gland tissue in which it was found); Kuehmsted v. Farbenfabriken, 179 F. 701 (7th Cir. 1910), *cert. denied*, 220 U.S. 622 (1911) (upholding validity of patent on acetylsalicylic acid to first inventor to develop process for producing it in sufficiently pure state to render it therapeutically available).
12. *In re* Bergy, 563 F.2d 1031 (C.C.P.A. 1977), *vacated sub nom.* Parker v. Bergy, 438 U.S. 902 (1972), *on remand*, *In re* Bergy, 596 F.2d 952 (C.C.P.A.), *cert. granted sub nom.* Parker v. Bergy, 444 U.S. 924 (1979), *vacated and remanded with instructions to dismiss as moot sub nom.* Diamond v. Chakrabarty, 444 U.S. 1028 (1980).
13. R. S. Eisenberg, *Emory Law J.* **39**, 721 (1990).
14. Brenner v. Manson, 383 U.S. 519 (1966).
15. 383 U.S. at 536, citing Application of Ruschig, 343 F.2d 965, 970 (1965).
16. 35 U.S.C.A. § 103 (West Supp. 1992).
17. Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207 n.3 (Fed. Cir.), *cert. denied*, 112 S. Ct. 169 (1991).
18. *In re* Chupp, 816 F.2d 643 (Fed. Cir. 1987); *In re* Papesch, 315 F.2d 381 (C.C.P.A. 1963).
19. *In re* Vaeck, 947 F.2d 488 (Fed. Cir. 1991). For a discussion of the relationship between extent of disclosure and patent scope, see R. R. Merges and R. P. Nelson, *Columbia Law R.* **90**, 839 (1990) (see pp. 845–852).
20. W. L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1557 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).
21. Priority of invention depends on the date on which the invention was conceived, the date on which it was actually or constructively reduced to practice, and the diligence of a party who was first to conceive but last to reduce to practice. See 35 U.S.C.A. § 102(g) (West 1984).
22. 927 F.2d at 1206.
23. A recent amendment to the patent statute imposes infringement liability on those who use a patented process abroad and then import the unpatented product of that process into the United States [35 U.S.C.A. § 271(g) (West 1984)], but there is no comparable protection available for holders of patents on products used abroad in an unpatented manufacturing process [Amgen, Inc. v. U.S. Int'l Trade Comm'n, 902 F.2d 1532, 1538 (Fed. Cir. 1990)].
24. 35 U.S.C.A. § 284 (West 1984).
25. Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605 (1950).
26. Kinzenbaw v. Deere & Co., 741 F.2d 383 (Fed. Cir. 1984), *cert. denied*, 470 U.S. 1004 (1985).
27. R. S. Eisenberg, *Univ. Chicago Law Rev.* **56**, 1017 (1989) (see pp. 1030–1033).
28. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).
29. *ABC Statement on NIH Patent Filing for the Human Genome Project* (Association of Biotechnology Companies, Washington, DC, May 1992).
30. It is interesting to note that the ABC takes a more favorable view of the NIH patent applications than does IBA. ABC is a larger organization than IBA whose roster of voting members includes not only companies that develop products but also numerous law firms and other entities with an interest in biotechnology. One might speculate that these other entities, particularly law firms, have more to gain from a proliferation of patent rights in the human genome than do the companies that need to decide about whether to commit capital to the development of biotechnology products. IBA's voting membership is comprised solely of such companies.

Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization

by Reid G. Adler

This article provides a historical perspective for the patenting of gene sequences and describes the fundamentals and evolution of patent law. It summarizes federal technology transfer law and policy and assesses the impacts of patenting on academic research. The patentability of gene sequences is then considered along with potential impacts that published sequence data may have on obtaining patent protection for downstream products. Industry's position on gene patenting is summarized and perspectives from the emerging public record on these issues are presented. The article discussing points at which the filing of patent applications and the licensing of patents may be appropriate. It concludes that technology transfer policies for genome research must be adopted carefully so that they remain viable in a time of rapid technological change.

The public benefits from its support of biomedical research through advances at the frontiers of knowledge as well as through the development of commercial health care products (*1*). While the internationalization of scientific research and the pursuit of patent protection are not incompatible (*2*), the question of when to seek patent protection on gene sequences is a "staggeringly complicated issue" (*3*). The National Institutes of Health (NIH) earlier published several thousand cDNA gene sequences and deposited the clones in an open repository (*4*) but sought patent protection for them as an interim measure. This action protected options, fostered public discussion, and forced no outcome or policy decisions (*5*). Development of appropriate policies will occur at the frontiers of patent and technology transfer law.

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Just as nonscientists involved in science policy must understand the differences between, for example, structure- and function-based research, and the importance of both approaches, scientists involved in technology transfer policy must understand patent law and product development. Other areas of research involving unprecedented amounts of data about informational molecules, such as structure-based (or "rational") drug design, raise similar patent and technology transfer questions. It would be unfortunate if misconceptions about the patent system lead to a self-fulfilling prophesy that international research cooperation will be impaired.

"Gene Patenting" Issues in Perspective

Genes traditionally were identified and cloned through a functional approach, starting with samples having observed biological activities, working backward to isolate and purify the responsible proteins, and then, through the use of degenerate DNA probes, locating the corresponding gene. Once a programmatic decision was made to characterize the human genome through a large-scale structural (in other words, sequence-based) approach, the present debate became inevitable. Wide dissemination of sequence data will encourage research, but due consideration must be given to protecting the market exclusivity necessary for the private sector to risk enormous sums of money in product development efforts. The biotechnology industry is critically dependent upon patent protection to maintain its threatened leadership in highly competitive world markets.

How to apply patent rights to genome research should have been a widely debated question, but it largely went unresolved during the establishment of the human genome project. Although the Office of Technology Assessment (OTA) concluded in 1988 that "genome projects raise no new questions of patent or copyright law," it did not consider how technology transfer principles would apply to sequence data that identified genes (*6*). Contemporaneously, the National Research Council rhetorically considered whether a central agency of the government should own the patents for commercially valuable new DNA clones, but concluded only that genome sequences should not be copyrighted (*7*). Contributing to this lack of foresight may have been an urgency to start the genome program, the absence of any expectation that gene sequences would be identifiable so soon with so little accompanying functional information, a general unfamiliarity with patent law (*8*), and a historical lag in the

implementation of the federal technology transfer laws enacted during the 1980s (9).

Historical perspective is important to the consideration of gene-related patents (10). For example, when the landmark "Cohen and Boyer" patent for recombinant DNA issued in 1980 (11), critics asserted that a preoccupation with patenting would destroy the academic tradition of freely exchanging and publishing information. It was contended that the best minds were being diverted into development at the expense of solving more basic biological research problems. These fears proved to be unwarranted, and several observers correctly had predicted "that just as branches of chemistry and physics evolved an acceptable association with industry, so will molecular biology, without rending itself apart" (12). The biotechnology industry presently sponsors academic research, conducts elegant independent studies, relieves academia of repetitive and technical tasks, provides employment opportunities for postdoctoral scientists, and offers the promise of revolutionizing medicine and agriculture.

Fundamentals of Patent Law

A patentable discovery or invention must be useful, novel, and nonobvious (13). Patent applications must conclude with at least one written "claim" that clearly and distinctly defines the invention for which patent protection is sought. Selected patent claims to various DNAs are presented in Table 1. Patented pharmaceutical inventions still require approval from the Food and Drug Administration before they are marketed. The patent application must contain a written description, called the "specification," similar to a scientific journal article that is sufficient to teach skilled workers how to make and use the claimed invention. This description may be supplemented by publicly accessible deposits of essential materials, such as genes or vectors, that are not reproducible from a written description alone. Once a patent application is filed, the novelty and nonobviousness of its claims are judged against public domain information as of that date. A decision to file a patent application does not automatically result in a patent.

Issued patents simply reprint the specification and whatever claims from among those the U.S. Patent and Trademark Office (PTO) finds allowable that the applicant for patent chooses to have issued. Filing a patent application and permitting allowed claims to issue in a patent are separate decisions entirely within the control of the applicant.

It may be advantageous to file a patent application, for example, claiming a partial gene sequence that is being published, with the intention of abandoning it in favor of a subsequently filed continuation-in-part patent application that discloses and claims the full gene. In this way, as discussed below, the applicant for patent might avoid the PTO rejecting a claim to the full sequence as being unpatentably obvious in view of the published partial sequence.

Table 1. Exemplary claims from issued U.S. patents.

1. Recombinant DNA coding for human precursor [plasminogen activator inhibitor]–2, comprising the following amino acid sequence. . . .
2. A method of testing for the presence or absence of a target sequence in a sample containing DNA [comprising hybridization with a probe . . .].
3. A recombinant expression vector, comprising [the coding sequence for protein x].
4. A double-stranded DNA segment comprising the sequence of a complete cDNA derived by reverse transcription of an RNA of alfalfa mosaic virus selected from the group consisting of RNA3 and RNA4.

Patent law and practice comprise a system of rules, procedures, and standards. Like scientists, patent practitioners observe, study, and sometimes interact with their system, and they formulate and test hypotheses about how patentability changes over time. In almost all cases, the PTO initially finds several reasons to reject as unpatentable the claims of a patent application. A dialogue then ensues involving technical evidence and legal theories. Thus, the initial PTO decision on the NIH cDNA patent application, expected late this summer, undoubtedly will argue that the claimed cDNA sequences are unpatentable but will provide minimal policy guidance. Each transaction with the PTO and each judicial patent decision represents an experiment that generates data about the patent system.

The United States is considered to have the most progressive patent system (14). However, because pharmaceutical products are marketed internationally, deficiencies and imbalances in foreign patent laws relative to U.S. laws create uncertainties that undermine the ability of the U.S. biotechnology industry to plan for and to conduct research and development. Without adequate patent protection in major markets, competitors may be able to copy existing products cheaply rather than develop new products that require a more substantial investment. Thus, patent law has become an important component, for example, of international trade negotiations.

The Evolution of Biotechnology Patent Law

The law—whether relating to patents, privacy, environment, or trade—is as vital as science, and both co-evolve with startling rapidity, replete with creativity and drama (15). Public policy aspects of the law often seem to be resolved in the courts rather than through a legislative process (16), however, and landmark court decisions in patent law deal with the state of the art of 5 to 10 years earlier. Fundamentally, advances in the patent law lag behind developments in science, as exemplified below for hybridomas (17). This is particularly significant for biotechnology, where new medical or industrial technologies emerge before basic questions of patentability are even framed clearly. The early public debate encouraged by NIH about when to file patent applications on gene sequences, when to permit the issuance of patents, and what to do with patents is virtually unprecedented.

Decisions about patentability, infringement, and the proper scope of protection (as defined by the claims to be accorded to inventions in biotechnology) will be based on older court decisions that have been developed for technological advances in organic and pharmaceutical chemistry. For example, the burgeoning chemical industry after World War II flooded the PTO with patent applications, yet basic legal questions of prima facie obviousness (is a new structural formula that resembles a known compound unpatentable) were not answered until the 1960s, and basic questions of enablement (the amount of "teaching" required in a patent application) were not answered until the 1970s. This body of law is relevant but is not necessarily a close fit to advances in biotechnology, and answers to the same patent law questions vary internationally (18).

Living microorganisms were determined in 1980 to be patentable subject matter by a 5 to 4 Supreme Court majority (19). Transgenic plants and animals subsequently were determined to be patentable by the PTO, although human beings are not patentable because the U.S. Constitution forbids the ownership of people. Linear informational molecules such as proteins and DNA sequences have been patented for many years without a perceived need for guidance by the courts.

Other concerns have also been expressed. A few commentators have suggested that the patenting of partial or full gene sequences is unethical on the theory that this would limit public access to our universal heritage (20). Similar criticism was offered against the patenting of microorga-

nisms, plants, and animals. There is validity to concerns that developing countries, for many reasons unrelated to patenting, do not fully participate in biotechnological advances. These issues are not unique to genome research and warrant due consideration.

Hybridomas as an example of transition in patent law. The production of monoclonal antibodies in 1975 by Cesar Milstein and Georges Koehler was rewarded by a Nobel Prize in 1984. In 1985, the PTO held that the art of making monoclonal antibodies in 1981, at least against cancer antigens, was not routine and predictable and therefore fulfilled the "nonobvious" requirement for patentability (*21*). A year later, the PTO concluded that it would have been obvious in 1981 to prepare monoclonal antibodies against human fibroblast interferon because it was a known antigen (*22*). The number of experimental steps required to create more than 100 hybridomas and select clones that produced specific monoclonal antibodies, as described in a 1980 patent application, was held in 1988 not to require "undue experimentation" or, in other words, an unduly extensive level of effort to reproduce (*23*). The law presently is undergoing a similar transition with respect to the patentability of DNA sequences.

Federal Technology Transfer Law and Policy

A progression of federal laws since 1980 encourages the transfer of technology through patenting from academic and government laboratories (*24*). The Federal Technology Transfer Act of 1986 (*25*) also strongly encourages government laboratories to enter into cooperative research and development agreements and to patent and license their inventions. Although some observers may consider these laws to have opened a Pandora's box of conflicts of interest, concern for tangible public benefit from research is a social responsibility (*26*). Moreover, appropriate participation in technology transfer is a statutory obligation of government scientists (*27*).

Patent protection usually is necessary to stimulate product development in the pharmaceutical and biotechnology industries where the demonstration of efficacy and safety is a lengthy and extremely expensive process (*28*). A key study reported, for example, that 60% of pharmaceutical products would not have been developed without patent protection (*29*). Patenting is even more critical for the biotechnology industry because it still is in its infancy (*30, 31*). Although patents or exclusive licensing of government-sponsored inventions are not mandatory for the development of all gene-related or other products, whether inventions are "patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives" (*19*).

Companies are unlikely to invest significant research efforts or to develop commercial DNA-based products that might infringe another's patent rights without first obtaining permission in advance through a license. If the applicant for a patent decides to permit an allowed patent to issue, its claims may be dedicated to the public or licensed. The ways that patented inventions are licensed to transfer technology (that is, exclusively, nonexclusively, or perhaps through a lottery) may be as important to encouraging product development as when a specific invention (such as cDNA or genomic DNA sequences) is patentable. The licensing of government-developed inventions by law is announced publicly, and terms and conditions, such as royalty rates, are negotiated (*32*). Questions about the impacts of patenting and licensing on academic research, however, are critical considerations in establishing a policy for the transfer of technology resulting from the genome research.

Effects of Patenting on Academic Research

Concerns about a negative impact of patenting DNA sequences on the conduct of genome research are largely theoretical. A frequently misunderstood concept about patenting is that liability for infringement attaches only to commercial activities rather than to academic studies as a practical matter. Virtually all of the relevant court cases involve disputes between commercial competitors over manufacturing-related activities or product sales (*33*), and purely academic research appears not to have been enjoined (*34*). It often is in a company's interests to encourage the discovery of new uses for its patented products. For example, although amplification by the polymerase chain reaction (PCR) is a process patented by Cetus Corporation, many thousands of journal articles have been published that report the results of PCR-related studies.

During the past decade, with increased industry funding of university research and institutionalized technology transfer programs, the dividing line between "academic" and "commercial" has become somewhat blurred (*35*). For example, notwithstanding academia's vast PCR literature, the PCR patent's licensee, Hoffmann–La Roche, has sought royalty payments from university hospital centers that use PCR diagnostics when patients are charged for those tests (*36*). There is some legal uncertainty in assessing whether infringement occurs through a university's more traditional academic uses of a patented product or a process to make what ultimately becomes a commercially valuable product (*37*).

NIH explicitly reserves the right to permit academic research uses of its inventions as reflected in NIH technology transfer policies and commercial license agreements. Whether gene sequences are patented by others should have little impact on the vigor with which government-funded academic research is conducted, in the absence of some precedent-setting court decision that would expose all fields of academic research to infringement liability. So far, patent holders seem reluctant to sue academic institutions. To minimize legal uncertainties, several commentators have proposed a statutory research exemption or suggested a more liberal judicial interpretation of existing law (*33, 38*), although industry may consider this to be unnecessary (*39*).

Additionally, some scientists apparently fear that major research institutions will take credit (by filing patent applications) for sequences deposited by others in their data bases. This is neither ethical nor permitted under patent law. Conversely, some scientists might delay publishing partial sequences in order to complete sequence or functional studies that might more clearly support the grant of a patent. Also, the costs and logistics of seeking patent protection might price smaller programs or institutions out of the market. However, these economic factors must be considered even at larger institutions.

When Are Gene Sequences Patentable?

Gene sequences, like any other invention, are patentable when they satisfy the statutory criteria for patentability mentioned above. The pending NIH cDNA patent application discloses 2700 gene-related sequences of variable lengths for which information regarding biological function ranges from unknown through general to specific. Because of this variability in sequence length and functional knowledge, the NIH cDNA patent application presents several patentability questions.

Are DNA sequences "useful" without an established biological function? Utility is considered to be a threshold statutory requirement that an invention possess a beneficial or practical utility, but the patent statute does not require a biological or commercial utility (*40*). A minimal utility requirement encourages inventors to publish their work and to file patent applications as early as possible, rather than delaying disclosure to

identify the ultimate marketable uses of a product. Patent protection for a useful "composition of matter" covers the product per se, and is not limited by any particular use or uses ascribed to it in a patent.

Partial and full gene sequences, whether derived from cDNA or genomic DNA, have practical utilities as markers for individual human chromosomes. Such are presently sold as commercial products (*41*). This is a relatively trivial utility to assert, compared with the effort that would be required to identify and demonstrate a pharmaceutical utility for the proteins encoded by the sequences. Nevertheless, the licensing of gene sequences patented on the basis of this utility might encourage product development if otherwise the publication of the sequences would limit later patent protection. Complementary DNA probes could also be used as sources of PCR primers to generate genetic fingerprints and for the differential identification of tissue types. The PTO must decide whether such utilities asserted for cDNAs are sufficient, but it lacks statutory authority to refuse patents on inventions having only one instead of multiple known, substantial utilities.

The seminal Supreme Court case on utility, decided in 1966 (*42*), held that a process to produce a compound may be patented only if the compound has "substantial utility," or "specific benefit . . . in currently available form." There is some legal uncertainty about applying the utility requirement to gene sequences of unknown biological function, because the Court discussed insufficient utility in a case where no practical utility had been asserted and did not clearly articulate the requisite level of utility. Subsequent appellate court decisions have reinforced the concept that the utility requirement is a low hurdle along the path to a patent. Reasonable people may differ about the height of the utility hurdle that patentable gene-related inventions should clear, but some gene sequences already are now commercial products for reasons independent of their biological function.

Are such DNA sequences patentably novel and nonobvious? "Taken together, the novelty and nonobviousness requirements express a congressional determination that the purposes behind the [Patent Law] are best served by free competition and exploitation of that which is either already available to the public, or that which may be readily discerned from publicly available material" (*43*). Novelty means that an invention did not previously exist in the public domain. NIH sought patent protection contemporaneously with the publication of the cDNA sequences because absolute novelty is a requirement for patentability in most countries, even though the United States provides a 1-year grace period. A nonobvious invention is an invention that could not have been made with a reasonable expectation of success by a hypothetical person of "ordinary skill" in the relevant scientific field from publicly available information and material.

The NIH cDNA patent application claims "enriched" or "purified" full-length polynucleotide sequences, which are related to genes that do not exist naturally in these forms. Uniqueness in the context of GenBank, other sequence databases, and published articles assures with a reasonable certainty that such sequences are novel (*44*), although once again the PTO will have to decide.

As noted above in the case of hybridomas, rapid scientific advances first expand and then somewhat contract the boundaries of patentable subject matter as revelatory laboratory techniques quickly become technologically and legally mundane. For example, the creation of recombinant DNA in 1972, for which Paul Berg received a Nobel Prize in 1980, may now be accomplished in some circumstances by workers of ordinary skill with a reasonable expectation of success (*45*). Patents are generally no longer allowed merely for the recombinant expression of a known protein, and patent legislation has been proposed to make such products patentable as an incentive for their commercial development (*46*).

As a matter of logic, one could not reasonably have expected to make any particular purified cDNA or genomic gene sequence corresponding to a previously unknown human gene even for use as a probe (*47*). One would have expected to find some important gene sequences in a cDNA library, but "obvious to try" is not the applicable legal standard (*48*). The manner in which an invention actually was made, however, whether through serendipity or a rapid computer-assisted analysis, does not negate nonobviousness (*49*). Nonobviousness will require another PTO decision. Patenting is not a value judgment about the elegance of an invention's underlying discovery, and the standards for patentability differ from the criteria applied to publication in peer-reviewed journals.

How broadly can gene sequence discoveries be patented? An inventor may claim everything that can be done with an invention described in a patent application to the extent that a worker skilled in the relevant field is "enabled" by the patent to make and use that invention without "undue experimentation" (*50*). If undue experimentation is required to reproduce a patented invention, this means that an unreasonably extensive level of experimentation is required to do so, not that the involved research might be low-yield, time-consuming, or expensive. For example, as discussed above, the production of monoclonal antibodies against a known antigen or the expression of recombinant proteins from an identified gene sequence generally is not considered to require undue experimentation.

Several cases are relevant to the issue of enablement. For example, the PTO ruled in 1987 that it would have been obvious (that is, readily discernable from publicly available material) to prepare a genomic library from bovine placenta in 1982 and to isolate by hybridization the gene encoding bovine growth hormone (*51*). A patent also was issued in 1987 claiming a general method of identifying genes for known proteins by preparing and probing an appropriate cDNA library and then isolating the responsible cDNA (*52*). The issuance of the patent implies that successfully utilizing this technique to produce intact cDNA coding sequences would not require undue experimentation.

The relative ease or difficulty of obtaining complete sequences for individual genes from a partial cDNA or genomic DNA sequence and the relevant cDNA or genomic DNA libraries may vary. When full-length coding sequences can be obtained through even a dozen or more conventional sequencing steps without undue experimentation, a patent application disclosing partial gene sequences should entitle their discoverers to patent the full cDNA coding sequence. The fact that the set of sequences may contain a few that cannot be applied to the asserted use does not negate the patentability of the rest (*53*).

In a case now pending on appeal, Biogen, Inc., contends that a skilled worker in 1980 would have been able to isolate and sequence the gene for interferon without undue experimentation by stimulating cellular production of that protein, isolating cellular messenger RNA, preparing a cDNA library, screening the library for a cDNA that would cause a transfected cell to exhibit antiviral activity, and sequencing and expressing the interferon cDNA (*54*). Whether or not all of these steps could have been accomplished with 1980 technology, the PTO must decide whether the sequence of partial cDNAs in the NIH patent application can be extended to completion in 1992 without undue experimentation. The law of patentability for genes once at least partial sequence information has been obtained is evolving and individual cases will be decided on their own specific facts.

Effects of Publishing and Patenting on Product Development

Companies are unlikely to develop products that cannot be adequately protected by patents (*55*). At some point, the publica-

tion of partial gene sequences or even full sequences with limited information about function could raise issues of lack of novelty and obviousness that might preclude future patent protection for more complete or better characterized sequences. Would this discourage rapid product development? At some point, the licensing of the results of taxpayer-funded genome research would encourage product development. Identifying these points requires data obtainable primarily from industry and from future PTO decisions.

There also are questions about the extent to which the publication of sequence information ultimately might interfere with the markets protected by existing corporate patents. For example, what would be the impact on Amgen, Inc., if variants of its patented erythropoietin cDNA (56) were readily discernable through homologies in published cDNAs? What impacts on Genentech, Inc., would result if other forms of its patented cDNA for tissue plasminogen activator were published? In part, the answer might depend on the extent to which the expression products sold commercially might be readily be discerned or attained from publicly available sequence data and DNA clones. Are there circumstances in which a license from NIH would be preferable, for example, to domestic or foreign competition involving such gene variants? Would licensing a sequence from NIH be preferable to litigating the scope of existing gene or recombinant protein patents when competitors sought to market novel product variants based on sequences published by NIH? (57) Is the public interest served by protecting or opening existing markets?

General effects of publication on downstream patenting. The patent system encourages the filing of patent applications as early as possible, in part to permit publication without jeopardizing potential patent rights. Whether or not sequences of unknown function are patentable, the effect of publication of sequence data on the patentability of downstream discoveries is still unknown (58). To some extent, the impact of PTO determinations of novelty and nonobviousness will depend upon what becomes readily discernable beyond the sequences actually published (59), and on the technical feasibility of extending partial sequences to full length and of expressing the full-length coding regions. As sequencing technology advances, there will come a time—if it is not yet here—when there may be little difference in effect between the publication of partial and full coding sequences. It will take the PTO and the courts several years, however, before they will construe the 1992 level of technological skill.

Also relevant to assessing the impact of publication will be the impetus for further investigation of particular sequences. About one-fifth of the partial cDNA sequences in the NIH patent application appear to correspond to specific genes previously identified in other species, and it has been estimated that as many as one-third of full cDNA coding sequences for expressed genes will at least have a recognizable general function (60). For these subsets of gene sequences, a relatively stronger motivation exists for expressing them and developing monoclonal antibodies against their expression products. Conventional technology and commercial services exist to accomplish both steps.

Would sufficient development incentives remain? If partial or full cDNA sequences without apparent biological function enter the public domain through publication, the sequences themselves would remain unpatentable even if applications were discovered later to genetic therapy or other emerging DNA-based therapies such as triple helix DNA or antisense RNA. Once their biological function is determined, pharmaceutical "compositions of matter" incorporating the cDNA expression products may still be patentable (61). Therapeutic and diagnostic methods of using such genes or their expression products clearly would be patentable. However, many countries, such as Japan, do not allow patents for human therapeutic or diagnostic procedures. Moreover, use patents are frequently difficult to enforce and do not deter the marketing of the same product for other uses. How much patent protection is enough?

The risks to obtaining downstream patents are the greatest when a general function is apparent from a partial or full sequence. Merely expressing recombinant proteins does not impart patentability to the resultant products. Also, an apparent but general biological function might render unpatentably obvious the successful demonstration of a specific biological function if that experiment merely confirmed what reasonably was expected. Companies and universities ubiquitously file patent applications prior to publication to establish early dates of invention and to avoid potential issues of lack of novelty and obviousness when at least a general biological function will be disclosed. Should NIH apply a different standard to protecting taxpayer-funded research? Should the PTO or Congress expressly set the utility hurdle at a level that requires a demonstrated specific pharmacological function rather than a biological activity or general function (62)?

Many second-generation products would be patentable notwithstanding the publication of partial or full cDNA sequences. These would include nonobvious polynucleotides, perhaps having altered sequences to produce tighter binding affinities, or bioactive fragments of the full sequences and bioactive portions of their expression products.

What Is Industry's Position on Patenting Genes?

The major impact of gene patenting and licensing policies will be felt by industry, because the research exemption presumptively shields academic institutions. One of the major reasons for preserving options by filing patent applications on cDNA sequences was to give industry time to consider the impacts of both publishing and licensing by NIH, and to formulate policy recommendations. Because of the complexity of the issues, only recently have the three major biotechnology and pharmaceutical trade associations proposed varying approaches to genome-related patenting and licensing. All supported NIH's interim policy of filing cDNA patent applications as an appropriate measure to preserve options while final policies are considered. All support patenting by NIH once a complete coding sequence and its biological function are known, but one association recommends continued filing of patent applications even on partial sequences of unknown function.

The Industrial Biotechnology Association (IBA) has 125 member companies and represents 80% of U.S. investment in biotechnology. The IBA recommended unanimously on 10 June that NIH unilaterally adopt a policy that it would file patent applications claiming genes only when the complete coding region and its biological function are known (63). However, the IBA did not define "complete" (which could mean 100%, 98%, or complete for enablement purposes, among other possibilities) or identify the threshold amount of "function" (for example, apparent biological activity based on homology to a known receptor or oncogene, demonstrated biological activity, or mapping to the same locus as an inherited disease) sufficient to justify the filing of a patent application. The policy of not filing patent applications at earlier stages would not apply to IBA members.

The IBA considered it improper for NIH to control product development when its own contribution to particular sequences was minimal. Furthermore, the IBA was concerned about the risk that a competitor might be licensed exclusively by NIH instead of the company that actually had developed a product based on a particular gene sequence. The IBA apparently concluded that this risk, as well as any potential negative impact on patentability from the publication of incomplete sequences,

outweighed any benefit to be derived from licensing patent rights from NIH unless a licensed sequence had been characterized fully. The IBA also was concerned about the transactional costs and logistics of obtaining license rights, and of theoretical (but unspecified) unacceptable provisions in license agreements.

The Association of Biotechnology Companies (ABC), with more than 280 member companies and other institutions, took a different approach by distinguishing the questions of when patent applications should be filed from when and how patent rights should be licensed (64). The ABC supported the continued filing by NIH of similar cDNA patent applications as well as continuation-in-part applications (65) for subsequent research that had characterized any partial sequences more fully. The ABC felt that it was important to preserve early filing dates for partial cDNA sequences to avoid potential rejection of future patents on the basis of lack of novelty or obviousness once NIH had determined full sequences and their biological significance.

The ABC recommended exclusive licensing by NIH only of substantially full-length cDNA sequences for which NIH has identified the corresponding protein and its biological activity. Otherwise, licensing of patented sequences should be nonexclusive to companies that were developing related commercial products. No company thereby would be blocked by the provisions from obtaining whatever licensing rights NIH could provide. The ABC also felt that NIH should receive some financial return through licensing royalties on the public's investment in genome research. ABC acknowledged that its members would have to live with the consequences of the appearance of published sequences that were based on their own patenting of downstream products.

The Pharmaceutical Manufacturers Association (PMA), an organization of about 100 companies that has several members in common with the IBA, opposed the patenting by NIH of genes of unknown utility (65). The PMA felt that this policy also should apply to government grantees and contractors. Rather than withdraw existing patent applications, the PMA suggested that NIH maintain the status quo until an international agreement on leaving such sequences in the public domain is finalized with other countries.

Interpreting the Public Record

Industry, academia, and NIH share the view that patenting and licensing should be pursued at the stage of research at which they will encourage commercial product development. The concerns of the academic community about the impacts of patents on genome research may be unfounded, but must be acknowledged. In assessing the recommendations of industry, it is clear that the trade associations are not interested in exclusively licensing sequences of unknown function, assuming that they are patentable, as an incentive for product development. It remains to be determined whether the nonexclusive licensing of such sequences would protect U.S. industrial interests, because U.S. law favors domestic manufacture of products sold in the United States (66), or facilitate achieving international agreement. However, when to file patent applications and when (and how) to license them are separate questions that may warrant different answers.

Even if the publication of partial sequences without known function rendered the full gene sequence unpatentable, industry has not expressed concerns that there would be insufficient remaining patent protection for expression products to encourage product development. Once even a general function seems apparent, however, publication alone would appear more seriously to threaten patenting for future products; if so, patenting and licensing by NIH at this stage may well serve the public interest. Until this point is clarified by PTO decisions or specifically addressed by industry, perhaps patenting and licensing optimally should be pursued only for complete coding portions of a gene for which a generalized biological function seems apparent, or at least for partial genes of sufficient lengths to surmise their function (5).

Given the uncertainty about the impact of publishing partial sequences on patenting full-length sequences, it may be prudent to file patent applications claiming sequences of unproven function—but not to permit them to issue as patents or, alternatively, not to license them. This would preserve early filing dates to support NIH's own future continuation-in-part patent applications once sequences were fully characterized. Again, the decision of when to file patent applications depends on future PTO decisions about gene sequences.

Achieving international agreement on an appropriate policy may be surprisingly quick, given the public positions taken by the French and British governments, although the Japanese position is unclear. Should NIH grantees also be bound by such an agreement? Whether the same standards for pursuing gene patents would be appropriate for industry may depend on how quickly large-scale cDNA and genomic DNA sequencing become private sector activities.

As new classes of DNA-based products are developed and PTO and court decisions emerge, the relevance of patent law to biotechnology must be evaluated carefully. Perhaps amending the obviousness requirement of the patent law would be salutary. Additionally, strengthening use patents internationally may become necessary to ensure adequate protection for sequence-related inventions in world markets. In the software field, the appropriateness and effectiveness of patent or copyright protection has been identified as warranting reassessment (67). Perhaps patenting is not the optimal system when unprecedented volumes of data about informational molecules are published. A registration system, like copyright, might be simpler and more affordable. To encourage the development of other important technologies, federal laws were enacted to create new intellectual property systems that would protect novel plant varieties and semiconductor chip masks (68, 69). This approach might be necessary for DNA sequence inventions.

Conclusions

The President's Council on Competitiveness has noted that for biotechnology "the appropriate definition of intellectual property rights is a crucial area requiring careful thought" (70). Creating appropriate definitions and developing responsible policies to attain the goals of advancing knowledge and developing products will require the concerted efforts of government, academia, and industry. Given the rapid pace of technological development, we must anticipate where research is heading to ensure that the policies we make today are valid even a year from now. Understanding the systems of both science and patent law are necessary for success in this endeavor.

REFERENCES AND NOTES

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3. "*Double Helix Battles*," The Washington Post (editorial), 1 May 1992.
4. M. D. Adams *et al.*, *Science* **252**, 1651 (1991); and *et al.*, *Nature* **355**, 632 (1992).
5. B. Healy, *N. Engl. J. Med.*, in press; "Remarks" presented at a public meeting convened by the Genome Patent Working Group of the Federal Coordinating Council on Science, Engineering and Technology in Washington, DC, on 21 May 1992.
6. Office of Technology Assessment, U.S. Congress, *Mapping Our Genes—The Genome Projects: How Big, How Fast?* OTA-BA-373 (U.S. Government Printing Office, Washington, DC, 1988), p. 16.
7. Chapter 8, "Implications for Society" in Report of the Committee on Mapping and Sequencing the Human Genome of the Board on Basic Biology, Commission on Life Sciences, National Research Council (National Academy Press, Washington, DC, 1988), p. 91.
8. R. Eisenberg, *Emory Law J.* **39**, 721 (1990).
9. *Technology Transfer: Federal Agencies' Patent*

Licensing Activities, (GAO/RCED-91-80, U.S. General Accounting Office, 1991).
10. "Those who cannot remember the past are condemned to repeat it." G. Santayana, vol. 2. *The Life of Reason* (Scribner, New York, 1905-06).
11. U.S. Patent 4 237 224 (entitled "Process for Producing Biologically Functional Molecular Chimeras") issued on 2 December 1980 to Stanford University.
12. J. D. Watson, and J. Tooze, *The DNA Story: A Documentary History of Gene Cloning* (Freeman, San Francisco, 1981), chap. 16.
13. 35, U.S. Code. Sections 101, 102, 103; R. G. Adler, *Science* **224**, 357 (1984).
14. Office of Technology Assessment, U.S. Congress, *Biotechnology in a Global Economy*, OTA-BA-494 (U.S. Government Printing Office, Washington, DC, October 1991), p. 17.
15. R. Adler, *Harvard J. Law Tech.* **1**, 1 (1988).
16. A. Solzhenitsyn, *Nat. Rev.* **30**, 836 (1978).
17. R. Adler, *Am. Intelect. Prop. Law Assoc. Q. J.* **16**, 287 (1989).
18. S. Bent *et al.*, *Intellectual Property Rights in Biotechnology Worldwide* (Stackton Press, New York, 1987).
19. *Diamond v. Chakrabarty*, 447 U.S. 303§ (1980), considered patentability issues associated with a 1972 patent application.
20. H. Curien, *Science*, **254**, 1710 (1991).
21. *Ex Parte Old*, 229 U.S. Pat. Q. 196 (PTO Bd. App. Int. 1985).
22. *Ex Parte Erlich*, 3 U.S. Pat. Q. 1011 (PTO Bd. App. Int. 1986).
23. *In re Wands*, 858 F.2d 751 (Fed. Cir. 1988). In this case, the court explained that the legal test was "not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the [patent application] in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."
24. "It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development." 35 U.S. Code, sect. 200.
25. P.L. 99-502.
26. "There are science and the applications of science, bound together as the fruit to the tree which bears it." L. Pasteur, *Rev. Scientifique* (1871); "Concern for man himself and his fate must always form the chief interest of all technical endeavors . . .," A. Einstein, Address, California Institute of Technology (1931).
27. "Technology transfer, consistent with mission responsibilities, is a responsibility of each laboratory science and engineering professional." 15, U.S. Code sect. 3710(a)(2).
28. The average cost to discover and develop one prescription medicine has been reported to be $231 million and to take 12 years. P. R. Vagelos, *Science* **252**, 1080 (1991).
29. E. Mansfield *et al., Rev. Econ. Stat.* (1979), p. 49.
30. The industry has been characterized as " . . . a research- and capital-intensive industry, grounded in intellectual property." G. S. Burrill and K. B. Lee, Jr., *Biotech 91: A Changing Environment* (Ernst & Young, Dallas, 1990), p. 5.
31. The Congressional Office of Technology Assessment (OTA) has also observed that "When discussing a nation's competitiveness in industries fostered by the new biology, protection of intellectual property is seen by many as a paramount consideration." Office of Technology Assessment, *Biotechnology in a Global Economy* (OTA-BA-495 U.S. Government Printing Office, Washington, DC, 1991), p. 203.
32. 37, Code Fed. Regul., Part 404.
33. R. Eisenberg, *Univ. Chicago Law Rev.* **56**, 1017 (1989).
34. In one case for which an interim court decision was reported, Cornell University was sued based on its alleged licensing of an infringing invention. *Tenneco Oil Co.* v. *Vector Magnetics, Inc.*, 7 U.S. Pat. Q. 1591 (N.D.N.Y. 1988).
35. *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984). This case held that pursuing FDA approval for a product about to go off-patent constituted infringement. In a statement not essential to the decision, the court appeared to exempt from infringement liability only experiments conducted for "amusement, to satisfy idle curiosity or for strictly philosophical inquiry."
36. R. Winslow, *Wall Street Journal.*
37. Theoretically, for example, the one-time use of a patented receptor by a university or a company in a screening assay to identify a commercially valuable therapeutic product might be challenged as an infringement.
38. N. Israelsen, *Amer. Intelect. Prop. L. Assoc. Q. J.* **16**, 457 (1988–89); I. Feit, *J. Pat. Trademark Off. Soc.* **71**, 819 (1989). Note that the U.S. Plant Variety Protection Act contains an express statutory exemption from infringement to use of a patented invention to make another invention, and many other countries have a statutory research exemption in their patent laws.
39. Comments by Lisa Raines, Vice-President, Government Relations, Industrial Biotechnology Association, at Public Meeting of FCCSET Committee on Life Sciences and Health Genome Patent working Group, 21 May 1992.
40. "A small degree of utility is sufficient. The claimed invention must be capable of performing some beneficial function . . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely. . . . *A commercially successful product is not required.*" *E.I. DuPont de Nemours & Co.* v. *Berkeley & Co.*, 620 F.2d 1247 (8th Cir. 1980); "Under our economic and patent systems, valuation of the *worth* of an inventor's contribution is left to the public, *not* to the judiciary in determining patentability." *Panduit Corp.* v. *Dennison Mfg. Co.* 810 F.2d 1561 (Fed. Cir. 1987); and the fact that an invention has limited utility and is only operable in certain applications is not grounds for finding lack of utility. *Envirotech Corp.* v. *Al. George, Inc.*, 730 F.2d 753 (Fed. Cir. 1984).
41. The ONCOR, Inc. 1992–93 Catalog describes a variety of molecular cytogenetics probes, including in situ hybridization reagent kits such as painting probes for individual chromosomes.
42. *Brenner* v. *Manson*, 383 U.S. 519 (1966).
43. *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489. U.S. 41 (1989).
44. S. Bent, *Genet. Eng. News* (January 1992), p. 4.
45. *In re O'Farrell*, 853 F.2d 896 (Fed. Cir. 1988). This case involved a 1978 patent application.
46. D. Beier and R. H. Benson, *Denver Univ. Law Rev.*, **68**, 173 (1991).
47. "[A]n association between a particular EST and a new brain gene probably could not have been predicted beforehand, undercutting any assertion that the EST is 'obvious' under patent law." (*44*).
48. See, for example, *In re O'Farrell*, *ibid.*
49. 35, U.S. Code sec. 103.
50. Eight factors may be considered in assessing enablement: the amount of experimentation necessary, the amount of guidance presented in the patent application, presence or absence of working examples, nature of the invention, state of the art, relative level of skill in the art, predictability, and breadth of the patent claims. See, for example, *In re Wands* (*23*).
51. *Ex Parte Rottman et al.*, Appeal No. 674–85 (PTO Bd. App. Int. 1987).
52. S. Clarke *et al.*, U.S. Patent 4 675 285 for "Method for Identification and Isolation of DNA Encoding a Desired Protein," based on a patent application filed in 1984.
53. *Atlas Powder Co.* v. *E. I. DuPont de Nemours & Co.*, 750 F.2d 569 (Fed. Cir. 1984).
54. *Fiers* v. *Sugano*, Appeals Nos. 92–1170 and 92–1171, before the U.S. Court of Appeals for the Federal Circuit. Brief for Appellant Fiers, 6 April 1992, pp. 7–8. In a related decision, a plan to clone the gene for erythropoietin from a genomic DNA library in 1981 without any knowledge of its DNA sequence was held to be mere speculation. *Amgen Inc.* v. *Chugai Pharmaceutical Co., Ltd.*, 18 U.S. Pat Q. 2d 1016 (Fed. Cir. 1991).
55. L. Raines, *Issues Sci. Tech.* **8**, 33 (1991).
56. The following composition-of-matter claim of Amgen, Inc., recently was upheld as valid by a federal appellate court: "A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a human erythropoietin."
57. A responsible biotechnology company might consider setting up a cDNA sequencing laboratory to seek to identify novel gene species related to existing proprietary products.
58. L. Greenlee, *Denver Univ. Law Rev.* **68**, 127 (1991).
59. Consider analogous case law. Claims to phenobarbital derivatives useful as anticonvulsant agents were rejected for lack of novelty over a reference that provided the structural formula in a table of compounds, *In re Samour* (CCPA 1978); claims to "tetramethylbiphenyl-4-4'-dicarboxylic acid" were rejected on appeal when a journal article identified the compound by name, *despite* the submission of an affidavit by its authors that they had never actually made the compound, *In re Dohonue* (Fed. Cir. 1985).
60. Transcript of remarks by Dr. Philip Sharp to the Advisory Committee to the Director, National Institutes of Health meeting (Bethesda, MD, 10 June 1992) at p. 250.
61. A separate issue is the scope to which such patents would be entitled. Such issues for biotechnological patents generally are controversial. R. Merges and R. R. Nelson, *Columbia Law Rev.* **90**, 839 (1990).
62. For example, U.S. Patent No. 4 721 672 of Harvard University claims genes that express angiogenesis factor. The patent application was filed in September 1985 with a statement that proteins "are useful in the diagnosis of malignancies, for promoting wound healing, and for other diagnostic and therapeutic purposes." But were these actual uses at that time or potential uses, primarily of interest to researchers, that were extrapolated from general biological functions? See P. Kelly, *Bio/Technology* **10**, 52 (1992).
63. IBA Position Paper: Recommended Federal Policy Concerning Human Genetic Sequences Discovered by Federal Researchers, Contractors and Grantees, 10 June 1992.
64. ABC Statement on NIH Patent FIling for the Human Genome Project, 17 May 1992; statement of Henry Wixon, Public Meeting of FCCSET Committee on Life Sciences and Health Genome Patent Working Group, 21 May 1992.
65. Letter of 28 May 1992 from G. J. Mossinghoff to B. Healy.
66. Section 209(b) of 35 U.S. Code, states that license rights to sell federally owned inventions in the United States "normally" are granted only to companies that agree to manufacture such inventions substantially in the United States.
67. Office of Technology Assessment, *Finding a Balance: Computer Software, Intellectual Property, and the Challenge of Technological Change* (OTA-TCT-527 Government Printing Office, Washington, DC, 1992).
68. The Plant Variety Protection Act of 1970, P.L. 91-577; and The Semiconductor Chip Protection Act of 1984, P.L. 98-620.
69. D. S. Karjala, *Jurimetrics* **32**, 121 (1992).
70. "Report on National Biotechnology Policy" by the President's Council on Competitiveness, February 1991 at p. 17.