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# Genome Research and Traditional Intellectual Property Protection -- A Bad Fit?

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## Introduction

Classic forms of intellectual property include patents, trademarks, copyrights and trade secrets. Of these, trademarks are of no particular relevance with regard to genome research in that products such as Amgen's erythropoietin or Genentech's human growth hormone pose essentially the same issues as does any commercial product.[1] Likewise, trade secret protection raises the issues that arise in any context — even if the relatively recent origins of this technology in academia may create a public relations overlay absent elsewhere. Also, while copyright protection for DNA sequences has been suggested, it has generally been considered inappropriate.[2] This leaves patents as the only mechanism seriously considered by the community involved in genome research.[3]

## Patents: Some Pros and Cons

Patents are often thought of in terms of holders' ability to exclude others from marketing a particular product or using a particular process, thus giving patent holders an opportunity to charge higher prices or to undermine competition. However, the ultimate purpose of the system

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1 Another form of protection for biotechnology products is Orphan Drug status, but this, too, presents only problems, and there are many, similar to those encountered with respect to small molecule pharmaceuticals.

2 Copyright protection is inadequate for two reasons. First, a nucleotide sequence, which appears to be simply a compilation of data is not protectable by copyright; Feist v. Rural Telephone Service, Inc., 111 S. Ct. 1282 (1991). Second, a copyright does not protect against independent retrieval of the gene and sequencing.

3 For further discussion of options other than patents, *see, e.g.,* Kate H. Murashige, *Overview of Potential Intellectual Property Protection for Biotechnology,* 5 Risk 119 (1994).

is seen today as attracting private investment in research and development. It seems to be successful in doing so. In 1994, of the $182 billion spent on research, the private sector contributed 59%, whereas the federal government and non-profits, including colleges and universities, contributed 36% and 5%, respectively.

In 1995, the biotech industry spent $7.7 billion on research and development. Per employee, the highest spender was Biogen ($210,724), followed by Genetics Institute ($114,943) and Genentech ($112,030). The biotech average was $71,000 — compared to the U.S. corporate average of $7,650 per employee.

Unlike the situation in 1783, when our patent system was founded, most progress is not made by individual inventors working alone. Particularly in the biotech industry; it is made by organized establishments with laboratories, equipment and technicians. And this would not happen absent means to recover private capital investments.

On the downside, intellectual curiosity does not rate highly when the connection between what might come out of intellectual curiosity and profit is not readily apparent. Also, the more technologically advanced and complex any activity is, e.g., even farming, the less it lends itself to individual or small business, and the more it is forced into activities that require large organizations. Further, the patent system discourages short-term dissemination of information.[4]

The patent system may also challenge morality when it brings into the commercial arena subject matter that was not quite there before. Some are offended by the very notion of patenting human genes or transgenic animals. It is not clear whether their objections reside in the realization that the availability of patents will result in more research that is itself objectionable, or whether it is just the idea of life forms being in the commercial domain — slaughterhouses of course aside.

A final problem I will mention is that genome research, and perhaps medical research in general, encouraged by patent availability creates a demand for sometimes expensive services. Health care already consumes 15% of the gross national product. Since it is possible, e.g., to assay for a breast cancer predicative form of the BRCA 1 gene, does society want to make it possible for all women to be tested? If

[4] And if it doesn't work properly, it may discourage dissemination of information over the long-term.

transplants of organs and tissue from pigs to people becomes viable, does society really want to pay for all of these transplants?

## The Patent System and Genome Research

Assuming that, overall, it is desirable to provide patent protection for genome research, the present statutory and administrative framework seem to provide an incredibly poor fit. Let's consider some issues that arise.

### *Patent Protection for Genes* per se

35 U.S.C. § 103 requires that an invention not be obvious to one of ordinary skill in the relevant art. The cameo genomic invention is cloning a gene that encodes a protein of known function. These were covered by early patents on, e.g., human growth hormone, insulin, G-CSF and erythropoietin. The U.S. Court of Appeals for the Federal Circuit has provided a reasonably bright line test for patentability of genes over prior art disclosing proteins which they encode: *Deuel* and its predecessors hold that the native sequence of the gene could not have been conceived prior to its actual reduction to practice, and it is, therefore, not obvious.[5] The Federal Circuit has squarely held that the fact that techniques for cloning genes based on known proteins could be applied by those of ordinary skill is irrelevant to a claim to the gene itself — drawn to a composition of matter which must be described so as to distinguish it from other compositions. The most reasonable way to do this is to provide the nucleotide sequence. These holdings, if maintained, might solve a problem with the current test for non-obviousness. However, it is reasonably certain, in my view, that this statement of the law will be dramatically modified.

The root of the problem is that, given an isolated and purified protein of known function, it might be within ordinary skill to retrieve the gene encoding that protein. Some genes are retrieved more readily than others, but I doubt that anyone would argue that the gene could not be retrieved and sequenced with sufficient time, resources and effort applied by ordinary practitioners. The nucleotide sequence *per*

5 In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995). *See also,* In re Bell, 999 F.2d 781 (Fed. Cir. 1993), Fiers v. Sugano, 984 F.2d 1164; (Fed. Cir. 1993), and Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, (Fed. Cir. 1991), *cert. den.,* 502 U.S. 856 (1991).

*se* is not obvious, but it may be obvious to extract the relevant DNA from nature and determine its nucleotide sequence.

Ample case law states that experimentation is not "undue," in the sense that an obviousness rejection can be overcome, merely because it is time consuming and laborious — as long as the result is clear. This has been rephrased as "obvious to try with a reasonable expectation of success."[6] One can argue that there is a reasonable expectation of success in cloning a gene and that the sequence is inherent. The U.S. Patent and Trademark Office (PTO) makes this argument consistently. Yet, once the gene has been cloned and sequenced, it would be simple for anyone to pirate its information content, and, without exclusivity, investors would not support the cost of obtaining the gene in the first place.[7]

Why is it unlikely that *Deuel* and its predecessors will be maintained in its present form? First, these are Federal Circuit *panel* decisions; such decisions cannot reverse those of the predecessor Court of Customs and Patent Appeals. Also, it is unclear that these decisions will bind other panels. The writer of all the opinions was Judge Lourie, whose background in pharmaceuticals logically led to the rationale that a method for making an invention is not complete without a concept of the invention itself. This would certainly be the case for pharmaceutical molecules that do not exist in nature. Second, the structural elements seemingly required do not appear to have been imposed on other molecules that are products of nature. For example, claims to monoclonal antibodies with respect to a particular antigen do not seem to require that the amino acid sequence of the immunoglobins be determined or disclosed. The antibodies can be claimed in entirely functional terms; this has been the practice of the PTO and the subject of its Board decisions.[8] However, I am aware of no Federal Circuit case related to the validity of such claims. Third, the idea that sequence is required to claim a gene is contrary to European law, where it has

6 The formula for obviousness as "obvious to try with a reasonable expectation of success" was established In re OFarrell, 853 F.2d 894 (Fed. Cir. 1988).

7 Even if copyright were available, it would be inadequate, *see supra* note 2. Commercial value would be intolerably undercut by allowing other to retrieve the information independently.

8 *See, e.g.,* Ex parte Old, 229 U.S.P.Q. 196 (BPAI 1985).

been held that a description of the process for preparation of the hepatitis B surface antigen-encoding gene is sufficient to support a claim to that gene.[9] Only if the gene is actually claimed in terms of its sequence is such sequence required.[10]

Finally, it should be clear that structural features of claimed molecules that exist in nature are inherent in the molecules. Claims involving natural products must distinguish over what occurs naturally. Applicants have been permitted to make this all-important distinction in the most trivial ways by specifying that claimed DNA molecules be purified and isolated or, e.g., that they be ligated to nucleotide sequences with which they do not ordinarily reside. That which has been made a central feature of claims (the sequence) is not what makes it *new.*[11]

### *Transgenic Animals*

The relatively low rate that patents on such subject matter issue makes this problem less prominent than otherwise. The rate seems to be more the result of a PTO policy decision than, necessarily, any lack of fit with patent requirements.[12] However, the same arguments can be applied; ways to manipulate the genome of certain animals, at least, are well known — microinjection of fertilized eggs with the transgene or transformation of embryonic stem cells and reimplantation into the blastula. Desirable transgenic animals are often suggested by the art. Thus, for many transgenic animals, it could appropriately be said that the invention is obvious to try with a reasonable expectation of success. Again, there is a need for tremendous investment to produce, e.g., a desired transgenic mouse and more to prepare transgenic cows. Yet, the ordinary practitioner knows, at least in theory, how to do it and is likely to succeed given enough time, effort and money. Again, the question is: If the cost cannot be recouped because the invention is "obvious" and unpatentable, who will make the effort?

### *Expressed Sequence Tags*

The challenge to the patent system presented by Venter's and Adams' work at the National Institutes of Health (NIH) in retrieving

9 Decision T 296/93, Technical Board of Appeal of the European Patent Office.

10 Decision T 886/91, Technical Board of Appeal of the European Patent Office.

11 35 U.S.C. § 101 requires that the claimed subject matter be "new."

12 *See, e.g.*, Brian Cunningham's paper in this issue of Risk.

several thousand, hitherto undisclosed, nucleotide sequences from cDNA libraries continues. Although the applications based on that work have been withdrawn, the PTO reports that, as of June 1996, approximately 80 applications are pending with thousands of nucleotide sequences each. Indeed, because of difficulties involved in evaluating patentability of this large number of sequences, the PTO estimates that it will take eight years to process these applications. To publicize the problem and seek solutions, hearings were held in April 1996. Involved commercial organizations offered advice, and the consensus seems to be that searching and examination could be more efficient. Nevertheless, single applications claiming several thousand nucleotide sequences are a new experience for the PTO.

Also, such applications do not fit well within the statute. Here is the problem: While these sequences seem to be new and presumably not obvious, their utility is questioned. Although uses for individual sequences have been proposed, it has been argued that these short Expressed Sequence Tags (ESTs) do not exhibit the type of utility contemplated by 35 U.S.C. § 101. Thus, while a claim including, e.g., 10,000 different, individual ESTs could theoretically be patented, this is inherently offensive to many. They argue that too much protection is afforded for too little contribution. Each EST, to be exploited, requires substantial further effort, and proposed claims presumably would block those, without licenses, who later make such effort.

Jurisdictions outside the U.S. have taken the approach that each EST is a separate invention. The PTO could join them. However, 10,000 applications would require an outlay of almost $5 million in filing fees alone.[13]

Since patents are particularly problematic for protecting this type of "invention," some companies have sought alternatives. Human Genome Sciences and its research arm, The Institute for Genomic Research, offer access to their secret database in return for a "right of first refusal" to license commercial sequelae. Also, Incyte Pharmaceuticals has made several deals with pharmaceutical companies in which millions of dollars have been paid for access to its database. Nevertheless, Merck has

[13] Yet, for applications filed prior to June 7, 1995, when GATT amendments came into effect, this could offer an advantage. Divisional applications for individual ESTs might be filed one after another over a considerable period, as interest warranted.

chosen not to rely on trade secret licenses; it is working with Washington University to generate a multiplicity of sequences to be made public.

*Processes for Preparing Recombinant Materials*

A recent decision by the Federal Circuit makes it clear that patents covering processes for making recombinant materials for the production of proteins may effectively extended to preissuance activities.[14] 35 U.S.C. § 271(g) extends infringement to offering to sell, importing or using the product of a patented process during the term of the process patent. The Court looked to the legislative history of that section and found that its drafters intended a process for preparing an expression vector for the production of a recombinant protein to be considered a process for production of the protein itself. It, thus, becomes apparent that, even if a plasmid is constructed prior to the issuance of a patent covering a process for its construction, using cells transformed with this expression system to produce a protein and selling it during the term of the process patent infringes that patent.

This temporal discontinuity is not a problem for traditional technology because processes usually must be repeated to make additional product which is fairly immediately sold. However, expression plasmids, need be made only once; they self-replicate and can be used again and again. Thus, for example, an expression system might have been constructed in 1990 and a patent issued on a process for its construction in 1992. The protein produced by the original system, even if it were maintained all along, could not be sold after 1992 without infringing the process patent.

*Algorithms*

Discovering how nature operates often leads to new therapeutic protocols, diagnostic methods and the like. Also, specific method steps can be followed in designing compounds for pharmaceutical use. In many cases, the devised methods are sufficiently complex that it makes sense to formalize them in a computer-based setting; in others, the steps may comprise simple deduction.

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14 Biotechnology General Corp. v. Genentech, Inc., 38 U.S.P.Q.2d 1321 (Fed. Cir. 1996).

U.S. Patent 5,463,564 is a good example of how claims can be obtained for a computer-assisted method to design compounds with desired physiological properties. In effect, claim 1 is simply directed to looking at several chemical structures and their structure/activity data and then picking ones that seem most promising. Since the claim requires that all of this be "under computer control," it has apparently escaped rejection on the basis of being a nonstatutory algorithm.

Recent Federal Circuit decisions have indicated a more liberal attitude toward algorithms.[15] The PTO has also provided potentially helpful guidelines for examining "software" inventions.[16] Still, it is unclear that the need to involve computers should be retained.

## Conclusion

In at least the five types of inventions set forth above, all common to biotechnology, the patent system poses considerable difficulty. It may be possible for the system to simply "muddle through" as in the past, fine-tuning the system with ad hoc decisions in individual cases. Yet, consideration might be given to making statutory changes which would more directly provide for encouragement of investment in research and development, even when the goals and means for obtaining the results of such research and development are obvious to those of ordinary skill.

15 In re Alappat, 33 F.3d 152 (Fed.Cir. 1994); In re Trovato, 60 F.3d 807 (Fed.Cir. 1995).

16 60 Fed. Reg. 7478 (1996).