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Human Gene Patents

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ABSTRACT

The concept of a patent on a human gene seems foreign to most people. Even those who understand the fundamentals of the patent system seem bewildered and confused by many issues relating to human genes. This article describes the scope and limitations of gene patents and the types of exemptions that have been proposed or allowed. It addresses and clarifies these and other issues, including the often reported and misdirected question, Who "owns" one's genes? The paper reviews the historical origins of patents as a mechanism to provide incentives for innovation. It also discusses the legal criteria unambiguously supporting patenting of human genes that are isolated and purified apart from their naturally occurring context. Concerning enforcement and issues related to academic research, there is no U.S. statutory exemption for non-commercial research on patented subject matter, but a narrow, judicially-created exemption does permit use of patented subject matter for non-commercial purposes. Patents and licenses on gene-based diagnostic tests are properly enforceable and do not permit academic or other clinical practitioners to practice such tests without license or other authorization from the patent holder. The paper concludes that an effective legal system cannot draw sharp distinctions that some genes or uses are patentable to some parties while other genes are not. In addition, precluding certain genes from patentability would be shortsighted in that it would create prohibitions that might well be regretted in the future.

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The concept of a patent on a human gene seems foreign to most people. It feels strange that someone can acquire private property rights over something as fundamental as the genetic makeup of a human being. Even those who understand the fundamentals of the patent system seem bewildered and confused by many issues relating to human genes. How is it possible to patent genes? Who owns our genes? Will patents on genes impede basic research? These are but some of many questions that we discuss in this paper.

WHAT IS A PATENT?

A patent is the embodiment of a social contract between an inventor and his or her government: If the inventor thoroughly discloses his or her invention to the public, the government in turn will enforce the inventor's right to be the only one who may commercialize it for about 20 years. The invention has to be useful, novel, and non-obvious and must be fully described. If the invention is neither useful, nor novel, nor non-obvious, nor is it fully described, the government cannot grant the patent, and if it grants the patent by mistake—a not uncommon occurrence—it can then revoke it. The full description requirement assures that inventions, especially industrial inventions, do not remain hidden for too long. This requirement is the cornerstone of the patent idea: That scientific and technical openness benefits the progress of society more than do confidentiality and secrecy.

Patents are granted for all kinds of inventions, such as chemical compositions, mixtures, machines, methods of manufacture, methods of use, and—coming to the point of this paper—human genetic materials.

We discuss how it is possible legally to patent natural substances such as genes, what kinds of human gene patents the U.S. Patent and Trademark Office (PTO) is issuing, and how easy or difficult it is to obtain them. Once obtained, the patents are either ignored or enforced, so we next discuss who has the right to enforce them and against what activi-

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ties, paying special attention to the roles of universities and those carrying out academic research. We end the paper with a discussion of the historical, economic, and philosophical rationales for a patent system and whether any of these apply to the patenting of human genes.

HOW CAN ONE PATENT NATURAL SUBSTANCES SUCH AS GENES?

Since natural substances, by definition, already exist in nature, they are not "novel" and cannot be patented. Thus, insulin or its gene as they exist in nature cannot be patented. However, the courts have long recognized that purifying or isolating materials from nature makes them novel and, thus, patentable. This is because "isolated" or "purified" materials do not exist in nature. Let us provide a few examples.

Purified proteins. The oldest-cited case with regard to patenting of pure natural substances is *Parke-Davis & Co. v. H.K. Mulford & Co.* (1912), where the applicant had patented adrenalin.[1] The first claim of the patent was as follows:

> A substance possessing the herein-described physiological characteristics and reactions of the suprarenal glands in a stable and concentrated form, *and practically free from inert and associated gland tissue* [emphasis added].[2]

The Court held that a substance derived and purified from nature could be patentable.[3]

Purified prostaglandins. In *In re Bergstrom* (1970) the inventors claimed "naturally occurring" prostaglandin compounds PGE2 and PGE3 that they had extracted and purified from the prostate gland.[4] The claim was as follows:

> 7-[3-hydroxy-2(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, *said acid being sufficiently pure to give a substantially ideal curve on partition chromatography* using an ethylene chloride: heptane: acetic acid: water (15:15:6:4) solvent system [emphasis added].[5]

The court held that the "sufficiently pure" prostaglandins did not exist in nature and ruled these to be patentable.[6]

Purified microbial cultures. In *In re Bergy* (1977) the applicant claimed a culture of a naturally occurring bacteria that produced an antibiotic.[7] The claim was to "a . . . biologically pure culture of the microorganism *Streptomyces vellosus* . . ."[8] The court again held that "biologically pure cultures" of microorganisms did not exist in nature and could be patentable.[9]

A few years later the Supreme Court in *Diamond v. Chakrabarty* (1980) held that a human-made non-natural microorganism was patentable.[10] The applicant in that case had genetically altered the bacteria to consume crude oil.[11] The Court stated that "anything under the sun that is made by man" is patentable.[12] Since a genetically modified microorganism such as that of *Chakrabarty* was not even a product of nature, the legal analysis was simpler than in *Bergy*.

Purified strawberry flavor extracts. In *In re Kratz* (1979) the patent was to compositions and methods involving a natural compound imparting a strawberry flavor.[13] Claim 18 stated:

> A flavor modifying composition useful in imparting a strawberry flavor to a foodstuff consisting essentially of (i) from 1 to about 20% by weight of said flavoring composition of synthetically produced *substantially pure* 2-methyl-2-pentanoic acid . . . [emphasis added].[14]

The Court held that the applicants tried to claim the compound only in a "substantially pure" form that did not exist in nature.[15] It was therefore patentable.

Purified DNAs. Since purified adrenalin, prostaglandin, microbes, and strawberry flavors are patentable, it follows that purified DNAs are too. As expected, the PTO will allow (and the courts will uphold) claims to DNAs, but only if they have been isolated or purified. Illustrative is *Ex Parte D* (1993), where an anonymous applicant unsuccessfully tried to patent a DNA sequence coding for human tissue plasminogen activator.[16] He requested the following claim:

> A DNA sequence containing the DNA sequence coding for human tissue plasminogen activator produced by human normal cells.[17]

The PTO ruled that the claim did not contain any indication that the DNA sequence had been isolated or purified, and rejected the claim partly because it was directed to a naturally occurring substance.[18] The clear implication is that had the claim contained language of isolation, it would have been granted. And that is precisely how human gene patents are obtained.

WHAT KINDS OF HUMAN GENE PATENTS IS THE PTO ISSUING?

The PTO is issuing patents to isolated or purified human genes encoding protein drugs, diagnostic probes, receptors, immunogens, and gene replacement therapies. Here are a few examples.

DNA encoding protein drugs. Genentech, Inc. received a patent (1988) for DNA encoding human tissue plasminogen activator (TPA).[19] Claim 1 of the patent reads as follows (note the word "isolate"):

> A DNA *isolate* consisting essentially of a DNA encoding human tissue plasminogen activator [emphasis added].

The Japanese Foundation for Cancer Research obtained a patent (1994) related to DNA that codes for a polypeptide with interferon activity.[20] Claim 1 of that patent reads:

> A DNA *which consists essentially* of a DNA which codes for human fibroblast beta 1 interferon polypeptide [emphasis added].

Note the phrase "consists essentially of," which is meant to exclude the DNA in its natural state.

Kiren-Amgen obtained a patent (1987) for "purified and isolated" DNA sequences encoding erythropoietin.[21] Claim 1 of that patent reads:

> A *purified and isolated* DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:
> (a) the DNA sequences set out in FIGS. 5 and 6 or their complementary strands; and
> (b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a) [emphasis added].

ARCH Development has patented (2001) "isolated and purified" polynucleotides encoding calpain 10 that can be useful in diagnosis and treatment of type 2 diabetes.[22] Claim 1 of that patent reads:

> An *isolated and purified* polynucleotide comprising a region encoding human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10 [emphasis added].

DNA encoding diagnostic probes. OncorMed has obtained a patent (1988) for coding sequences of the BRCA1 gene.[23] These sequences can be used for screening individuals with an increased genetic susceptibility to breast or ovarian cancer because of the inherited mutation of the BRCA1 gene. Claim 1 of that patent reads:

> An *isolated* coding sequence of the BRCA1 gene as set forth in SEQ. ID. NO.: 5 [emphasis added].

University Technologies has obtained a patent (2001) for a tumor suppressor gene DNA designated ING1.[24] The claim reads:

> An *isolated* nucleic acid comprising a sequence selected from the group consisting of:
> (a) a nucleic acid sequence of at least 200 nucleotides which is a portion of SEQ. ID. NO.: 9 or the complement thereof; and,
> (b) a nucleic acid sequence of at least 200 nucleotides which hybridizes to SEQ. ID. NO.: 9 or the complement thereof, under stringent conditions [emphasis added].

This DNA sequence is useful for diagnosing breast or brain cancer and for decreasing proliferation of cancer cells in patients diagnosed with such cancers.

DNA encoding targets such as receptors. Human Genome Sciences, Inc., has obtained a patent (2001) for polynucleotides encoding human tr10 receptor, a member of the tumor necrosis factor (TNF) receptor superfamily and the TRAIL receptor subfamily.[25] The first claim reads:

> An *isolated* nucleic acid molecule comprising a polynucleotide sequence selected from the group consisting of:
> (a) a polynucleotide sequence encoding amino acid residues -55 to 331 of SEQ. ID. NO.: 2; . . . and
> (g) a polynucleotide sequence encoding a fragment of the polypeptide of SEQ. ID. NO.:2 wherein said fragment binds a Tumor Necrosis Factor (TNF)-family ligand [emphasis added].

The expressed receptor is useful in high-throughput drug screening for TNF agonists or antagonists.

WHAT DO "ISOLATED" OR "PURIFIED" MEAN?

Note that all of the claims we have exemplified use words such as "isolated," "purified," or "consisting essentially of," so that these patents are consistent with the adrenalin, prostaglandin, and strawberry flavor precedents. It is fair to ask, however, what these words mean. How purified? Isolated from what? Generally, "purified" means excluded from the way the particular DNA occurs in nature.[26] However, the term "purified" does not have an exact and identical definition in all circumstances. Applicants are encouraged to define the term in the patent specification for each case.[27] The term "isolated" also should be defined in the patent specifications. The "Utility Examination Guidelines" that the PTO uses in evaluating all patent applications interpret the word "isolation" to mean separation of DNA "from its natural state."[28] So, at the very least, the "isolated" DNA cannot be identical to any naturally occurring DNA.

As could be expected, there has already been litigation on the interpretation of patent words used to denote degrees of purity. The Court of Appeals for the Federal Circuit (CAFC) in *Johns Hopkins v. Cellpro* (1998)[29] had to interpret the meaning of certain language used by inventor Civin with the intent of defining how pure a claimed mixture of stem cells had to be. Civin's claim read:

> A suspension of human cells comprising pluripotent lymphohematopoietic stem cells *substantially free of mature* lymphoid and myeloid cells [emphasis added].[30]

In trying to understand what "substantially free of mature cells" meant, the court turned to Civin's own definition. Civin, however, had failed to clearly define what he meant by the critical phrase.[31] The court, therefore, construed the claims to encompass at least the disclosed examples of the patent, and concluded that the claims required less than 10% mature cells.[32] This interpretation was pivotal to Civin's (and Johns Hopkins') success in the lawsuit.

HOW DIFFICULT IS IT TO OBTAIN HUMAN GENE PATENTS?

Novelty and non-obviousness. The PTO and the courts have made the obtainment and upholding of human gene patents a relatively easy task when tested against novelty and non-obviousness. For example, an isolated human gene is not novel only if it has been isolated previously and the details of its isolation—which should at least include its characterization, such as the DNA sequence—are in the public domain. In the United States (but not in Europe) an isolated human gene is non-obvious even if the sequence of the protein it encodes was already in the public domain.[33] The reason is that a protein sequence could be encoded by myriad DNA sequences due to the degeneracy of the genetic code. Any one of those DNA sequences (and even certain subgroups of sequences) is not obvious. An isolated DNA sequence encoding the complete open reading frame for a gene is still not obvious even if a partial subsequence was in the public domain. The reason is that under U.S. law the existence of obvious methods to find genes does not render specific gene sequences (or subgroups of sequences) obvious.

Utility. In contrast to the relative ease of overcoming the non-obviousness requirements for human gene claims, the PTO is stricter with the requirement that the gene be "useful." In January 2001, the PTO issued the "Utility Examination Guidelines," under which its examiners will test the utility requirements of U.S. patent law.[34] The PTO has indicated that it will apply a three-way test in its examination for utility. To be acceptable, a utility has to be "credible," "specific," and "substantial."[35]

A brief explanation may help clarify these criteria. Let us assume an applicant applies for a claim to a sequence encoding what he asserts is a novel form of the hormone insulin. However, if the examiner realizes that the sequence is homologous to the well-known enzyme trypsin and the data in the specification are inconsistent with hormonal activity, the examiner may reject the claim for lack of "credible utility." If all an applicant says in his specification is that a novel sequence encodes a receptor, without specifying what kind, then the utility is said by the PTO to not be "specific" enough. Finally, if all an applicant says in the specification is that the sequence encodes a protein and that the use is to do research on its function, the PTO will say that this is not "substantial," or "real-world," utility.

The PTO has published its own illustrative examples of genes that satisfy the utility requirement and those that do not. A few of these examples follow:

1. An uncharacterized gene with a known sequence but no disclosed utility and no further chemical, physical, or biological properties does not satisfy the utility requirement.
2. Thousands of DNA fragments from a human epithelial library disclosed to be a part of a coding sequence for an epithelial protein, with the only disclosed utility being to study its use by finding and expressing the protein, does not satisfy the utility requirement.
3. Several thousand open reading frames from a library, one of which is identified as being a ligase by homology similarity: that one satisfies the utility requirement.
4. A DNA sequence for a receptor protein isolated from a membrane preparation that binds to partner X of unknown function, with a utility in assays for X, does not satisfy the utility requirement.
5. Same as in 4, but with a selective appearance of the receptor DNA in melanoma cells, satisfies the utility requirement.

Example 3 shows that the PTO will consider homology similarity to be sufficient to confer credible, specific, and substantial utility. In other words, without doing any "wet chemistry," an applicant can obtain a claim to DNA and deduced protein sequences based purely on bioinformatics. Of course, if the functional annotation is ultimately proven to be false, then the claims would be found invalid. This is the case even if the true use is later discovered by others. A real use must be present in the application on the date it is filed.

Gene fragment claims: the scope problem. One of the areas of most controversy in the patenting of human genes has been the filing of claims on gene fragments, the so-called expressed sequence tags (ESTs). Take for example a classic patent claim to an EST:

> An isolated DNA *comprising* the sequence of EST #1.

Let us assume for simplicity that EST#1 is a cDNA fragment which, because of sufficient homology with prior art sequences, is concluded to encode part of the complete open reading frame (ORF) for the gene of an enzyme whose absence causes a severe metabolic deficiency. The complete ORF will encode the enzyme, and the administration of the enzyme (as protein) to deficient patients has been well understood and described in the literature. In addition, the EST encoding part of the ORF for the enzyme is useful in pre- and postnatal DNA diagnostics. These assumptions are

made here so that the utility of the EST is not at issue in our example. (If the fragment does not have homology to anything known in the databases and thus has no acceptable utility, it is unlikely that it will be patentable in the first place). The only issue before the PTO in this example, then, would be that the applicant is seeking a claim to a useful fragment of the enzyme gene, does not yet know the complete DNA sequence, and is requesting a claim with the word "comprising" in it.

To understand the importance of the issue it is necessary to know that the word "comprising" has a special meaning in patent law. It means "including." When a claim uses this word, it is "open-ended" to the addition of elements not recited in the claim itself, and would be infringed even if the accused sequence contains elements other than EST#1. In contrast, if a claim were to use the word "consisting" (as in "An isolated DNA sequence *consisting of* the sequence of EST#1") the claim is said to be "closed," and is not infringed by the addition of other, unrecited elements to the basic elements of the claim. Thus, a claim to the EST with the word "comprising" may be found to encompass the complete ORF when discovered, while a claim with the word "consisting" will not encompass the complete ORF and will be limited to the EST#1 known at the time of filing and nothing more.

The Court of Appeals held in *Genentech v. Chiron Corp.* (1997) that claims to DNA sequences with the word "comprising" in them are open-ended and encompass DNA constructs that include other non-recited sequences.[36] The Court said:

> "Comprising" is a term of art used in claim language which means that the named [DNA sequence] elements are essential but other [DNA sequence] elements may be added and still form a construct within the scope of the claim.[37]

The Court's holding gave concern to those in the gene-hunting business. Open-ended claims to useful ESTs containing the word "comprising" such as those of our example would, under the *Genentech v. Chiron* rationale, dominate later discoverers of the complete ORFs, forcing both sides to cross license for the commercial use of the ORF. It seems that the PTO has taken the side of those concerned by this result, and now adheres to the position that it will not allow claims to useful ESTs with the word "comprising" in them. The PTO's rationale is that unless the ORF is described in the specification, a claim will not be allowed if it would "read on" or dominate the ORF. This is a controversial position because, if carried to its logical conclusion, it would disallow the use of open-ended language when there is a possibility that a claim would dominate any unrecited genetic elements, such as fused sequences. Such a position is not without supporters, and only a specific decision on an EST claim by the Court will lay the controversy to rest.

THE ENFORCEMENT OF PATENTS ON HUMAN GENES

We have so far discussed the question of whether and how the PTO will grant patents on human genes. This, however, represents only half of the equation. The other half deals with what to do once such a patent is obtained. What kinds of activities may infringe the rights of the owner of a human gene patent?

Generally speaking, infringement occurs when someone makes, uses, sells or offers to sell a patented isolated or purified human gene or a construct containing such a gene. In addition, it is patent infringement to import an isolated gene made by a process patented in the United States. These activities—making, using, selling, or importing—are generally known as "direct infringement." It is also possible to aid and abet such activities if one induces or contributes to the using, making, selling, or importing. Such activities, not surprisingly, are known as "indirect infringement."

The question now arises as to whether all making, using, selling, importing, inducing, or contributing to these activities constitutes patent infringement. The answer is "No." There are in the law both Congress-enacted and judge-created exemptions.

Congress-enacted exemptions. Over the years, the Congress has developed a body of statutes that provide certain specifically defined exemptions to patent infringement.

Clinical research. Anyone who wishes to obtain regulatory approval under the FDA statute for the manufacturing of a protein drug using patented recombinant DNA technology is immune from liability for patent infringement for all "reasonably related" activities.[38] Such a person or company may, without fear of liability or injunction, make a patented gene construct, create a recombinant host with it, express a protein from it, and sell it to any other entity involved in carrying out clinical research. If the activities are not reasonably related to obtaining U.S. FDA approval, however, the infringer loses his or her immunity and becomes liable for patent infringement. As the reader can imagine, the scope and extent of this so-called "clinical research exemption" are the source of a fair amount of litigation.

Medical procedures. Of particular interest to our readers is the "medical procedures exemption" to patent infringement.[39] This section of the patent statute exempts any "medical practitioner" or "related health care entity" from injunction or damages if the practitioner or entity is carrying out a "medical or surgical procedure on a body." The "entity" includes nursing homes, hospitals, medical schools, HMOs, or group medical practices. The scope of the exemption, however, is extremely narrow and applies mainly to operations and in vivo diagnostic procedures, but not to the instruments used. For example, while a doctor may carry out a patented diagnostic procedure on a patient (say, for

example a novel colonoscopy technique) free from fear of liability, he may not use a patented probe in the procedure.[40] Likewise, he may freely use a patented method of administering genes to the patient, but may not freely use the patented genetic constructs or isolated human genes. The narrowness of this exemption is responsible for its very limited role in the overall scheme of things.

Judge-created exemptions. Other than the statutorily defined exceptions, there is no generalized experimental use exception to patent infringement in the United States. There is a very narrow judge-created exemption to patent infringement for anyone who makes, uses, or sells a patented invention purely to satisfy scientific curiosity or for philosophical reasons. For example, a university professor might investigate the ability of a patented gene to produce human EPO, or a company researcher might try and reproduce a patented DNA hybridization assay to confirm that it works. If they go no further than their noncommercial investigations it is highly unlikely they would be found to infringe. However, if they were to work with the patented materials or assays with commercial intent, it is equally likely that they would be liable for patent infringement.

The test used in the United States today for determining whether an activity is actionable patent infringement is whether the activity is carried out with commercial intent. It is generally assumed by commentators that anything a corporation does has some sort of commercial intent, no matter how remote. On the other hand, the activities of most university laboratories are without any commercial intent, and therefore, are not actionable patent infringement. Universities, however, have slowly been blurring the boundaries between commercial and noncommercial activities. For example, a university laboratory that is fully funded by the corporate research grants of a major multinational corporation, and has contractually committed to give the corporation exclusive patent rights, might have a difficult time arguing that the research it is carrying out does not have ultimate commercial intent. A medical school laboratory that runs a diagnostic service utilizing patented human gene sequences might have a difficult time arguing that it is doing so purely for curiosity or philosophical purposes.

It is, therefore, quite conceivable that a university could be sued for patent infringement if its activities were to cross the border from philosophy to commerce.* Few, if any universities, however, have been sued for patent infringement.

Compulsory licensing. Is there then in the United States an absolute right to stop any and all patent infringers who have commercial intent? Yes, the right to injunction is considered to be pretty much absolute: If a *commercial* infringer does not fall under the clinical research or medical procedures immunities, it could be permanently enjoined from continuing its activities. In many other countries in the world, however, it is possible—under certain narrow circumstances—for an infringer to obtain a so-called compulsory license. This license amounts to a court-enforced contract to make, use, or sell a patented invention in exchange for a royalty. The patent statutes in the United States do not contain provisions for compulsory licenses, and the courts have rarely, if ever, granted such licenses. One could, however, envision a situation where a dire public need, such as the AIDS epidemic, might lead a court to force the holder of a patent on certain successful viral gene constructs to grant a license to manufacture vaccines to the only commercial lab in the world with sufficient capacity.

The reader might be familiar with the recent controversial lawsuit by several multinational pharmaceutical companies against the government of South Africa. The subject matter of these lawsuits was the constitutionality of price controls on patented drugs against HIV/AIDS. The resolution of the lawsuits was based—ironically—on the acknowledgment by the companies that the government of South Africa had the right under international treaties[41] to force compulsory licenses of the companies' HIV drugs in order to ameliorate the health emergency in that country. Given the adverse publicity generated by the lawsuit, the companies much preferred a regime of compulsory licensing to price controls. They saw it as the lesser of two evils.

WHO "OWNS" YOUR GENES?

With the issuance of all of these patents to human genetic material, the popular press has become fond of asking the question of who "owns" a person's genes. We submit that this is the wrong question. A more appropriate question is, Who owns the *intellectual property* associated with a person's genes? The threshold question as to whether anyone *may* own intellectual property on genetic material has been answered clearly in the affirmative, as we have demonstrated above. Newly discovered genetic material can be patented as long as it is isolated from its natural environment and purified so as to separate it from extraneous material.

Thus, does the existence of a patent owned by Amgen on purified genes for EPO, or by Genentech on isolated genes for TPA, mean that Amgen or Genentech owns my genes for these proteins? Of course not. The genes in my body are neither "purified" nor "isolated." Consequently, these companies' patents do not cover my genes, and that settles the issue.

What happens if the EPO genes are isolated from my

*As predicted, Duke University was recently held to be potentially liable for patent infringement notwithstanding its academic, nonprofit status, in that the accused activities "unmistakably further the institution's legitimate business objectives."[40a]

body? Who owns them now? There is some precedent for this. The courts have taken the position that a person does not own any tissues or cells once they are outside the person's body.[42] They belong to the doctor or hospital. In *Moore v. Regents of U. of California* (1990), a patient (Moore) sought ownership of a cell line that the University of California (UC) researchers had developed for cancer research using his cells.[43] The Supreme Court of California held that, for policy reasons of promoting medical research, a person does not retain ownership of any tissue or cells that have been excised from the person's body with his informed consent.[44] The same would logically and legally be true for DNA material excised from the body. Thus, if EPO genetic material is isolated from me with my informed consent, I cannot lay claim to owning it anymore.

Let us now go one step further. Let us assume that my EPO genes are isolated from my body, and that through some arrangement with my physicians and hospital I maintain ownership of these materials. Would I be free to commercialize (i.e., use, make, or sell) them if Amgen held a patent on them? The answer is No. I would certainly own the tangible EPO gene taken from my body, but not the intellectual property associated with it. I could not commercialize the material I own. This is analogous to owning a copy of *Harrison's Principles of Internal Medicine*, but not its copyright. Its copyright is owned by McGraw–Hill Publishing Company. Only McGraw–Hill has the right to reproduce the book. I own the *tangible property*, the book, but McGraw–Hill owns the *intellectual property*, the copyright. They are two different concepts.

There has recently been an interesting case in the bid to control the fate of isolated patented genes. Sharon Terry, the mother of children with the genetic connective tissue disorder PXE, pseudoxanthoma elasticum, apparently helped with the conception of the gene discovery itself.[45] This made her a co-inventor and, therefore, a co-owner of a patent application on the isolated genetic material. As a co-owner of the intellectual property rights she may be able to control to a larger or lesser extent how the gene patent will be exploited and might be able to steer research towards finding a treatment for the disorder. This situation is unusual because it is highly uncommon for tissue donors or patient providers to be legally entitled to co-inventor status of patents in derived materials (An inventor has to provide conceptual solutions to a problem at hand, not just tissues). Nevertheless, the PXE case reflects a growing unease among patient groups with the widespread commercialization of what they—legal accuracy aside—perceive to be their biological property.

WHO HAS BEEN SUED FOR PATENT INFRINGEMENT ON HUMAN GENE PATENTS AND FOR WHAT ACTIVITIES?

Predictably, the cast of characters in the dozens of lawsuits involving human gene patents has been composed mainly of corporations. For example, in 1994, Genentech sued the Wellcome Foundation on its isolated TPA gene patent, asserting that Wellcome's modified TPA infringed, although Wellcome's TPA was missing a region of the native protein.[46] The court found that the "TPA" in the claim referred to naturally occurring TPA and did not dominate the modified TPA of Wellcome.

In 1996, Novo Nordisk sued Genentech seeking a declaration from the court that Novo did not infringe Genentech's patent on a recombinant process of making human growth hormone (hGH).[47] The issue was whether Genentech's patent included cleavable fusion expression of hGH or whether it was merely for direct expression of hGH.[48] The court held that the claim included only the direct expression of hGH, and that Novo Nordisk did not infringe.[49] Genentech then returned to court with a follow-up lawsuit on a second patent, claiming another method of producing hGH.[50] The court, however, frustrated Genentech again, holding the second patent invalid for failure to sufficiently disclose how to make the claimed materials.[51]

Since U.S. universities have entered the arena of biotechnology patenting in force, a number have also found themselves involved in lawsuits. In some cases the universities have asserted their rights in patents they own, license, or assign and are, therefore, plaintiffs in these lawsuits. In other cases they have been sued by plaintiffs seeking to declare the university-owned patents invalid and/or not infringed. For example, in 1999, Carnegie Mellon University sued Hoffman-LaRoche, which was manufacturing DNA polymerases that the university alleged were infringing on its recombinant DNA patents.[52] The university lost, and Hoffman-LaRoche was found not to infringe Carnegie Mellon's patent.[53]

The University of California (UC) in 1997 sued Eli Lilly on its patents claiming recombinant methods of producing human insulin.[54] Eli Lilly countersued for patent invalidity. The university tried to argue that as an agency of the State of California it was immune from Lilly's counterclaims, but the court held that the university had waived its immunity by bringing the suit in the first place.[55] The court further held that the claims were invalid because the written description specific to rat insulin cDNA was inadequate to describe human insulin cDNA.[56] Lilly was found not to infringe any of UC's patents.

Then, in 1998, Genentech sued UC in an action to declare the university's patent on recombinant DNA transfer vectors for human growth hormone invalid, unenforceable, and not infringed.[57] The parties settled before the court could decide on any substantive issues.

There are very few cases alleging patent infringing activities by universities and none on gene patents. In one reported case, Teknekron Software Systems sued Cornell University in 1993 for patent infringement, alleging that a

networking program distributed by a Cornell subsidiary infringed Teknekron's patent.[58] Again, the court did not decide any substantive issues.

On the other hand, universities have been sued on a number of patent-related issues other than infringement. For example, in 1994, in *Brown v. Regents of the University of California*, Mrs. Brown claimed that she was entitled to co-inventor status of a university patent because she had played a role in discovering a feline virus, having provided and taken detailed notes on the cats' illnesses.[59] The court, however, held that she was not a joint inventor of the patents in question.

Professor Kucharzyk in 1999 sued UC for breach of contract.[60] The professor had signed an employment agreement assigning to the university all patents that resulted from his employment with the university.[61] An additional clause stated that the professor would get 50% of all the royalties the university earned from the patents.[62] The professor claimed that UC did not get the "best deal" on its exclusive license to Nycomed, a company that was supporting the university financially.[63] The court held that since the professor had assigned his invention to UC and there was no evidence that the university had acted in bad faith in licensing the patent, Professor Kucharzyk had no right to dictate what kind of license agreement the university could sign.[64]

The lack of patent litigation on universities' potentially infringing activities is not surprising. The legal boundaries between commercial activity and bona fide research are unclear when it comes to universities, and any corporation suing a university for patent infringement needs to deal with a potential public relations problem, in that it could be depicted in the press as squelching scientific research on the altar of commerce.

WHAT CONTROVERSIAL ACTIVITIES ARE GOING ON IN THE MARKETPLACE?

The marketplace has, generally speaking, absorbed the existence and impact of patents on isolated human genes quite well. Patented genetically-engineered human protein drugs, as well as antigens, vaccines, and diagnostic probes, are available. The patents on these products are for the most part respected. Of course, there is litigation, but not dramatically more so than in other active fields of high technology. There is no doubt that when an important human gene patent issues, the competitors of the owner go into high gear in their attempts to invalidate the patent and/or to circumvent and design around it. "Inventing around" is an activity that benefits society in that it leads to technological advances. It is one of the positive consequences of a healthy patent system.

We discuss here some activities that have become the source of controversy, in order to shed some light on the underlying issues.

Cease and desist letters. In an article published in the *AAMC Reporter* in 2000, Dr. Debra Leonard, director of the Molecular Pathology Laboratory of the University of Pennsylvania Health System, complains that she has apparently received several cease and desist letters from patent holders or their licensees, insisting that the laboratory stop conducting tests for a number of neurodegenerative diseases because they utilize patented materials such as, we assume, patented DNA sequences.[65] This is lamented by her and Gina Shaw, the writer of the article, as representative of "modern medical science." Dr. Leonard says: "We may have spent years developing these tests, and educating our clinicians in performing them. They become the standard of medical practice. Then the patent is issued, and one or two labs get the exclusive licenses, and we can't do the testing for our own patients. We can't give academic input to clinicians who have specific questions about testing. We can't do further research."

Further evaluation of the situation, however, reveals that the Molecular Pathology Lab advertises itself on the Web very much in commercial terms.[66] It says that it

> offers broad experience in diagnostic and monitoring applications using molecular techniques. A variety of regional, national and international clients take advantage of the laboratory's expertise on a regular basis. Molecular assays may be integrated with comprehensive consultative services (e.g. hematopoietic neoplasia) in the Department. Our network of clinical and basic research collaborations ensures that we can offer you the latest useful tests. Our staff is available for basic science research consults as a Core Research Facility.

Note that their Web page talks in terms of "national and international clients," having access to the "latest useful tests." The "basic science research consults" are treated almost as an afterthought. In other words, this laboratory appears to be a revenue-generating facility, as it is entitled to be. And while it may be concerned about receiving cease and desist letters from patent holders, it would have no defense that it is just doing research for philosophical purposes. Any activities with commercial intent, as we have seen, are patent infringements. Dr. Leonard is not prevented from giving advice on the tests to the physicians at her hospital. She might even be able to carry out research on the tests to see whether they work and how to improve them. She is not prevented from doing academic research, as she complains. In fact, if she can prove that she developed the tests before the filing of the adverse patent applications, she might even invalidate the patents by showing prior invention, use, or sale. But what she cannot do without a license is to make, use, or sell the tests with commercial intent.

Restrictions on dissemination. A more difficult problem, in that it affects purely academic researchers as well as commercial entities, is the existence of a plethora of barriers to free dissemination of biological materials such as genes, antibodies, and cell lines. We are all painfully aware that before access is given to such materials, the recipient is routinely urged to sign a long contract that imposes restrictions on the ultimate use. The contract may prevent further dissemination, may prevent use for commercial purposes, may request grant-backs of ownership to future intellectual property developed with the materials, may request preview of publications, and generally creates roadblocks to the quick availability of valuable research tools. We in the legal community are as guilty as anybody in coming up with ever-more-creative ways to maximize the benefits for our clients. If we represent the recipients, we negotiate even harder to soften the restrictions or to eliminate as many as them as possible. The result is delay and frustration to all parties, especially the scientists.

The National Institutes of Health (NIH), aware of the situation, created a working group that published a study in 1998[67] and subsequently issued a set of *Principles and Guidelines for Recipients of NIH Research Grants* in 1999.[68] In these documents the NIH urges the increased use of a short Uniform Material Biological Transfer Agreement, promotes without legal entanglements the dissemination of research tools developed with its support, and undertakes review and strengthening of NIH policies for sharing research tools and materials. The policies of the NIH essentially are to maintain academic freedom, including the freedom to publish research findings, and to continue to implement the Bayh–Dole Act that mandates technology transfer. Reflective of the increased consciousness raised on these issues, a recent amendment to the Bayh–Dole Act, called the Technology Transfer Commercialization Act of 2000,[69] mandates that inventions by nonprofit organizations and small businesses are to be "used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery." While it is too early to evaluate the success of these efforts, a healthy public debate has been occurring on these topics since at least 1997, and many technology transfer specialists have become more keenly aware of the negative consequences of lengthy and onerous contractual negotiations.

DISCUSSION

The history and philosophy behind the patent system. In the 15th century there was a steady migration of artisans from Byzantium into Europe. They were skilled in the arts of silk, powder, artillery, canals, and cuisine

The Venetians wanted to keep them in Venice, and so they devised a system of incentives, which in effect said that the artisan would, if he stayed there for a long period of time, be the only one in Venice to practice his craft if the craft was novel. While the foreign artisan remained in Venice, however, he had to teach the local artisans fully and completely what he knew. Then he could leave.[70] One can see that the basic components of our present day Jeffersonian patent system were there already: full disclosure in exchange for a state-enforced monopoly of limited duration.

We could call this the *full disclosure* conceptualization of patents. It is understood best when applied to the otherwise secret knowledge of 15th-century artisans and 21st-century corporations. Without patents, the knowledge remains secret, and society does not benefit. A modern corporation will not reveal its trade secrets unless it gets something in return.

Another, less academic and more *financial*, view of patents is that they are devices for allowing investors to take risks more willingly. In this conception, patents are essential to capital formation for unproven technologies. Abraham Lincoln said that they work like fuel: "The Patent System [adds] the fuel of interest to the fire of genius.[71] A modern corporation will not invest to develop a risky technological proposition without having the exclusive rights to it, even if only for a limited period, in order to profit from its investment or at the very least to recoup its investment.

There is also a philosophical underpinning of the patent system based on the so called "tragedy of the commons." When a population is faced with commonly owned property and has no incentive to conserve or replenish it, the common property may be wasted. If everyone's sheep graze on the public commons, the commons will be overgrazed and disappear as a resource for the town. Only by privatizing the commons and allowing its rental does society provide the necessary incentive for conservation. Applying this concept to the patent system, it is said that technology that is published and dedicated to the public is wasted. Only by privatizing bits of it (those that are novel, non-obvious, useful, and fully described) for limited periods of time is it possible to exploit it for the benefit of all. This philosophical debate took place in 1980 and became the cornerstone of the Bayh–Dole Act, which allows U.S. government grantees to have exclusive rights in federally funded technology, and to license the same exclusively or non-exclusively to firms in the private sector.

The classic pharmaceutical industry. The poster child for the *financial* model of patents is the pharmaceutical industry and its development of synthetic chemical drugs. It is at the interface of organic chemistry and private pharmaceutical research that the *financial* conceptualization of patents works best. PhRMA, the Pharmaceutical Research and Manufacturers of America, estimates that it costs an average of $500 million to discover and develop one new medicine. It takes 12–15 years to bring a new medicine from the laboratory to

the pharmacy shelf. Only one in 5,000 to 10,000 compounds screened eventually becomes a new drug.[72] These numbers and the consequences for the public health system make an easy case for a strong patent system that encourages risk-taking. The *full disclosure* model is not as applicable to the pharmaceutical industry because by selling a drug a company puts it in the public domain, and the secrecy of its formulation is then lost in any event. Same with the "tragedy of the commons" and the need to privatize: these are not applicable here because most of the industry does not operate with public funds, and its discoveries start off as being private property anyway.

The academic entanglement with patents. Most of the classical research on synthetic drugs has been carried out, and continues to be carried out, by private industry. Human gene research, especially in its uses and applications, however, can be found equally in the labs of companies such as Amgen and Genentech and in those of academic institutions such as the University of California, Columbia, and MIT. It is hard to explain the role of patents in academia using the *full disclosure* model, since it is not necessary to offer exclusivity incentives to a university in order to get it to publish. The raison d'etre of academic research is to publish. The *financial* model alone does not explain the role of patents in academia either, unless one considers it in conjunction with the "tragedy of the commons." It is useful in this analysis to distinguish two types of inventions: specific inventions and platform technologies.

Specific inventions. Let us first isolate the role of patents in universities by analyzing it in the context of synthetic drugs. In order to develop a specific university-invented synthetic drug into a commercial pharmaceutical product, it has to be taken out of the "commons" by privatization. No firm will invest in publicly available knowledge because there does not exist the possibility of exclusivity in order to recoup investments. Published synthetic drug discoveries linger in the journals without exploitation. The patenting of synthetic drugs that are the results of university research provides the necessary exclusivity, through licensing to risk-taking firms, to raise capital and bring the discovery to the public.

Platform technologies. On the other hand, there are university-made inventions that, regardless of the patent system, will be used by industry and will have a major impact on society. We include in this category what we would call *platform* technologies. Examples of platform technologies are the Cohen Boyer invention of gene transfer, and all of the genetic paraphernalia employed in the process: plasmids, transformed hosts, etc.[73] This invention had such a fundamental impact on society that the biotech industry would have used it whether Stanford and UC had patented it or not. These universities did indeed obtain U.S. patents on the technology, although the patents were almost an afterthought.[74] In fact, the two universities missed foreign patenting altogether. Even though only U.S. patents were involved, the two universities benefitted very nicely from the development of the biotech industry. Other examples of university-developed platform technologies include the *dhfr*-methotrexate gene amplification techniques patented by Columbia[75] and the H9 cell line and HIV-1 viral isolates patented by the NIH and Pasteur Institute.[76] All of these have been licensed widely.

Patents on platform technology inventions developed at universities cannot be cleanly justified by any of the economic or philosophical models of patents we have touched upon. They are not like synthetic drugs. They are the technologies whose time has come, and no exclusivity incentives are necessary in order to get them fully disclosed or utilized by industry. They come from the "commons," yet there is no need to privatize them in order to bring them to wide public utilization.

University administrators who are lucky enough to come across one of these platforms and prescient enough to have them patented can foresee that their institutions will receive healthy financial rewards. Industry looks at these patents (which are normally licensed non-exclusively on reasonable terms) as one more tax on the sale of their products, and they add the royalties to the cost of doing business. It is not a bad thing for society that universities receive license fees and royalties for such platform technologies. Society should strive to provide incentives for the invention of new platforms. The patent system here works to funnel funds to the very places where such paradigm changes are most likely to occur.

Are human genes, then, more like synthetic drugs or platform technologies? As we hope to demonstrate, the answer depends on the genes.

Synthetic drugs vs. human genes. The ultimate issue is whether the poster example of "synthetic drugs developed by private industry" is applicable to human genes and to other institutions of discovery. For example: Is any conceptualization of the patent system applicable to "isolated human genes developed by private industry"? Or, "isolated human genes developed by universities"? Before we delve into these, however, let us address a preliminary question: What, if any, are the similarities and differences between human genes and synthetic drugs? There are several.

The supply of human genes is limited. There is a virtually infinite number of synthetic drugs, their design limited only by the knowledge and creativity of the scientist. In contrast, there is a finite number (presently estimated to be about 30,000) of human genes. In other words, the supply of human genes is like the supply of lots on an island. (We limit our discussion here to naturally occurring genes, not artificial modifications, truncations, or mutations of these genes. The latter are more like synthetic organic drugs in that their supply is unlimited.) The fact that there is a finite number of

human genes leads to possible "land rush" phenomena. There may, therefore, arise a perception that patents should not be granted when the supply is short because no one person should monopolize such a limited resource.

Genes are available from nature. Synthetic drugs are designed on paper or computer screen and then synthesized. Genes, in contrast, are isolated from nature. There may be a perception that the acts of design and synthesis are somehow more "inventive" and deserving of a patent than the act of finding and purifying a human gene. We have already discussed the long-established precedents that patents can be granted on isolated natural substances like genes, provided that the isolated material is useful and non-obvious. In the early years of gene hunting (interferon, TPA, EPO, etc.) the researchers knew a function and possibly had a protein, and their task was to find the corresponding gene sequence. The gene sequence was a priori useful. It was a task described at times as finding a needle in a haystack, and the heroic efforts of the early gene hunters bore out the perception that this was useful and non-obvious work. In the genomics era the paradigm is different. Sequences abound, the task seems to be to find functions for them, and much of the work is computerized. There may be a changed perception that this is more obvious work than finding needles, and less worthy of patent protection.

The fact that human genes are available from nature and "belong to all humanity" seems to have also led to a perception that it is acceptable to isolate them and go into business independently from the patent holder. This practice would be inconceivable if, instead of a natural gene, the patented material was a drug that would have to be synthesized in the laboratory. Genes self-replicate by cloning, whereas synthetic drugs do not. The ease of obtainment and reproduction appears to have led to the—legally incorrect—conclusion that it is more acceptable to infringe human gene patents than synthetic drug patents.

Structure–activity is more predictable for human genes. In order to obtain a patent on a human gene that has been isolated and annotated, it is necessary to put the knowledge of its sequence and its utility in the public domain. There may be a perception, however, that the PTO is granting human gene patents that are too broad and not limited to the gene that has been isolated and annotated. Perhaps the following explanation may demonstrate why applicants are requesting such breadth.

In order for the patent to a human gene to be of any worth to the patent holder, it cannot be limited to the actual isolated sequence found in nature. Since the genetic code is degenerate, and most amino acids are encoded by more than one codon, it would be simple for a copyist to replace natural codons of the actual isolated sequence by non-natural ones, and avoid infringement on the patent. It would be equally easy for a copyist to replace, in a patented protein sequence, a neutral amino acid such as alanine by another neutral one, such as glycine. It might even be possible to delete one or two amino acids at the N- or C- termini and obtain an equally good protein that avoids infringement of the patent. Many such changes can be made to DNA and protein sequences that, by virtue of our present-day understanding, can be used to avoid literal, narrow patent claims. This has resulted in the drafting of isolated human gene patent claims that are quite broad, and are not limited to the actual gene isolated from nature, but encompass myriad predictable mutations, permutations, deletions, truncations, and substitutions. This is the only way to assure for the patent holder a fair return in exchange for full disclosure.

The same is not necessarily true for synthetic drug patents. Even though dramatic advances have been made in structure–activity relations, especially those based on computer-assisted rational drug design, the predictability of the effect of a structural variation on physiological response is still at its infancy. Thus, the scope of patents in the organic chemical industry is more restrictive than that in modern patents on isolated human genes. It is relatively easier to avoid or "invent around" a patent claim to a small molecule than it is to do the same with a broadly claimed DNA.

Many human genes are also discovery tools. As more human genes are discovered and annotated, it is becoming clear that many of them encode for receptors important in transduction pathways. The availability of such isolated genes leads to valuable drug discovery tools. The pharmaceutical industry can use the receptors (produced by expression of the patented genes) robotically to screen voluminous libraries of synthetic compounds for drug leads. This is a far advance over the labor-intensive trial-and-error methods of the past. There are few, if any, analogous drug discovery tools among the synthetic drug leads.

The patenting of drug discovery tools, such as receptor genes, in turn leads to the possibility that their owners will demand so-called "reach-through" royalties based on the sale of ultimate drugs. Those drugs, but for the use of the expressed receptors, might have never been discovered. These reach-throughs are seen by some in the drug industry as profit-draining encumbrances, and by others in the academic world as an unwelcome privatization of research materials that hinders scientific work.

We have now arrived at our destination: a discussion of whether privatization and patenting of human gene discoveries are of benefit to society or not.

IS PRIVATIZATION OF HUMAN GENES STILL A WISE AND SOCIALLY USEFUL DEAL?

Protein drug genes. Let us start by analyzing the question from the point of view of a private company such as

Genentech. The gene sequence for TPA is obviously useful in the recombinant production of TPA. The production can be made predictably, in high yields and purity, and the supply of TPA to hospitals worldwide can be assured for the benefit of humanity. Having a patent on the isolated human gene for TPA allowed Genentech to invest the time and money it took to obtain FDA approval and bring the drug to the marketplace. The patent on the isolated human TPA gene cannot be used to stop an academic researcher from doing basic research on the DNA, or on the protein, or on new uses. And, as we have seen, the patent does not encompass the TPA gene in anyone's body.

Such a patent, in addition, is more useful as a financial risk-taking instrument than a patent on a method of production of TPA using the gene, or a patent on a method of treating thrombosis using the protein. A patent on the isolated gene itself covers any and all of its uses, be they production, diagnosis, or gene therapy, and covers the various constructs used for such uses. It gives special reward to the first isolator and purifier of the gene.

It is hard to argue that in this context society should not allow the Genentechs of the world to obtain patents on purified human genes. It is also hard to argue that because there is a finite number of human genes no one should have patent protection on any of them. Such an argument will not lead to TPA's being available in the hospital pharmacies of the world, ready to be used on the next infarct patient who is rolled in through the emergency department doors.

Does it make any difference if the human gene is purified by Genentech after finding it like a needle in a haystack or, in contrast, by Celera after discovering a utility for an otherwise orphan sequence in the literature using bioinformatics? In other words, should society allow patents for the needle finders but not the annotators? There is no legal difference between one and the other. After all, regardless of how the inventive contribution occurred, both companies still needed to invest substantial amounts of time and money in order to bring their discoveries to the pharmacy. If the Celeras of the world can prove to the satisfaction of the PTO—and ultimately of the courts—that annotation of a given sequence was non-obvious, they should be entitled to patent protection.

Does it make any difference to our analysis if the TPA gene had been purified at a university and not in private industry? We don't think so. We have already seen that the *financial* and *commons* models explain the purposes of university patents on synthetic drugs. The same is true for university patents on human genes for protein drugs. A corporate licensee of a university patent on TPA is in the same shoes as Genentech was with its own TPA gene. It is entirely possible that there would be no TPA in the pharmacies of the world had the discovery been made at a university and published without patent protection.

Our analysis has led us to conclude that it makes no difference whether the patent holder of purified human genes for protein drugs is corporate or academic. Society benefits by allowing the privatization of such purified human genes in either instance. Let us now explore other genes.

Diagnostic genes. Does it make any difference if the human gene encodes not an initially uncertain drug such as TPA, but a less risky candidate, like the diagnostic probe of Dr. Debra Leonard at the University of Pennsylvania? Obviously, the cost of entry was quite accessible to Dr. Leonard. The Molecular Pathology Lab did not need a patent in order to set up the tests and provide them for its clients. It did not seem to worry about commercial competition, apparently relying on its lead time and know-how to keep ahead of the pack. Her complaint seemed to be that she was somehow "ambushed" by the later appearance of a patent, and that she felt she could not do research with the material.

We have already clarified the "research" issue: Dr. Leonard is free to do research without commercial intent. Her complaint of ambushing, however, is fair. The PTO, until March 2001, did not publish pending patent applications or their prosecution. There was no way anyone could know if a "submarine" patent was pending. This changed in March 2001. Commercial labs in the position of Dr. Leonard's have always been well advised to carry out thorough freedom-to-use searches before going down the road of commercial activities. Even before March 2001 it was possible to study the filings of others in places such as the European Patent Office that did publish their pending applications. Since March 2001 it is also possible to do so in the U.S. PTO.

What about the need for patents in the diagnostics industry? They may not be as weighty as patents in the drug arena, but private firms who seek international markets for their products still rely heavily on patents in order to compete effectively and to raise the initial capital to develop new assays. Large-scale production and distribution of assay kits are still expensive propositions. Health regulatory agencies are still involved, and their approval is still needed. Therefore, the *financial* role of patents is still important for commercialization.

Research tool genes. Does it make any difference if the human gene patent is for a receptor or some other research tool used in the discovery of drugs? Here perhaps the role of patents is the most confusing, largely because the receptor is not the primary product to be sold but is instead an upstream product used to discover future products. These receptors are more like platform technologies than synthetic drugs in that they enable future inventions. There are complex problems in enforcing such patents in the first place: difficulty in policing, use abroad, use before the patent issues, use before any products are in the market, difficulty in valuation, reluctance to enter into reach-through agreements,

royalty stacking, etc.[77] It is not immediately clear that privatization of such genes helps society.

We have already discussed the role of the NIH in the debate on research tool dissemination. The NIH does not favor patents on research tools obtained with federal funds and, if patents are obtained, favors their wide availability by non-exclusive licensing.[78] Many private firms take the position that they will not file patent applications on research tools, and apparently ignore the patents of others. In many universities, isolated human genes for receptors are published and not patented as a matter of policy. The cost–benefit analysis of obtaining patents on genes for such receptors is quite complicated, and the commercial and legal consequences have yet to be worked out. For those who are interested in further exploration of this interesting topic Eisenberg[79] and Mueller[80] have written extensively and thoughtfully on the subject of research tool patents.

CONCLUSIONS

Whether at academic institutions or private corporations, privatizing isolated or purified human genes promotes commercialization and risk-taking. These are beneficial to society. There is a spectrum of human gene patents, however, depending on the subject matter they encompass. This spectrum ranges from those for which the pro-patent arguments are clearest, such as patents on DNA-encoding protein drugs, to those for which the arguments are the most confusing, such as patents on DNA-encoding human molecular receptors. Human gene patents on molecular receptors have more in common with platform technologies than with synthetic drugs, in that they are broadly enabling and allow the generation of many subsequent inventions. In this sense, the role of patents in their discovery and exploitation, especially in an academic context, is at the outer edge of the spectrum. Diagnostic human DNA probe patents are in the middle, closer to the synthetic drugs.

It is not possible to create an effective legal system that distinguishes between the different classes of human genes or the different institutions of discovery. This is especially so because within a given class of genes there are multiple uses. A human receptor can be used as a drug discovery tool, or as an antigen for the generation of blocking therapeutic antibodies. A human DNA sequence can be used as a diagnostic hybridization tool or as a template for recombinant production of a protein drug. A university receiving federal funds is urged not to seek patent exclusivity to human receptor genes, whereas a private firm whose main source of income is the discovery of novel receptor genes and their uses in drug screening wants to be assured some exclusivity in order to protect its investments.

The lines are not clear at all. The law would be foolhardy to try and draw sharp lines, asserting that some genes or uses are patentable to some parties while other genes are not. In addition, precluding certain genes from patentability would be shortsighted, in that it would create prohibitions that we might well regret in the future.

Luckily, the system is self-adjusting. For example, if patenting isolated human gene receptors is seen by some in the market as not a worthy endeavor, patents will not be filed —as seems already to be occurring.

Human gene patents can be enforced against those who are involved in profit-seeking ventures with commercial intent. They cannot be enforced against those who are doing research for the joy of curiosity or seeking knowledge. The patents do not cover human genes in your body or mine. We own our genes until such time as they are removed from our bodies, at which point we no longer do, unless we are prescient enough to do a deal with our doctor before the nurse starts drawing blood. Even at that time, however, we may not be able to make, use, or sell our own genes with commercial intent if someone else has a patent on them.

Neither the founders of the patent statute in Venice nor Jefferson, the founder of the U.S. patent system, could have imagined this discussion. If they heard us now, they might think of this idea of patenting human genes as lunacy. Of course, they might not have imagined that the patent system would still be alive and well hundreds of years later, supporting astounding and diverse technological developments such as birth control pills, jet engines, and computers. Patentable inventions, by definition, cannot be obvious. Therefore, if the Venetians and Jefferson thought about it some more and took the time to listen to us, they would understand that it had been precisely their intent to create a system to protect shockingly unexpected and unpredictable areas of human research. They would be pleased that the system has worked so well. They would then no doubt lustily join us in the debate as to whether university-held patents on purified genes for human molecular receptors should be exploited by reach-through royalties or not.

We can see them arguing in our mind's eye and, although we cannot hear them, we have a pretty good guess as to what their views would be.

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ENDNOTES

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[55]*Ibid* at 1564.
[56]*Ibid* at 1568-1569.
[57]*Genentech, Inc. v. The Regents of the Univ. of Cal.*, 143 F.3d 1446 (Fed. Cir. 1998).
[58]*Teknekron Software Systems, Inc. v. Cornell Univ.*, 1993 WL 215024 (D. Cal. 1993).
[59]*Brown v. The Regents of the Univ. of Cal.*, 866 F.Supp. 439 (D. Cal. 1994).
[60]*Kucharczyk v. The Regents of the Univ. of Cal.*, 48 F. Supp.2d 964 (D. Cal. 1999).
[61]*Ibid* at 970-971.
[62]*Ibid.*
[63]*Ibid* at 977-978.
[64]*Ibid* at 970 note 6; 972-973.
[65]AAMC Reporter Vol 9, February 2000; also cited at ⟨www.aamc.org/newsroom/reporter/feb2000/gene.htm⟩, accessed June 5, 2002.
[66]⟨www.med.upenn.edu/path/MolecDiag/molec-diag-brochure.html⟩, accessed July, 2001, now inactive.
[67]Report of the National Institutes of Health Working Group on Research Tools (June, 1998).
[68]64 Fed. Reg. 72,090 (Dec 23, 1999).
[69]Technology Transfer Commercialization Act of 2000, 15 U.S.C.A. §3701, Pub. L. No. 106-404, §1, 114 Stat. 1742 (2000).
[70]This is the Venice Patent Statute of 1474: "We have among us men of great genius, apt to invent and discover ingenious devices; and in view of the grandeur and virtue of our City, more such men come to us every day from divers parts. Now, if provision were made for the works and devices discovered by such persons, so that others who may see them could not build them and take the inventor's honor away, more men would then apply their genius, would discover, and would build devices of great utility and benefit to our Commonwealth. Therefore: Be it enacted that, by the authority of this Council every person who shall build any new and ingenious device in this City, not previously made in our Commonwealth, shall give notice of it to the office of our General Welfare Board when it has been reduced to perfection so that it can be used and operated. It being forbidden to every other person in any of our territories and towns to make any further device conforming with and similar to said one, with out the consent and license of the author, for the term of 10 years." Quoted in Mandich, Venetian Patents (1450-1550), 30 J.PAT.OFF. SOC'Y 166, 176-77 (1948).
[71]Abraham Lincoln, Second Lecture on Discoveries and Inventions, in 3 The Collected Works of Abraham Lincoln 363 (Roy P. Basler ed., 1953).
[72]⟨www.phrma.org/publications/value/facts.phtml⟩, accessed July, 2001, now inactive.
[73]U.S. Patent No. 4,237,224; U.S. Patent No. 4,740,470.
[74]Kenneth Sutherlin Dueker, 52 Food Drug L.J. 453, 494 (1997)_*Biobusiness on Campus: Commercialization of University-Developed Biomedical Technologies*.
[75]U.S. Patent No. 5,149,636.
[76]U.S. Patent No. 4,708,818; U.S. Patent No. 5,135,864.
[77]Jorge A. Goldstein, *Patenting the Tools of Drug Discovery*, Drug Discovery World, 9-18 (Summer, 2001).
[78]⟨http://ott.od.nih.gov/NewPages/RTguide.htm#sharing⟩, accessed June 5, 2002.
[79]Michael L. Heller and Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, Science Vol. 280: 698-701 (May 1, 1998).
[80]Janice M. Meuller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 Wash. L. Rev. 1 (2001).