an obvious shortcut would led him right to the genes themselves". But in spite of that, Dr. Venter's achievements did not impress much his colleagues, and even less his coordinator in the Human Genome Program. Watson was instead reported to be indignant at the NIH request ("shear lunacy"), and somehow underrated Dr. Venter's claims to both patents and glory as work which "virtually any monkey" could do (animal protectionists should relax: no offense was meant for

monkeys, since good sequencing is still quite a demanding effort).

It is fair to state that most of the scientists share Watson's blunt reaction rather than the agiographic tone of the New York Times coverage.

Interestingly enough, in the US several lawyers seem favorable to the NIH move: this is understandable, given complex nature of the legal issues plus the remarkable increase in lawyers number over the last decade, and the consequent relative decrease in lucrative litigations.

Needless to say also the response of a group of capitalists-philanthropists was prompt: they seized the opportunity of benefitting at the same time US biotechnology and mankind (or at least their own subset) and offered Dr. Venter a grant of 70 million $ to develop his genomic research outside NIH. Venter has accepted and has left NIH with some thirty associates. The ranks of the mercenary troops deserting the Project and eager to comb the human genome map in search of genetic treasures are growing. An erosion of the global dimension of the Project follows necessarily, but possibly not of its spirit, since most of these initiatives are started obviously under the banners of non profit enterprises.

To complicate the issue on the international scene, it so happened that as soon as the English human genome group at the MRC (Medical Research Council) heard of the unexpected NIH move, they felt obliged to retaliate. They threatened first to protect their own conspicuous human brain cDNA sequences under the aegis of commercial secret. Later, ostensibly "obtorto collo", decided to

follow suit "to protect the UK position", since other countries' moves on the issue "could place the UK at a relative disadvantage" (UK Science Minister's response to a parliamentary question on March 4th, 1992). The whole patent system seems approaching a halt for excess of applications. An easy solution would be if the PTOs were to deny the patents: but at the present rate of their functioning, years would be required even for a cursory examination of the thousands and thousands of applications. But it is comforting that a PTO refusal has been suggested in a petition recently signed by some 36 illustrious scientists. Oddily enough also Dr. Venter has been reported to co-sign it (Nature 375: 525, 1992). An even better solution would be if NIH and MRC were to withdraw their requests, and thus set an example even for the private sector. This would be similar to what happened in the '80s when the private biotechnology companies not enjoying financial support from NIH decided nevertheless to pay allegiance to the guidelines imposed by NIH to their institutes and grantees for the reduction of the risks in the practice of genetic engineering.

Indeed the public in general as well as the scientific and the industrial communities (Nature 358: 272, 1992) seem to ostracize the decision to apply for patents of this sort. The objections are mainly based on the facts that the "gene" sequences for which patents had been requested are incomplete and code for unknown proteins. This is all right, but, at least inmy opinion, one should go further.

Accordinlgy, my thesis here is to demonstrate that "gene" sequences do not meet the patent requirements even when they

represent complete and identified genes coding for useful products, as long as the genes under discussion code for proteins. Two reasons are presented. First, if it is a protein that meets the patent requirements, patents should cover it, for both its production and its use: to patent their "genes" is redundant and unjustified, also because of the following considerations. Second, the relationship between "genes" and proteins is hardly direct, especially in the light of by now classical molecular genetics. The dogma of colinearity of gene sequences and gene products has great historical validity since Beadle and Tatum, but limited generality nowadays: more than one gene often concur to code for a unique protein (due to allelic polymorphisms as well as to non-allelic configurations, or to trans-splicing) and more than one protein could be coded for by a single "gene" (i. e. a transcription unit, as in the case of the pituitary hormones).

This does not imply that "gene" sequences should not be patented. It could be totally proper to patent "gene" sequences or better "nucleotidic" sequences, thus including also the versatile RNA. That should be the case when, of course, the relevant findings are non obvious and novel, and, most important, the "gene" sequences turn out to be useful directly and "per se": as diagnostic probes, promoters, antisense regulators, or in other unknown functions.

Patents or other forms of protection should be granted to DNA sequences, provided they as such meet the three above mentioned requirements; and, additionally, are properly disclosed. The latter point is particularly relevant: it means that the "gene" sequences ought to be made promptly available for scientific investigations, without depriving them of a legitimate protection

against improper commercial exploitations. Patents or other sources of litigation must not interfere with the free exchange of research data: AIDS docet.

Finally, in this particular perspective, data arising from work performed in publicly supported institutions or with communitarian funds should be routinely made more available to researchers for the benefit of (tax paying) mankind, as compared to those privately financed.