Patents on Random Complementary DNA Fragments?

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The proposal by the National Institutes of Health (NIH) to patent products resulting merely from sequencing the human genome is a mistake: at worst, it is wrong in patent law; at best, it relies on deficiencies in law concerning what is "useful" as a requirement for patents. The proposal is symptomatic of a problem besieging biotechnology—attempts to control the raw material of scientific experimentation before research has determined the practical value of such material—that needs curing on many fronts. Corrective measures are proposed for adoption by the Executive branch, the Congress, and the courts.

The U.S. Constitution permits patents explicitly to "promote the progress of science and useful arts" (*1*). However, far from promoting progress, the trend of patent law in biotechnology today is toward the debilitation of science.

The fundamental premise of the patent system is a quid pro quo in which the public receives sufficient information to practice an invention after a limited grant of the right to exclude such practice expires. Fairness dictates that grant of a substantial power to exclude be offset by a substantial benefit to the public. Therefore, it is said the scope of protection or "breadth" of patent claims should be more or less coincident with the teaching content of the patent. However, when the patent claim is to a new composition of matter, its effect is to exclude others from making, using, or selling that composition of matter for any purpose, even though only one use for it is recognized by the inventor.

NIH now seeks to patent as compositions of matter partial cDNA fragments, derived from the human genome and sequenced under the direction of its employee, Dr. Craig Venter. These are called "expressed sequence tags" (ESTs). NIH also seeks patents on full-length cDNAs containing the ESTs with a view toward controlling expression of any associated protein, even though Venter has stated "he still has no idea what it does" (*2*). Since the patent statute requires that to be patentable inventions must first be shown to be "useful" (*3*), the problem with these patent applications is apparent.

The NIH proposal for patents is only an extreme example of a widespread practice in biotechnology that seeks to control not discoveries but the means of making discoveries. Patents are being sought daily on insubstantial advances far removed from the marketplace. These patents cluster around the earliest imaginable observations on the long road toward practical benefit, while seeking to control what lies at the end of it. In the NIH case, it is not clear whether appeals to the requirement that patented inventions be useful will suffice to brook this phenomenon, because that requirement approaches being a dead letter in current practice.

More is required than just rejecting the NIH patent applications because the underlying inventions lack the requisite utility, if even that can be done under the dilute version of the statutory requirement that now operates. Both judicial and legislative remedies will likely be needed to cure the rush to control the raw materials on which inventors operate, as distinct from whole inventions ready for consumption by the public.

In quiet times Congress is slow to act on the patent law. Under the Constitution, courts may take cognizance only of actual controversies, as the Supreme Court did when in *Diamond* v. *Chakrabarty* (*4*) it affirmed the availability of patents on living things and jump-started the biotechnology industry. Now the controversy surrounding the NIH patent applications may serve as a vehicle for judicial and legislative resolution of overarching issues concerning the usefulness of inventions. The associated questions, if anything, are further ranging than those dealt with in *Diamond* v. *Chakrabarty*.

The NIH Decision to Seek Patent Protection

For many years it was thought wrong to grant exclusive rights in inventions arising from publicly funded research, but since 1986 government policy has shifted to encourage such grants (*5*). According to proponents of the new approach, the promise of exclusivity is required if we are to induce private investors to develop such inventions into forms that are useful to the public, such as drugs approved by the Food and Drug Administration (FDA). In short, we are to patent research that the government does to encourage development that the government does not do.

In the case of Venter, this policy became wrapped up in another issue altogether. Would publication now of genome-derived sequence encoding a protein of unknown function preclude later patenting, once the protein's utility had been discovered and the public stood to gain? The bar to patenting would arise from another provision of law that says patentable inventions cannot be "obvious" from previous work (*6*); for example, a protein might be made obvious from publication of a DNA encoding it.

The NIH patent applications arose from its belief that patents on cDNA sequences could stand in lieu of later protein patents that current publication might preclude and be licensed as necessary to induce industry development (*2*). To preserve a putative patent position against imminent publication by Venter, NIH filed its applications without first publicly debating their broad policy implications. With patent rights pending, policy discussion could proceed at the deliberate pace it deserves. It is unfair to say there was no sense in this.

Another reason that may have compelled NIH's actions has gone undiscussed. Under federal statutory law, when an agency refrains from patenting or otherwise promoting commercialization of an employee's invention it must allow the employee to retain title to the invention (*5*). It would follow that if NIH elected now to abandon its patenting effort, Venter would have the right to take up the applications himself. How would that be for controversy, when billions of dollars from the public coffers are sought for related work?

Conventional wisdom holds that if a composition of matter is in the public domain in poorly characterized form, it does not become new for patent purposes when it is described better by solving its structure or finding a use for it (*7*). On the other hand, a natural product can be claimed as a "new" substance when it is purified and isolated from the *gemisch* in which it is found in nature. This has been the situation for adrenalin, prostaglandins, vitamin B12, tissue plasminogen activator, and many other substances.

There is nothing in the patent statute (*8*) that says old substances become "new" when first offered in purified and isolated form. This is law that judges have engrafted on the statute for good and sufficient reason.

By similar reasoning future judges could find to be "new" a substance "purified and isolated" from Venter's *gemisch* of random brain DNAs by the discovery of its utility.

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It could be claimed, for example, as "a protein [of sequence so-and-so] for the manufacture of a drug for amelioration of Alzheimer's disease." Claims of this kind are now accepted in Europe, even though the underlying substance is old (*9*).

There can be no assurance that U.S. courts, unaided by the legislature, will extend the law in this direction, and there is some evidence they will not. Thus, in *In re Thuau* (*7*) the Court of Customs and Patent Appeals refused patent claims to metacresolsulfonic acid–aldehyde condensation products as treatments for "diseased tissue" because the same agents had earlier been known for other purposes. Because of decisions like *Thuau*, U.S. practice permits "method of treatment" claims to those who discover new uses for previously published compositions, for example: "a method of treating [a certain disease] comprising the administration of an effective dosage of a protein of [a certain] amino acid sequence" (*10*). Such claims are enforceable not only against physicians (who are seldom sued) but also against manufacturers who actively induce physicians to use the composition in such treatment (*10*).

The short answer is that there may be something to NIH concerns about the publication of ESTs precluding later composition-of-matter patents, after useful work has been done to identify the biological activity of encoded sequences. However, I am left with a distinct feeling of unease if the solution is to file patents so prematurely as in effect to remove the requirement for utility from the Patent Act. To the extent that method of treatment patents are thought less desirable than patents on products, the cure—a grant to NIH of patents on thin grounds—may be worse than the disease. Ironically, because NIH seeks patents on encoding sequences but not on encoded proteins, the very manufacturers whose cause NIH purports (*11*) to promote would be competitively disadvantaged by their grant. Such patents would be enforceable here against expression of encoded sequences but not against overseas manufacturers who export the unpatented protein to American shores.

If these patents are issued to NIH, companies will face the usual choices—pay up (assuming licenses are available at any price), fight, or switch.

The Requisite Degree of Utility

A casual reader might suppose that the U.S. Supreme Court intended to rule out patents of the kind proposed by NIH. In *Brenner* v. *Manson* (*12*) the Court rejected claims to 2-methyldihydroxytestosterone derivatives, substances whose sole utility, in the words of the Court: "consists in [their] potential role as an object of use-testing" (*12*), because such claims "may confer power to block off whole areas of scientific development without compensating benefit to the public" (*13*). According to the Supreme Court: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion" (*14*). The Court stated that since "a patent system must be related to the world of commerce rather than to the realm of philosophy" (*15*), what is needed is "substantial" utility representing "specific benefit in currently available form" (*16*).

In effect, the NIH patent applications claim cDNAs individually, while asserting each to be "useful," say as a member of a set for use in chromosome mapping or in distinguishing brain-specific transcripts from other things. To speak plainly, these are utilities concocted to carry the patents until someone finds out what the DNA is really good for. Since the real purpose of the applications is to control individual DNAs and thereby commerce in the proteins they encode, this approach, in my opinion, amounts to a cynical resort to deficiencies in the law concerning what utility is sufficient for patents.

Suppose I were to write down and propose to publish all DNA sequences likely to include those expressed naturally. These could be synthesized with available technology, so I need not actually do that. I'll just constructively reduce my "inventions" to practice by filing patent claims on each of them. I'll say each sequence is useful as a member of a set that I can use to screen the rain forest for new kinds of bananas! I need to file this patent application so my publication will not preclude patents that will induce others to ship the bananas when they find some. I'll be a billionaire if some of these DNAs turn out to be good for anything other than banana searching!

Have I satisfied the standards for utility announced in *Brenner* v. *Manson*? A regrettably large number of patent attorneys can be found to say "yes," proceeding from what I will call "banana utility." According to these, *Brenner* v. *Manson* was a narrow decision because no utility was asserted by the patent applicant, who relied wholly on speculation. My not-so-hypothetical case would be recognized by these attorneys as different because, by conventional wisdom: (i) law does not look to the degree of utility; (ii) I need know only one use, not all uses, to which my invention can be put; and (iii) at least in prospect: "Yes, we have some bananas!"

Despite its constitutional basis, U.S. courts have paid little attention to the requirement of utility, imagining that if an invention is not useful, people will not come before them to fight about access to it. Once some threshold utility is found, law does not attempt to quantify it.

That tradition stems from a different time than today—from a time when inventions proceeded largely from the hands of mechanics as things complete in their own right. Either the public would want inventions and buy them for their own intrinsic utility or they would not. In the latter case the inventions would simply sink into disregard and the patents into disuse, with no one but the inventor any the worse for wear (*17*). The different situation today demands a fresh look at standards for utility and at whether in *Brenner* v. *Manson* the Supreme Court thought it was authorizing banana utility as sufficient underpinning for patents.

Effects of the Cumulation of Biotechnology Patents

Today, patents are avidly pursued all along the lengthy road from the most basic science through to the marketplace for pharmaceuticals. Because every step along the way draws another patent application, the path toward public possession of real benefit is increasingly obscured by dense thickets of intersecting, overlapping, and cross-blocking patents. Those operating at the beginnings of the road are most insistent on their right to nail down leverage that will remain formidable despite marketplace rejection of the uses to which they say their inventions may be put. The frank aim of these early stage workers is to control ultimate applications discovered by others. The system is abused if those who would benefit in this way from the later labors of others can posit patents on the most strained utilities imaginable. Typical is the suggestion by NIH that organ differentiation (*18*) is sufficient utility for a patent reaching to dominate the later discovery by others of a life-saving application for a cDNA!

Many of the more diaphanous patent applications one sees in biotechnology come from the university sector whose work is, perforce, distant from that applied end of things where emerges what the *Manson* Court called "specific benefit in currently available form." NIH, which occupies pretty much the same end of that spectrum, now reaches for government control over a vast number of proteins encoded in the human genome.

Should we rely on the public spirit of these public and quasipublic institutions to ensure that patents built on banana utility are wielded only in the public interest? My experience with university offices of technology transfer suggests not.

In my opinion, these institutions now regard themselves as profit centers whose administrators are judged by the royalty income they generate. I would not be surprised to learn that NIH technology transfer officers have the same motivation.

It is universally understood that at some point the cumulation of taxes can stunt industrial development. The cumulation of royalty obligations threatens to have the same effect in biotechnology. The widespread imposition of nonexclusive licenses under NIH patents would amount to another tax on an industry already returning dividends on public investment in science by the payment of taxes on income. The imposition of such a tax on all parties would be contrary to the justification for NIH's action that opportunities for exclusivity must be preserved as an incentive to development by one party. Indeed, the possibility that NIH would grant to single parties the power to exclude others from particular fields is sufficient answer to those who belittle the controversy by saying "companies will just need to get a license." There is no assurance that all will receive a license. The possibility of exclusive licenses under the NIH patents raises the clear prospect of their being used to stifle more productive work of others, as a result of having been awarded to the wrong party. Finally, if NIH makes available EST licenses to all comers for nominal or no royalty, it still establishes the principle that such patents are good. Now that Venter, with 25 to 30 other NIH employees, is reported (*19*) to be leaving NIH to continue genome sequencing and patenting in the private sector, that is a precedent NIH should not hope to establish. It is unlikely that the for-profit company slated to receive intellectual property rights from Venter's proposed institute will be content to make licenses widely available, either for substantial or nominal royalty.

Another alternative would be for NIH to seek international accord that governments and their research grantees will not seek patents on DNAs of unknown in vivo activity. Obstacles are formidable to the attainment of this prospect within anyone's planning horizon. Not least among the difficulties will be defining in the abstract language of treaty what activity information is sufficient, a task better left to courts when adjudicating concrete cases. Any such accord will leave unresolved the problem of private sector patents having no greater basis than those NIH has filed.

All of NIH's alternatives are Hobson's choices, but one. Rather than abandon its applications and leave open questions of EST and related patentability or cede those applications to Venter, NIH should use them as a vehicle to ask the Supreme Court if banana utility is enough and if, despite *Brenner* v. *Manson*, minimal contributions will continue to merit the grant of substantial monopolies.

Judicial Remedies: *Comer* v. *Venter*

The Patent and Trademark Office (PTO) should expedite review of the NIH patent applications, reject them for failure to meet the *Brenner* v. *Manson* standard, and expedite appeal from the rejection to the Court of Appeals for the Federal Circuit, where all interested parties can make their views known by learned briefs amici curiae (*20*). NIH or the PTO, depending on who loses at this stage, should then seek review in the Supreme Court on a properly made record. The matter will be styled *Comer* v. *Venter*, after the acting Commissioner of Patents. In other words, the courts and the PTO alike should be asked to restore teeth to *Brenner* v. *Manson*.

This will not be easy. It is hard to draw bright lines between what is useful and what is not. For example, if scanning tunneling microscopes are useful only for research, we should not want to deny patents on them for fear that people will stop inventing and then selling them. However, difficulty in drawing lines is familiar in patent law and is overcome all the time. Our patent statute says, with little more instruction, that proper subjects for patent should not have been "obvious" to ordinary workers. Courts every day deal more or less successfully with these metaphysics. They should do even better with such a word as "useful," which every child knows, once the rubric is gone that banana utility is enough.

The first time "obviousness" reached the U.S. Supreme Court the Court managed to say enough to guide lower courts for the next quarter century (*21*). By extension, the Supreme Court in *Venter* might say, as the British do for their own purposes, that under our statute a patent must be "capable of industrial application" (*22*). Or the Court might say "substantial" utility *means* substantial, or that when it said in *Brenner* v. *Manson* "specific utility in currently deliverable form," it meant just that, and the NIH patent applications do not measure up. It could say again that patentable inventions must be "related to the world of commerce" (vide "industrial application"). Or it could adopt some better formulation, guided by its own intellect and the help of briefing from interested parties, that incorporates the view that patents are not socially useful if inventions are not substantially useful, as and when first disclosed.

Sole reliance on the Supreme Court approach is fraught with problems: (i) it will take time, while feathers stay ruffled and genome sequencing work is delayed; (ii) the NIH patent claims might be ruled "obvious," raising the possibility that high court resolution of the utility question will become moot (*23*); (iii) the NIH might win in the PTO under the current sloppy standard for utility. Unless the PTO can appeal from its own decision (an unlikely prospect), we may need to await a suit by NIH against an alleged infringer (*24*). In this case, many years may pass before we know what law will control the further evolution of biotechnology. And even if the matter reaches the Supreme Court, the justices might throw up their hands, as they did in *Diamond* v. *Chakrabarty*, and say that changing patent law involves questions too complex for resolution other than by Congress, which is better situated to resolve competing social considerations.

Legislative Remedies

Congress should change law that now permits research efforts that use patented inventions to be shut down. The object would be to free scientific research wherever it gets done from the threat of foreclosure by injunction. The new criterion for injunction should be whether an already patented invention is itself placed into the stream of commerce, as distinct from its being used en route to the invention of a different thing. The middle ground, where research for hire uses someone else's patented invention, should be immunized from judicial foreclosure in the interest of encouraging new discoveries.

Currently, no court that I know of has said use of another's patent by academic scientists amounts to infringement because practice of inventions merely for "amusement, to satisfy idle curiosity, or for strictly philosophical inquiry" is not regarded as infringing (*25*). Perhaps this is so only because no one has yet sued a university for systematic use of patented technology to "do science," coupled with an aggressive program of licensing out the product. But such use happens every day, and these suits will surely come—perhaps as a counter to a suit by a university on its own patents. The more active universities are in asserting their patent rights, for financial rather than "philosophical" reasons, the more likely this is to come around.

As for commercial organizations, any use of someone else's invention seems vulnerable to challenge, including use by such an organization sequences patented by NIH for any purpose. This principle would even apply, for example, to finding out what they are good for (*26*).

The patent statute lets courts shut down by injunction the activities of any who infringe patents (*27*). NIH patents could shut down the efforts of a company aiming to find out whether one of the Venter brain sequences cured Alzheimer's disease, unless terms were agreed under threat of injunction. The patent could shut down university research tinged with such a commercial motive as licensing to industry or having been funded by industry. Congress should therefore change the patent statute to eliminate the possibility of injunction against the use of a patented invention "for research, by any person, for any purpose" (*28*).

What would be left to those who seek to patent the means of discovery? What would be left to those who established banana utility for their patents because the Supreme Court could not or would not root that idea out of law? The answer is reasonable compensation, determined on a case-by-case basis. If parties are unwilling or unable to agree on what is reasonable, courts can do that for them, as they do commonly in imposing "reasonable royalty" as a measure of damages for patent infringement (*29*). If we now leave courts to figure out what a bad nose job is worth in money damages, we might trust them to figure out what an NIH sequence contributed to a cure for Alzheimer's disease!

It would also be useful to amend the patent statute to provide explicitly for product patents on "old" substances when new uses have been found for them, as Europe now permits (*9*). For example: "Previously published protein X, for use in preparing a composition for treating AIDS" (*9*). This would eliminate altogether NIH's excuse for its patent claims that exclusive rights of some kind must be preserved against publication, lest there be no incentive to develop. Here, the patent would be won by the group that did the hard work of inventing something more beneficial to the public than a mere catalog of mystery DNAs.

However, it would be a flat mistake to urge Congress or the courts to now say that DNA or other natural products should be unpatentable even after they have been isolated and their biological activity has been worked out, lest we eliminate patent incentives for the development of important medicines.

Executive Intervention

The White House Office of Scientific and Technology Policy has entered the controversy ignited by the NIH patent applications (*30*). It should expedite reasoned and deliberate resolution of all these interesting questions. To provide NIH the full benefit of the public debate it aims to sponsor, the Executive branch should ensure that the NIH applications and proceedings in the PTO concerning them remain open to public view. This will make clear the full range of control NIH seeks and permit interested parties to follow and to comment to the PTO concerning proceedings that otherwise take place in secrecy.

Finally, let the Executive branch now seek to change federal law to ensure that agencies can prohibit patents on inventions made by their employees where, after due process, the agency determines those are not in the public interest.

NIH should also say that it will support legislation to ameliorate upstream burdens on the ability of science anywhere to deliver public benefit, that it will expedite review of its patent applications right up to the Supreme Court, and that it will charge no more for operation under patents it might win for ESTs than is now charged for access to existing genetic information data banks (*31*).

REFERENCES AND NOTES

1. U.S. Const. art. I § 8.
2. L. Roberts, *Science* **254**, 184 (1991). The NIH applications also claim expression constructs, antisense and triple helix expression blockers, and DNAs that hybridize under stringent conditions to EST-related cDNAs.
3. 35 U.S.C. § 101 (1952).
4. 447 U.S. § 303 (1980).
5. 15 U.S.C. § 3713 (1986).
6. 35 U.S.C. § 103 (1952).
7. *In re Thuau*, 135 F.2d 344 (C.C.P.A. 1943).
8. Title 35, U.S.C.
9. Article 54(5), European Patent Convention. See "Hydropyridine," FRG Federal Court of Justice 20/9/83, Case No. XZB 4183. There is a rebuttable presumption that substances found in commerce are intended for the patented use.
10. 35 U.S.C. § 271(b).
11. 383 U.S. 535 (1966).
12. *Ibid.*, p. 519.
13. *Ibid.*, p. 534.
14. *Ibid.*, p. 536.
15. *Ibid.*, p. 536.
16. *Ibid.*, pp. 534–35.
17. According to Supreme Court Justice Storey, riding circuit and instructing a Massachusetts jury regarding a shoe-making patent in 1817: "whether [the invention] be more or less useful is a circumstance very material to the interests of the patentee, but of no importance to the public. If it be not extensively useful, it will silently sink into contempt and disregard" [Lowell v. Lewis, 15 F. Cas. 1018, 1019 (CC Mass.)].
18. At page 28 of its second application NIH says panels of ESTs can be used to distinguish their organs of origin from others. We might as well say banana sequences can be used to distinguish rain from deciduous forests.
19. S. Usdin, *BioWorld Today* **3** (no. 131), 1 (1992).
20. Friends of the court.
21. Graham v. John Deere, 383 U.S. 1 (1966).
22. This seemingly higher standard might even now prevent retaliatory patenting by British participants in the Genome Project, at least in the United Kingdom and likely elsewhere in Europe, but these and citizens of other countries than the United States (who file about half of all applications for U.S. patents) will be able to patent in the United States to the same extent as NIH.
23. NIH encounters a dilemma when it prognosticates utility for certain human ESTs by pointing to animal sequences of known function in gene data banks. The human homologs can be argued to be obvious from these.
24. Or by a private bill in Congress the review authority of the Court of Appeals for the Federal Circuit might be expanded for this case only, to permit another federal agency, for example, the Department of Justice, to appeal a ruling of the PTO favorable to the NIH.
25. Roche Products Inc. v. Bolar Pharmaceutical Co. Inc., 733 F.2d 858 (Fed. Cir. 1984).
26. An exception is made where the activity is "solely for uses reasonably related" to development and submission of information for FDA registration of a drug. The exception has been construed narrowly. See *Scripps Clinic and Research Found. v. Genentech, Inc.*, 666 F. Supp. 1379 (ND. Cal. 1987). But see *Scripps Clinic and Research Found. v. Baxter-Travenol Laboratories Inc.*, 7 USPQ 1562 (D. Del. 1988).
27. 35 U.S.C. § 283 (1952).
28. According to a report of the House Committee of the Judiciary: "Congress should, at some future point, amend title 35 [the Patent Act] to provide that use of a patented invention or process is not an act of infringement if done for the purpose of experimentation or research." "Transgenic Animal Patent Reform Act" H. Rep. 100-888 at 51, 100th Cong., 2d Sess. (1988). The Report accompanied H.R. 4970 (Kastenmeier), 100th Cong., 2d Sess. (1988), from which the research exemption had been deleted as arguably unnecessary in light of judicially fashioned doctrine. H. Rep. 100-888 at 3.
29. See 35 U.S.C. § 284 (1952).
30. L. Roberts, *Science* **254**, 1104 (1991).
31. The author was formerly vice president and general counsel and vice president for corporate development of Genentech Inc. He authored Genentech's "Friend of the Court" brief in Diamond v. Chakrabarty, in which the U.S. Supreme Court in 1980 affirmed the availability of patents on living things.

32. I thank Paul Berg for asking me to think about this and to address on 3 January 1992 the Program Advisory Committee on the Human Genome, members of the Committee for discussion that ensued, and William Smith of the San Francisco law firm of Townsend and Townsend who contributed to that discussion.