Patent Rights in the Human Genome Project

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GENE MAPPING
Using Law and Ethics as Guides

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Patent Rights in the Human Genome Project

Rebecca S. Eisenberg

The various research efforts that comprise the Human Genome Project will inevitably both draw on and yield a multitude of patentable inventions. The broad subject matter of the patent laws potentially reaches every phase of the Genome Project, from the discovery of new research technologies, such as techniques and equipment for DNA sequencing, through the ultimate development of new products, such as screening tests for genetically transmitted diseases. Even bits and pieces of the human genome itself may be, and sometimes have been, patented. Nor does the fact that the public is paying for the Genome Project through federal funding mean that the public may freely enjoy the fruits of that research. Quite the contrary, existing law not only permits, but affirmatively encourages, patenting and private commercial exploitation of inventions made in the course of the Genome Project.

Nonetheless, the prospect of private ownership of knowledge emanating from the Genome Project has provoked controversy. The National Research Council Committee on Mapping and Sequencing the Human Genome concluded in its 1988 study that “human genome sequences should be a public trust” not subject to the intellectual property laws, while the Office of Technology Assessment’s 1988 report on the Genome Project suggested that federal agencies and Congress should instead promote early filing of patent applications followed by prompt release of data. By early 1992, the controversy had focused on the filing by the National Institutes of Health (NIH) of patent
applications on some 2,375 partial cDNA sequences identified in its laboratories, along with the as-yet unidentified full genes and gene products to which they correspond.

Given the magnitude of resources invested in the Human Genome Project in both the public and private sectors and the tremendous potential benefits to be reaped from this research, the role of the patent laws in this area deserves careful thought. Ideally, patent law should promote the progress of research and product development and the dissemination of research results. This chapter clarifies some of the implications of patent law for the Genome Project, with a view to identifying problems that might interfere with the smooth operation of the patent system in this context.

Summary of Existing Law and Policy

A U.S. patent confers the exclusive right to make, use, or sell the patented invention in the United States for seventeen years from the date the patent issues. During this term, the patent holder has the right to prevent anyone from using the invention—even an innocent infringer who develops the same invention independently, and even a subsequent inventor who improves on the basic invention to such a degree that the improvement itself earns a patent. In exchange for these broad exclusive rights, the inventor must disclose the invention to the public in terms that enable others who are “skilled in the art” to make and use it. So long as the disclosure requirement is satisfied, it is not necessary for the patent applicant to have actually made a tangible embodiment of the invention in the laboratory. Judicial decisions characterize the disclosure as the “quid pro quo” of the patent monopoly. In order to obtain a patent, the applicant must first contribute “a measure of worthwhile knowledge to the public storehouse.” A patent consists of a written description of the invention and of how to make and use it, often accompanied by figures or drawings, and one or more “claims” specifying exactly what it is that others may not make, use, or sell.

It is a fundamental axiom of patent law that one may patent only that which is new. Section 101 of the Patent Act defines as patentable subject matter “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.” The Supreme Court has construed this language broadly to include “anything under the sun that is made by man,” including genetically engineered living organisms. Although products of nature may not be patented as such, patents have been issued on such products in human-altered form. For example, bacteria or chemicals that are newly isolated and purified may be patented in an isolated
and purified state if they exist in nature only in an impure state. Consistent with these principles, patents have been issued on proteins and DNA sequences from the human genome that have been purified and isolated through human intervention. The requirement that a patentable invention be "useful" excludes from protection certain scientific discoveries that, although interesting as a subject of further research, cannot yet be used for any practical human purpose. Some critics of the NIH patent applications on partial cDNA sequences have argued that these inventions fail to satisfy this utility requirement, but few patents are rejected on this basis. Patents have been issued for DNA sequences that code for useful proteins or that serve as probes to detect genetic susceptibility to disease.

In addition to being new and useful, an invention must satisfy the further statutory requirement of nonobviousness to be patentable. One may not obtain a patent by disclosing an "invention" that is already available to the public, whether because it was previously known or because it is readily discoverable through obvious advances over the prior art. As the prior art in a field grows, the nonobviousness requirement makes more and more subsequent discoveries unpatentable.

For the past decade federal patent policy has actively encouraged the patenting and commercialization of inventions made in the course of federally sponsored research. Legislation enacted in 1980 requires small businesses and nonprofit organizations, including universities, to report promptly to the funding agency any potentially patentable inventions made in the course of sponsored research. The statute permits recipient institutions to retain title to their inventions if they agree to file patent applications in a timely manner and to ensure that the inventions are utilized. Patent holders may either exploit their patents themselves or license someone else to exploit them, but if they do neither, the government reserves "march-in" rights to grant licenses in order to ensure practical application of the inventions.

The underlying premise of this statutory scheme is that the public benefits more from inventions made in the course of federally sponsored research when those inventions are patented and exploited commercially in the private sector. Inventions left in the public domain are presumed to languish in government and university archives rather than to be freely and widely exploited. Note that this vision of the role of patents is different from the time-honored justification for the patent system as a means of promoting investment in research to make new inventions. The traditional conception of the role of patents concedes that patents actually restrict dissemination of the inventions they cover, but nonetheless justifies the creation of patent monopolies as a means of inducing firms to undertake the necessary research to
make such inventions in the first place. In the context of federally sponsored inventions, the government is not offering patent rights as an *ex ante* incentive to stimulate future inventions, but rather is insisting on patent protection *ex post* for inventions that have already been made. The justification is that existing patent rights facilitate the commercial dissemination of products embodying the results of prior research, not that the prospect of future patent rights will stimulate future research. While this philosophy may seem counterintuitive to scientists whose norms enjoin them to make their research results freely available to the public, for the time being it seems to be firmly entrenched in federal law and policy.

## Impact on the Genome Project

What is the likely impact on the Genome Project of a policy that encourages patenting of federally funded inventions? Will such a policy ultimately promote or impede full utilization of knowledge gained through this research? A thorough response to this question would require a broad reexamination of the effectiveness of the patent system as a whole. Rather than taking on such a daunting task in these brief remarks, I will instead assume, along with federal policy makers, that in many contexts the patent system is an effective means of promoting widespread dissemination of new discoveries through commercial channels. The question I will pose is whether there are particular reasons to question its effectiveness in this specific context. I shall first analyze the likely impact of patent incentives on the conduct of the research itself and then consider the effectiveness of patent law in promoting full commercial utilization of knowledge generated in the Genome Project.

### Impact on the Conduct of Research

One reason for concern that a broad federal policy in favor of patenting research results might be unsuitable for the Genome Project is that the Project is a long-term, ongoing research project in which continued progress will depend on prompt, unfettered access to prior discoveries. To the extent that patent law creates barriers to such access, it may impede progress.

Perhaps the biggest danger that patenting presents to progress in the Genome Project is that researchers seeking to preserve patent rights will defer publication of their findings and thereby retard the dissemination of new knowledge. While the patent system ultimately compels disclosure of whatever information is necessary in order to make and use a patented invention,
disclosure through the U.S. patent system does not occur until a patent issues,\textsuperscript{27} which is likely to be years after a discovery is made. Academic researchers who want to earn recognition for their discoveries in the scientific community may wish to publish their inventions in journals at an earlier date, but early disclosure is risky for those who plan to seek patent protection. A scientist who discloses an invention in a publication before applying for a patent forfeits patent protection immediately in most of the world, although U.S. patent law allows filing of an application up to one year thereafter.\textsuperscript{28}

The solution to this dilemma might seem to be for scientists to file patent applications promptly and then publish their research results,\textsuperscript{29} but there are problems with this strategy. For one thing, research may yield publishable results before it yields a patentable invention.\textsuperscript{30} In this situation publication of early results could prevent patenting of later-developed inventions emanating from the same research if the publication makes the subsequent inventions “obvious.”\textsuperscript{31} Another risk is that publication of a narrow form of an invention may preclude patenting of a more broadly claimed invention at a later date.\textsuperscript{32} Thus a fully informed scientist who wants both patent protection and scientific recognition may publish her discoveries later than she would if she had no interest in patent protection. Delays in publication of research results pertaining to patented inventions could be minimized by accelerating the progress of patent applications through the Patent and Trademark Office, but this problem is hardly unique to the Genome Project.

One might question how many scientists participating in the Genome Project will actually delay publishing their work to any significant degree because of patent considerations. For commercial scientists, the possibility of obtaining patent rights might make publication more likely than it would be if they had to rely on secrecy to preserve intellectual property rights in their discoveries.\textsuperscript{33} As for scientists in universities, a recent empirical study found that academic scientists receiving funds from biotechnology companies both patented and published their research results at a higher rate than their colleagues who did not receive such funding,\textsuperscript{34} suggesting that patent considerations need not interfere unduly with publication. But it stands to reason that, faced with the risk of losing patent rights through premature publication, some scientists will publish research results later than they would if they had no concern about patents.

A potentially more harmful consequence of patenting discoveries made in the course of the Genome Project is that patent holders could restrict access to these discoveries in ways that impede subsequent research. A patent holder normally has complete discretion whether to exploit the invention as a monopolist, to license it on an exclusive or nonexclusive basis, or to suppress the invention entirely. Such broad exclusive rights could potentially retard
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scientific progress, particularly in the case of patents on research technologies developed early on for use in later stages of the Genome Project.

But present law does provide exceptions to the general rule of private control over access to publicly funded inventions. These exceptions might be invoked to retain some measure of public control over the results of the Genome Project. Specifically, the statute allows the funding agency to exercise "march-in" rights to grant or compel the granting of licenses to federally funded inventions if it determines that such action is necessary "to achieve practical application of the subject invention." So far, the meaning of this language has not been tested in litigation.

At the very least, this provision should permit mandatory licensing of inventions that would otherwise go unused. It is less clear whether it permits such licensing in the case of inventions that are being used exclusively by the patent holder. For example, a grant recipient that discovered and patented a group of partial cDNA sequences might want to keep the sequences to itself in order to give its own researchers an advantage over competitors in finding (and possibly patenting) the corresponding full genes and gene products. In such a situation, the patent holder might try to avoid the exercise of march-in rights by arguing that it has achieved "practical application" of the inventions in its own laboratories, and thereby satisfied the statute, without having to make the inventions available to others. On the other hand, if the practical effect of such exclusivity is to restrict utilization of the invention to a significant degree, a compelling case could be made for the exercise of march-in rights. As articulated in the patent statute, the purpose of allowing grant recipients to retain patent rights is "to promote the utilization of [federally funded] inventions," to be sure that such inventions "are used in a manner to promote free competition and enterprise," "to promote the commercialization and public availability of [such] inventions," and to "protect the public against nonuse or unreasonable use of inventions." Hoarding of patented research intermediaries for the exclusive use of patent holders, to the detriment of research in other laboratories, flies in the face of these policies.

Two additional exceptions in the statute appear potentially applicable in this context, although so far funding agencies have construed both of them narrowly. One provides that a funding agency retains a paid-up, nonexclusive license "to practice or have practiced for or on behalf of the United States [the federally funded invention] throughout the world." On its face, this language arguably permits agencies to authorize subsequent grant recipients to use the inventions of prior grant recipients without payment of royalties on the theory that they are practicing the inventions "on behalf of the United States" when they use them in federally sponsored research. So far, however, agencies have viewed this provision as limited to situations where the govern-
ment wants to obtain a patented product for strictly governmental purposes from someone other than the patent holder.\textsuperscript{38}

The other statutory exception allows an agency to prevent recipients of research funds from retaining title to inventions "in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter."\textsuperscript{39} The language of the statute and regulations promulgated thereunder suggest that this exception should be used sparingly.\textsuperscript{40} The statute presupposes that its objectives are ordinarily best achieved by allowing fund recipients to retain patent rights. In order to show "exceptional circumstances," it would seem necessary at the very least to distinguish the research results at issue from other inventions made in the course of federally funded research, and to explain why the patent system is less likely to promote utilization and dissemination of inventions in this context than in other contexts.

Finally, apart from these statutory provisions, the courts have recognized a limited, nonstatutory exception to a patent holder's exclusive rights for the use of a patented invention in pure, noncommercial research.\textsuperscript{41} It is difficult to determine the scope of this exception with clarity because, although many courts have acknowledged its existence in principle, almost none have actually applied it to the facts of the cases before them to excuse otherwise infringing activity. A recent judicial decision characterized the experimental use defense as "truly narrow,"\textsuperscript{42} and it seems unlikely to provide significant protection for researchers until its terms are clarified through further caselaw or legislation.

A statutory "experimental use" defense to permit the use of patented inventions in the Genome Project would not be without precedent\textsuperscript{43} and has much to recommend it as a matter of policy.\textsuperscript{44} One difficulty with a royalty-free experimental use exemption for subsequent researchers is that in the case of a patent on research technology, researchers are the only consumers of the invention. A rule that exempts these consumers from infringement liability entirely would eliminate the patent holder's profits and effectively eviscerate the incentive for commercialization offered by the patent. Nor would such an exemption ordinarily be necessary in order to make patented research technology available to researchers: holders of patents on such technology will generally view researchers as potential customers and will want to extend licenses to them in order to collect royalties. But in some situations, particularly when the subsequent researcher is doing further research in competition with the patent holder, the patent holder might have more to lose by allowing the use to proceed than it stands to gain by collecting royalties from the researcher. In this context an experimental use defense may be necessary
for the research to proceed, although it might be appropriate to compel the subsequent user to pay royalties to the patent holder.\textsuperscript{45} In effect, this would amount to a compulsory license in favor of subsequent researchers rather than an exemption from infringement liability.

If the only purpose of an experimental use exemption is to compel the holders of patents on federally funded inventions to extend licenses to subsequent researchers, this objective might possibly be achieved without any new legislation through the exercise of march-in rights by funding agencies. A statutory experimental use exemption might nonetheless be useful in that it could clarify ambiguity as to the scope of the exemption under existing case law, obviate the need for funding agencies to go through cumbersome procedures to exercise march-in rights,\textsuperscript{46} and ensure researchers access to inventions whether or not they were made with federal funds.

The problem of patent seekers deferring disclosure of new findings may be more intractable than the problem of patent holders restricting access to their inventions.

\textit{Impact on Practical Utilization of New Knowledge}

The argument for patent protection is less threatening to the research community when the invention at issue is a medical product or process for use by the public rather than research technology for use in the laboratory.\textsuperscript{47} For example, mapping and sequencing a gene of interest may lead to the development of a screening test for a genetic disease or to the production of a useful protein through recombinant DNA technology. Patent protection for such inventions is less troubling and more compelling than it is for inventions that are primarily of interest to researchers. Making a new invention available to a market of ordinary consumers is a function traditionally performed by commercial firms in our economy, even when there is a strong public interest in widespread availability of the invention at low cost, as in the case of a new drug. It stands to reason that commercial firms will be more willing to perform this function if their profits are protected by patent rights than if they can recover only a competitive rate of return. Moreover, if an invention has a significant market outside the research community, the patent owner might focus its enforcement of the patent on the more lucrative nonresearch market and leave the occasional laboratory user alone. Indeed, the patent owner may welcome the use of its invention by researchers in the hope that they will develop new uses for the patented technology and thereby open up new markets for the patent owner to exploit.

Assuming that patent protection is necessary to encourage firms to make these discoveries available commercially, one might ask whether current law
provides adequate protection. It is helpful to distinguish different types of inventions emanating from the Genome Project and to consider the availability and consequences of patent protection for different categories of invention separately.

So far, new biotechnology products have typically emerged from the following sequence of discoveries. First, a naturally occurring protein is identified as having medical significance, perhaps because its absence causes disease symptoms in individuals who fail to produce adequate quantities of it in their own systems. The protein is then isolated and purified from natural sources, allowing it to be characterized and perhaps making it available in small quantities for therapeutic purposes. Next, the gene for the protein is cloned, disclosing the DNA sequence encoding the protein and allowing its production in larger quantities through recombinant DNA technology. The recombinant protein is then clinically tested and eventually displaces the natural protein in sales for therapeutic purposes.

As the Genome Project proceeds, the direction of discovery is reversed in some cases as researchers look for genetic causes of diseases whose biochemical mechanisms are not yet understood. In this "reverse genetics," 48 the first step is to locate the gene on a specific region of a particular chromosome through genetic linkage studies using DNA markers. At this point it may be possible to use the markers to develop a genetic screening test to identify carriers of the disease gene. Depending on the distance between the closest known markers on either side of the gene, it may be necessary to undertake biochemical studies of differences in gene product in the tissue of affected and unaffected individuals in order to find the actual gene of interest. Eventually, the disease gene itself is found, cloned, and sequenced, and the protein associated with the disease is identified.

The NIH patent applications on partial cDNA sequences reveal yet another discovery path, in which the first step is to sequence portions of randomly selected clones from a cDNA library representing the genes expressed in a given tissue sample. These partial sequences, called expressed sequence tags or ESTs, may then be used to isolate the full gene, the function of which is subsequently determined.

The foregoing trails of discovery yield a series of candidates for patent protection: purified, naturally occurring proteins; protein purification processes; DNA sequences coding for proteins of interest; DNA sequence markers for use in genetic screening tests; DNA sequences whose function has not yet been determined; recombinant vectors and host cells; cloning processes; recombinant proteins; processes for obtaining recombinant proteins from host cells; and processes for administering natural or recombinant proteins in the treatment of disease. Some of these discoveries are end products for sale
to consumers, and some are processes for using these end products. Others may be thought of as manufacturing processes yielding end products or starting materials for use in manufacturing processes, or research intermediaries for use in developing products and processes of more immediate commercial interest.

From the patent holder's standpoint, generally the most effective commercial protection is offered by a patent on the end product that is sold to consumers. Such a patent is superior to a patent on a process of using the end product in that it is not limited to any particular use of the product, and it is superior to a patent on the manufacturing process in that it is not limited to any particular method of production. Somewhat less effective is a patent on starting materials for use in making the end product. Such a patent offers no protection against use of the patented starting materials abroad and then importing the unpatented end product into the United States for sales in competition with the patent holder. Weaker still is a patent on products or processes used only during product development, since an injunction against infringement of such a patent would not serve to keep a competitor off the market so long as the use is not continuing.

Problems with Process Claims. Before the Supreme Court upheld the patentability of living organisms in *Diamond v. Chakrabarty*, process patents were the mainstay of patent protection for biotechnology inventions. Patents were issued and their validity upheld on claims to processes using bacteria to treat sewage, or to produce chemicals or drugs, although the bacteria used in these processes were generally assumed to be unpatentable. Today it is clear that recombinant microorganisms and host cells may be patented in their own right, assuming they are new, useful, and nonobvious. But there are still advantages to obtaining patent rights in processes using these biological materials to make end products, particularly if the end products themselves are not patentable.

The most significant advantage is that a process patent offers superior protection against competing imports of the end product. The difference is due to peculiarities in the definition of infringement arising from recent amendments to the patent statute to fortify process patent protection. Prior to 1988, the commercial effectiveness of process patents was largely limited to use of the claimed process in the United States. A competitor could use the patented process abroad and import the unpatented products of the process into the United States for sale without infringement liability, although in some cases the patent holder had a limited remedy against importation of the products under the Tariff Act. This gap in process patent protection was largely remedied with passage of the Omnibus Trade and Competitiveness Act of 1988.
which included a provision expanding the definition of patent infringement to include importing into the United States or selling or using within the United States a product made by a process patented in the United States. 55

But the statutory change failed to provide comparable protection against imports to holders of product patents on essential starting materials such as recombinant organisms. As a result, the holder of a patent on a recombinant organism useful to make a valuable protein has no remedy against a competitor who uses the organism abroad and imports the end product into the United States. 56 In order to obtain such a remedy, it is necessary to obtain a patent on the process of using the recombinant organism to produce the protein.

In recent years, however, the Patent and Trademark Office has taken a restrictive view of the patentability of such biotechnology processes. Relying on a 1985 decision of the Court of Appeals for the Federal Circuit, 57 the Patent and Trademark Office has rejected as obvious patent claims to conventional processes using novel and nonobvious starting materials to produce novel and nonobvious end products. 58 Legislation is currently pending in Congress that, if passed, would provide that process patent protection shall not be denied on grounds of obviousness for a process of making or using a patentable product. 59 In the meantime, firms that use standard processes to express recombinant proteins in novel recombinant organisms may find that they are unable to patent the processes and must instead try to patent the recombinant starting materials or protein end products.

Even apart from questions of patentability, there are problems with detection and proof of infringement of process patents. Unless the patented process is the only means of making an unpatented product, it may be difficult to tell whether a competitor used the patented method or some other, noninfringing method. Moreover, even if the patented process is initially the only means of making the product, a process patent offers no protection against competitors who develop noninfringing means of making the product in the future. Patents on processes for using, as opposed to making, unpatented products suffer from a similar problem. A patent on a process of using an unpatented product for a certain purpose, such as to treat a particular disease, is difficult to enforce if the product has other, noninfringing, uses because it may be hard to monitor just what purchasers are doing with the product. Thus even where process patent protection is available, the commercial monopoly it offers may be narrow, difficult to enforce, and short-lived.

Problems with Protein Claims. As a general rule, a patent on an end product provides more powerful protection than a patent on either starting materials or processes for making or using the end product. In the biotechnology indus-
try the end product is often a protein. Claims to the protein product itself would avoid the difficulties cited above for monitoring and enforcing process patent claims and would be less vulnerable to changes in technology that allow manufacture of the product through other means.

On the other hand, the validity of patent claims to proteins may be more vulnerable to challenge than that of process claims. One ground for challenge is that proteins are unpatentable products of nature. The proteins that are likely targets for commercial production through recombinant DNA technology for the most part exist and perform important functions in nature. So far patent holders have avoided this difficulty by limiting their claims so as not to cover the naturally occurring product. For example, the claims may specify a degree of purity for the protein that is not duplicated in nature without human intervention. Such limitations on the scope of the claim, while possibly avoiding a "product of nature" rejection, may also narrow the scope of the patent to a degree that allows significant competition beyond the reach of the patent monopoly. For example, a competitor might avoid infringement by selling a product that is either more or less pure than that claimed in the patent.

A competitor might also be able to avoid the scope of the patent monopoly by varying the chemical structure of the protein if it is possible to do so without destroying its function. Sometimes minor changes in amino acid sequence do not interfere with the biological activity of a protein. Some patent applicants have attempted through careful claim drafting to include minor variations in amino acid sequence within the scope of the patent, but a recent decision of the Court of Appeals for the Federal Circuit calls into question the effectiveness of this practice.60

Another limitation to patents on proteins is suggested in a recent Federal Circuit opinion in a lawsuit brought by the holder of a patent on purified Factor VIII:C against a firm that was making recombinant Factor VIII:C.61 The court noted that although the patent claims on purified Factor VIII:C obtained from blood plasma literally covered the recombinant product, the recombinant manufacturer might nonetheless be able to avoid infringement liability under the rarely invoked "reverse doctrine of equivalents"62 if it could show sufficient differences in specific activities and purity between the recombinant product and the plasma-derived product.63

A further problem with protein claims is that the protein may have been known and characterized in the literature before the gene encoding it was cloned. In this situation the protein may have become unpatentable on grounds of prior knowledge, use, or publication,64 or it may even be claimed in a prior patent65 that presents an obstacle to subsequent innovators who wish to produce the protein through recombinant DNA technology.
Even previously unknown proteins may become unpatentable on grounds of obviousness as the Genome Project progresses. Indeed, once the complete DNA sequence of the human genome is known, it might be argued that all proteins encoded in that known sequence have become obvious.

Problems with DNA Sequence Claims. The foregoing discussion reveals a number of circumstances in which a patent applicant's best hope may be a product claim on a DNA sequence or recombinants incorporating that sequence, although such a claim offers less effective commercial protection than either a product claim on the protein end product or a process claim on the method of producing the protein. The protein itself may be unpatentable because it was previously known or even patented, and the process may be unpatentable because it is obvious. A DNA sequence may also be the most likely target for a patent claim where the invention consists of identifying a gene that is associated with an inherited disease or a DNA marker in close proximity to that gene rather than cloning a gene for the purpose of expressing a protein. In this situation the DNA sequence itself may be thought of as an end product, useful in a genetic screening test, rather than as a starting material in making a protein.

Like proteins, DNA sequences are arguably unpatentable products of nature. So far the Patent and Trademark Office and the courts have allowed patent applicants and patent holders to get past this hurdle by limiting their claims to an "isolated and purified" DNA sequence, or to a human-engineered recombinant vector or host cell incorporating the sequence.

Claims to chromosomal DNA markers not coding for any identified gene product might face a further hurdle in the requirement that a patented invention be useful. The fact that markers are useful to scientists seeking to map and sequence the human genome may not be sufficient evidence of utility to make them patentable. On the other hand, a marker that is sufficiently close to a disease gene to be useful in screening for carriers should certainly satisfy the utility test. In its patent applications on partial cDNAs, for example, NIH asserts that the sequences are useful for forensic identification and tissue typing.

As cloning procedures become more routine, it is likely that DNA sequences coding for known proteins will be deemed obvious, especially when the amino acid sequence for the target protein is known. It is also possible that knowledge of partial cDNA sequences will make obvious the corresponding full genes. So far, in assessing the obviousness of patent claims to DNA sequences the courts have focused on the obviousness of the process of cloning and identifying the gene of interest, upholding claims to sequences that were difficult to isolate. As the Genome Project progresses, greater expe-
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rience will inevitably make more DNA sequences obvious under this approach.

Even when they are patentable, claims to DNA sequences may have limited commercial value. Where DNA sequences are, in effect, starting materials for making desired proteins, patents on the DNA sequences offer less effective commercial protection, particularly against foreign competition, than either patents on the proteins themselves or process patents on the method of making the proteins. Patent claims to partial gene sequences used only as research intermediaries to find the full genes offer even less effective protection.

Another potential problem with claims to DNA sequences as starting materials has to do with the scope of the claims in light of the degeneracy of the genetic code. Numerous substitutions may be made in a nucleotide sequence without changing the amino acid sequence of the gene product. Do these substitutions remove the altered sequence from the scope of the patent claim? The answer certainly should be no, but the matter is not entirely free from doubt.

The Court of Appeals for the Federal Circuit touched on this issue in its recent decision in the case of Amgen Inc. v. Chugai Pharmaceutical Co. One of the patents at issue in that case included a broadly worded claim to any purified and isolated DNA sequence "encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of [biological properties of erythropoietin]." The court held this claim invalid for lack of an adequate disclosure of how to make more than a few of the many "analog genes" that would fall within the scope of the claim. The court was careful to note, however, that it did not "intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant."

Although the opinion is not free from ambiguity on this point, a reasonable reading would allow patent holders to claim DNA sequences in sufficiently broad terms to include, at the very least, analogous sequences that do not alter the gene product. It is well understood among geneticists that the genetic code is redundant in that certain amino acids may be encoded by any of a number of "codons" of three nucleotides. These interchangeable codons have long been identified, and the substitution of one for another in a DNA sequence would be obvious to anyone skilled in the field. To permit competitors to avoid the patent through such inconsequential substitutions would be manifestly unfair and contrary to established principles of patent law. By contrast, changes in DNA sequence that alter the gene product in ways that do not change its biological activity are far more difficult to predict. Thus a sensible reading of the Amgen decision would prevent generic claiming of DNA
sequences when the variations claimed yield different gene products, but not when the variations in the sequence amount to substitutions of recognized equivalents that yield the same gene product.

Conclusion

The enormous potential commercial implications of knowledge gained through the Genome Project make it inevitable that some of that knowledge will be patented. Federal law encourages this result by promoting the patenting of inventions made in the course of federally sponsored research. This federal policy rests on the assumption that patenting helps to ensure widespread availability of the results of sponsored research through commercial dissemination. The wisdom of this policy rests in large part on the empirical validity of this assumption. If the assumption is valid, then there may be cause for concern that patent law provides inadequate protection for some biotechnology inventions at this time. Of particular concern are limitations on the patentability of biotechnology processes and possible limits on the scope of protection available for proteins and DNA sequences. On the other hand, the current federal policy may cause scientists to retard dissemination of new findings within the scientific community and to restrict access to new inventions among scientists, all to the detriment of progress in the Genome Project. If it turns out that patent protection is not necessary in order to ensure widespread public dissemination of these inventions, this may be a big price to pay for little or nothing in the way of social benefits.

Given the importance of funding from private industry to biomedical research today, one should not assume that patent protection for the results of the Genome Project is unnecessary. The small amounts of federal funding projected for the Project cannot be expected to displace private funding in this area. Moreover, even if public funding were sufficient to cover mapping and sequencing efforts, lack of patent rights might undermine incentives for the private sector to support subsequent research to put this information to practical use. In the meantime, obstacles to progress in the Genome Project as a result of patent rights might be addressed through more limited reforms without calling into question the wisdom of promoting patent protection. Problems of interim secrecy could be ameliorated by decreasing delays in the prosecution of biotechnology patent applications in the Patent and Trademark Office. Concerns about restrictions on the use of patented inventions in subsequent research might be met through the exercise of march-in rights by funding agencies or through enactment of an experimental use exemption to infringement liability in this context. These sorts of reforms might help min-
imize friction between the patent system and traditional scientific norms without jeopardizing incentives for private support of research in this area.

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NOTES


6. In this situation neither patent holder would be able to use the improvement without first obtaining a license from the other.

7. 35 U.S.C.A. § 112 (West 1984). Section 112 also requires that the inventor disclose the "best mode" for making and using the invention known to the inventor at the time the application is filed.


(S.D.N.Y. 1911), rev'd in part on other grounds, 196 F. 496 (2d Cir. 1912) (purified adrenalin composition); Kuehmsted v. Farbenfabriken, 179 F. 701 (7th Cir. 1910), cert. denied, 220 U.S. 622 (1911) (acetyl salicylic acid).


22. 35 U.S.C.A. §§ 202(a), (c) (West Supp. 1990). If the recipient does not elect to retain title, the agency may step in and pursue patent rights itself. 35 U.S.C.A. § 202(c) (2) (West Supp. 1990). Alternatively, the individual inventor may retain rights to the invention. 35 U.S.C.A. § 202(d) (West 1984).


27. 35 U.S.C.A. § 122, 11 (West 1984). If the inventor also seeks foreign patent protection, the contents of the patent application will be disclosed eighteen months after it is filed.


29. This is the recommended approach in the OTA Report, 1988.


35. 35 U.S.C.A. § 203(a) (West Supp. 1990). The government may also exercise march-in rights if it determines that “health or safety needs... are not reasonably satisfied” by the patent holder, or that “such... action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied” by the patent holder. 35 U.S.C.A. § 203(b), (c) (West 1984). See also 35 U.S.C.A. § 203(d), which permits the exercise of march-in rights in order to ensure that preference is given to U.S. industry in exploiting the invention.
40. In order to invoke this exception, the agency must comply with procedural requirements set forth in the statute and in Department of Commerce regulations. 35 U.S.C.A. § 202(b) (West Supp. 1990); 37 C.F.R. § 401.3 (1990). The agency must file with the Secretary of Commerce a written determination that exceptional circumstances exist including an analysis justifying the determination.
41. This exception is analyzed at length in R. Eisenberg, “Patents and the Progress of Science: Exclusive Rights and Experimental Use,” University of Chicago Law Review 56:1017, 1989.
44. See generally Eisenberg, 1989.
45. Ibid., pp. 1075–8.
46. See 37 C.F.R. § 401.6 (1990).
47. Of course, there is no bright line between discoveries that are useful in medical applications and discoveries that are useful for scientists working in the laboratory. An example of a patented technology that finds markets among both medical consumers and researchers is polymerase chain reaction (PCR). PCR, which is the subject of several patents owned by Cetus Corporation, for example, U.S. Patent No. 4,965,188 (October 1990), U.S. Patent No. 4,683,195 (July 1987), U.S. Patent No. 4,683,202 (July 1987), permits selective amplification of extremely small amounts of DNA by as much as a billionfold. “Cetus Corp. Obtains Fifth Patent on Its PCR Gene Amplification Technology,” Business Wire, Inc., October 24, 1990 (Lexis wire service).
49. See notes 53–6 and accompanying text.
50. Cameron Septic Tank Co. v. Village of Saratoga Springs, 159 F. 453, 462 (2d Cir. 1908), cert. denied, 209 U.S. 548 (1908); City of Milwaukee v. Activated Sludge, Inc. 69 F.2d 577, 582–83 (7th Cir. 1934), cert. denied, 293 U.S. 576 (1934).
51. *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403, 410 (D. Del. 1931), aff'd 61 F.2d 1041 (3d Cir. 1932), cert. denied, 288 U.S. 614 (1933).


56. See *Amgen, Inc. v. U.S. Int'l Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990); *In re Pleuddemann*, 910 F.2d 823 (Fed. Cir. 1990), although the opinion is not entirely coherent on this point and its implications for subsequent patent applications are therefore unclear.

57. *In re Durden*, 763 F.2d 1406 (Fed. Cir. 1985).


62. The doctrine of equivalents holds that an “accused product” may infringe a patent even though there are differences between the accused product and the literal language of the patent claims if the accused product nonetheless “performs substantially the same function in substantially the same way to obtain the same result.” *Graver Tank v. Linde Air Products*, 339 U.S. 605 (1950). Conversely, the reverse doctrine of equivalents holds that an accused product may avoid infringement, even though it falls within the literal language of the claim, if it is “so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way.” Ibid., pp. 608–9.

63. *Scripps*, 927 F.2d at 1581.

64. 35 U.S.C.A. §§ 102(a),(b) (West 1984).

65. Ibid.

66. See, For example, *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991) (“It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel purified and isolated sequence which codes for EPO . . . .”) (emphasis in original).
67. See, for example, U.S. Patent No. 4,970,161 (November 13, 1990), claiming plas­
mids and recombinant animal cells incorporating chromosomal DNA sequence
 coding for human interferon-gamma.


69. See generally Eisenberg, 1990, pp. 729–36. The Federal Circuit followed this

70. See notes 53–6 and accompanying text.

71. 927 F.2d 1200 (Fed. Cir. 1991).

72. Ibid., p. 1212. See note 60.

73. Ibid., p. 1214.

74. Ibid.

75. Indeed, in the situation described in the text, the competitor would probably be
 liable for infringement under the doctrine of equivalents even if the patent claims
did not specify that they covered such obvious substitutions. See Graver Tank v.
Linde Air Products, 339 U.S. 605 (1950); see also discussion in note 62.