Structure and function in gene patenting

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The United States patent system treats DNA sequences as large chemical compounds in determining their patentability. This approach has been helpful to those who seek to patent previously unidentified DNA sequences, but it may prove less advantageous from the perspective of those who elucidate biological functions and disease relevance of previously identified genes. A current controversy over patent rights for DNA sequences encoding leptin receptors provides a useful case study for illustrating some of the issues that are likely to arise in applying doctrine derived from chemical patent cases in the context of gene discovery.

—A gene is a chemical compound, albeit a complex one ...[1]

—From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing[2].

The nature of inventive activity and the importance of patent incentives differ markedly from one field to the next, and change over time as fields evolve. Yet with rare exceptions, inventors in all fields face a unitary, one-size-fits-all patent code. Code provisions that determine patentability according to the level of "ordinary skill in the art"[3] accommodate differences across fields to some extent, and case law has in fact tended to evolve along somewhat different lines for broadly designated categories of subject matter, such as 'chemical' versus 'mechanical' arts. Beyond these broad distinctions, however, there is little fine-tuning of the applicable rules to accommodate the needs of particular fields at particular points in time. Although patent law operates at the frontiers of technology, like all fields of law it resolves new controversies by looking to how similar issues have been resolved in the past. In theory, this approach should make the applicable legal rules stable and predictable. In practice, however, it can yield surprising outcomes that contradict the intuitions of researchers who work in rapidly changing fields.

International treaties constrain variation in national patent laws to some extent[4], yet patent laws remain national in scope, with distinctions in the applicable rules in different parts of the world. In Europe, for example, those who seek patents on discoveries in the life sciences have had to contend with arguments that such patents raise ethical issues, calling for exceptional treatment under the European Patent Convention[5,6]. Although similar arguments have been raised in the U.S.[7,8], in the absence of an applicable statutory exclusion from patent protection, the burden of inertia has rested on those who oppose such patents rather than on those who seek them. The U.S. courts have accordingly confronted certain doctrinal questions concerning such matters as the patenting of DNA sequences before some of their counterparts in other countries. It is therefore instructive to consider the approach that the U.S. courts have taken so far and to reflect upon its future consequences.

DNA sequences as chemical compounds

The U.S. Patent Act authorizes patent protection for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," provided certain statutory standards are met[9]. These statutory standards require that the invention be new[10], useful[11], nonobvious in light of the 'prior art' (previous knowledge in the field as reflected primarily in publications and other patents) [12], and described in a patent application in enough detail to enable others working in the same field to make and use it[13]. In elaborating the meaning of these requirements for patents on DNA sequences, U.S. courts have generally looked to the rules that have evolved for chemical inventions. DNA sequences, from this perspective, are large chemical compounds, and may be patented as 'compositions of matter' under the same principles previously applied to smaller molecules.

The characterization of DNA sequences as chemical compounds has so far been mostly good news for patent seekers, who have therefore had little motivation to challenge the analogy. For example, although patent claims to naturally occurring DNA sequences might be expected to trigger the time-honored rule against patenting 'products of nature[14], courts have had no trouble upholding patent claims covering 'purified and isolated' DNA sequences, and recombinant vectors and host cells that include these sequences[15], as new compositions of matter resulting from human intervention[16]. The path to this result had previously been cleared by cases upholding patent claims to purifications of other naturally occurring chemicals, such as adrenaline[17], prostaglandins[18], vitamin

"I take it all of you read that the PTO rejected our patent application?"

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B-12 (ref. 19) and acetylsalicylic acid[20].Another advantage, from the standpoint of patent seekers, of the chemical legacy of DNA sequence patents has been the willingness of courts to uphold patents on sequences found by obvious methods. The courts have routinely upheld patents on novel chemicals that are 'obvious' in the sense that any competent chemist would be able to make them if motivated to do so. Rather than assessing the obviousness of the method of making a new chemical, the courts have focused on structural and functional differences between the claimed compound and other compounds in the 'prior art', asking whether others in the field would have been motivated to make the new chemical and could have envisioned its structure and properties. Relying on this line of cases, the U.S. Court of Appeals for the Federal Circuit has held that disclosure in the prior art of a partial amino acid sequence for a known protein does not render obvious (and therefore unpatentable) corresponding DNA sequences, even if it is obvious how to go about cloning the gene, as the redundancy of the genetic code allows for an enormous number of possible DNA sequences to code for a protein[21,22], making it impossible to envision the structure of the gene in advance. The case of *In re Dueul* typifies this approach (see Box 1).

Box 1 • DNA not obvious in light of amino acid sequence

In the case of *In re Deuel*[21], the patent applicant claimed purified and isolated DNA sequences encoding heparin binding growth factors. Prior art references disclosed the isolation and partial amino acid sequencing of proteins that matched the first 19 amino acids encoded by the claimed DNA sequences, as well as general methods for cloning a gene by designing a probe based on a partial amino acid sequence. In reversing rejection of the claims by the Patent and Trademark Office (PTO) on grounds of obviousness, the court noted that a novel chemical is generally not presumed obvious unless it is structurally similar to a known compound, and proteins are not structurally similar to DNA sequences. The court was unmoved by the argument, which had been persuasive to the PTO, that "when the sequence of a protein is placed into the public domain, the gene is also placed into the public domain because of the routine nature of cloning techniques." The court reasoned that "the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein" and therefore does not make obvious any one of the possible sequences, except perhaps in the case of very small proteins for which the redundancy in the genetic code is minimal. That researchers of ordinary skill in the field, equipped with knowledge of the partial amino acid sequence, could have used known methods to isolate the corresponding native DNA sequence was, in the court's view, "essentially irrelevant to the question whether the specific [DNA] molecules themselves would have been obvious."

In effect, then, the patentability of a novel DNA sequence appears to turn not on the level of inventive skill necessary to obtain the sequence, but rather on the absence of disclosure of structurally similar DNA molecules in the prior art. This approach may fit poorly with perceptions of scientific achievement among research scientists. But *patent applicants* have little incentive to challenge a rule that helps them past a potential obstacle to patent protection, and opponents of patent protection have few avenues available for bringing their concerns to the attention of those who evaluate pending patent applications.

So far, the most significant obstacles to obtaining patent protection for DNA sequences have been the utility requirement (which limits protection to inventions that have a demonstrated practical use) and the disclosure requirements (which limit the scope of allowable claims). The utility requirement in particular, by withholding patent protection until an applicant is able to disclose "specific benefit" for the invention "in currently available form,"[23] has been thought to preclude the patenting of so-called 'orphan genes,' or DNA sequences for which no biological function is yet known[24]. This was one of the grounds cited by the PTO examiner in rejecting patent claims by the National Institutes of Health covering thousands of randomly sequenced cDNA fragments[24]. But as more DNA sequences become known and characterized, it is increasingly easy, through bioinformatic homology searching, to make a good educated guess about the general function of a newly discovered DNA sequence, even though far more research may be necessary to arrive at a thorough understanding of its biological function and disease relevance. It is an open question at what point this sort of informed speculation amounts to a credible assertion of utility in a patent application[25].

As the attention of the research community shifts from identifying new sequences to understanding their functions and disease relevance, we may be entering an era in which rules of law derived from chemical patent cases may make it more difficult to obtain effective patent protection for discoveries that represent considerable scientific achievement. To explain the basis for this concern, it is first necessary to review how the courts have applied the requirements for patent protection in the chemical arts, and then to consider the potential implications of this line of cases for discoveries related to DNA sequences.

Patents in the chemical arts

From the perspective of DNA sequencers, the primary obstacles to obtaining patent protection so far have been the utility and disclosure requirements. From the perspective of those who identify the biological functions or disease relevance of previously disclosed DNA sequences, it is the novelty and nonobviousness requirements that are more likely to present obstacles to obtaining effective patent protection.

It has long been established that one who discovers a new use, property, or advantage of an old product may not obtain a patent on the product as such[26,27], although the discovery may give rise to a patentable process[28]. Process patents, although generally narrower in scope than product patents (because they are limited to a particular use) and more difficult to enforce (because of the need to determine what it is that users are doing with an unpatented product in order to establish infringement), can sometimes nonetheless provide enough protection to make it profitable to develop an old product for a new use. A case in point is AZT, an unpatented chemical whose use in the treatment of HIV is covered by process patents[29–32] as well as product patents on particular pharmaceutical preparations[33,34].

But even a process of using an old product for a new purpose may be unpatentable if, although the new *purpose* was previously unrecognized, the *process* itself is not new[35]. Thus in *Ex parte Novitski* the applicant was unable to patent a method of protecting plants from nematodes by inoculating them with a bacterial strain that had previously been used to protect plants from fungi. Although the prior art did not disclose the nematode-inhibiting properties of the strain, the PTO took the position that the strain had inherently protected plants from nematodes when it was used in the past to protect them from fungi. Absent some change in the process steps to achieve the new purpose, the patent applicant had merely disclosed an inherent, although previously unnoted, advantage of performing an old process, and the claimed process therefore failed the test of novelty. There are few cases, however, that have reached a similar result; in general, the discovery of a new use for an old product will yield a process that differs from previous processes enough to survive the legal test of novelty.

Apart from process patent rights, it may be possible to obtain product patent rights by modifying the product itself for use in the new process (although a product patent that is limited to the new form of the product obviously would not be infringed by those who make or use the old form of the product, and thus would have limited commercial value unless the new form is superior to the old.) A slight change in the form of a chemical to distinguish it from the prior art will satisfy the novelty test, but it

Box 2 • Obviousness in new product patents

In *In re Dillon*[37], the inventor in that case discovered that adding tetra-orthoester compounds to hydrocarbon fuel will reduce soot emissions during fuel combustion. She sought to patent as a novel composition of matter a product consisting of hydrocarbon fuel plus the tetra-orthoester compounds. Tetra-orthoesters were a known class of chemical compounds, but the prior art did not disclose their combination with hydrocarbon fuel. The prior art did, however, suggest adding structurally similar tri-orthoester compounds to hydrocarbon fuels for the different purpose of 'dewatering' the fuels. The Federal Circuit affirmed rejection of the claims, noting that the value of tri-orthoester fuel additives as water scavengers would motivate researchers to try out tetra-orthoesters for the same purpose. This was enough to create a *prima facie* case of obviousness, which could only be overcome by data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art compositions do not have. That the prior art references did not address the soot emission problem solved by the patent applicant was irrelevant to the court unless the applicant could show that the tri-orthoester compositions in fact lacked the newly identified property of the tetra-orthoesters.

may not be sufficient to satisfy the nonobviousness requirement. The courts have held that a new chemical compound is *prima facie* obvious — that is, presumed to be obvious until proven otherwise — if it is structurally similar to a known compound, provided that the old compound is sufficiently useful to motivate chemists to search for similar compounds with the expectation that they would have similar properties. The applicant may overcome the presumption of obviousness and obtain a patent by showing that the new product has unexpected properties that the prior art product does not share[2]. It is not enough, however, that the newly identified properties were simply unrecognized; the patent applicant has the burden of showing that the prior art product in fact lacks the properties in order to overcome the presumption of obviousness arising from structural similarity to a known product[36]. The newly discovered properties will sometimes also provide the basis for process patent claims to a new method of using both old and new products. This doctrinal approach is illustrated by the case of *In re Dillon*[37], where the court denied a product patent for compositions consisting of tetra-orthoesters added to hydrocarbon fuel based on the structural similarity of tetra-orthoesters to known compounds, tri-orthoesters, even though the prior act did not suggest using compositions of hydrocarbon fuel with tri-orthoester additives for the applicant's purpose of reducing soot emissions (see Box 2).

The court did not separately consider whether the applicant might have been entitled to a *process* patent on a new method for reducing soot emissions. Presumably the failure of the prior art to suggest using tri-orthoesters for this purpose would be relevant in determining whether the process itself was nonobvious. A similar issue was presented in the case of *In re Shetty*[38], where the court allowed a process patent on the use of a new chemical for a new purpose, notwithstanding the existence of a structurally similar chemical in the prior act, where the prior act did not suggest the new use (see Box 3).

Box 3 • Obviousness in new process patents

In *In re Shetty*[38], the patent applicant sought a process patent on a method of curbing appetite in animals by administering adamantane compounds. The prior art disclosed administering structurally similar adamantyl compounds to animals as an antiviral agent. The existence of structurally similar compounds with a known use in the prior art was sufficient to make *product* claims to the new compounds *prima facie* obvious, and the applicant failed to rebut the presumption of obviousness by showing any actual difference in properties between the two classes of compounds. Nonetheless, the court concluded that the applicant's *process* claims were nonobvious, given that the prior art references did not suggest the use of the compounds for appetite suppression.

Implications for discoveries of gene functions

This line of cases could potentially restrict the patent rights of those who discover the natural biological functions associated with DNA sequences that have previously been identified (and perhaps patented) by others. If a sequence itself is in the prior art, subsequent researchers may be precluded from obtaining effective product patent rights. Moreover, if the newly identified biological functions are inherent properties of the prior art product, it may sometimes be difficult to obtain effective process patent protection.

Although the implications of the foregoing legal principles for future cases are uncertain and debatable, some of the potential problems are illustrated by a controversy that is brewing over patent rights to a gene that encodes a leptin receptor, *OBR*. Receptors are less likely to be sold as commercial products than the ligands that bind them, but the commercial stakes of this particular dispute are heightened because of the tremendous potential market for products to control weight. Cloning of the gene for leptin itself, *Ob*, by Rockefeller University scientists in late 1994 (ref. 39) excited considerable commercial interest, culminating in the grant of an exclusive license to Amgen in exchange for $20 million up front plus future payments that could total as much as $100 million according to accounts in the press[40]. But reports of high serum leptin concentrations in obese persons relative to normal-weight subjects[41–44] suggested that leptin itself might be of limited value in controlling obesity without further understanding how the ligand interacts with its receptor.

The leptin receptor

Researchers from Millennium Pharmaceuticals and Hoffmann-LaRoche announced cloning of the gene for the leptin receptor from mouse and human cDNA libraries and published the sequence (presumably after filing a patent application) in December of 1995 (ref. 45). Although the Millennium/Roche team was apparently the first to recognize the role of *OBR* as a leptin receptor, it soon became apparent that others had previously sequenced DNA molecules containing portions of the *OBR* gene. A GenBank search revealed the prior disclosure in the public domain of an expressed sequence tag (EST) of unknown function showing great similarity to a small portion of the *OBR* gene[46]. More ominous, Millennium and Roche soon learned that in 1994 another firm, Progenitor, Inc., had identified — and sought to patent — several somewhat shorter forms of a receptor encoded by sequences showing great similarity to *OBR* for most of its length[47]. Progenitor's international patent application, published by the International Bureau of the World Intellectual Property Organization 18 months after its filing date under the Patent Cooperation Treaty[48], identifies the invention as "a novel member of the hematopoietin receptor family, herein referred to as Hu-B1.219", and makes no mention of leptin or obesity[49]. But Progenitor's press release announcing the publication identifies the subject of the patent application as a leptin receptor, and makes no mention of haematopoiesis[47].

The sequences identified by Progenitor and Millennium are not identical, and the differences may have important functional significance. A recent paper by Progenitor authors characterizes the Millennium sequence as an "isoform of B219 with a nearly identical ligand binding domain" and proposes a role for leptin and the rechristened "B219/OBR" in reproductive and haematopoietic biology in addition to obesity[50]. On the other hand, the Millennium sequence has a different and longer cytoplasmic domain,

which may be critical in initiating leptin-mediated signal transduction. The Millennium sequence encodes a total of 1,165 amino acids, including a cytoplasmic domain of about 303 amino acids[45]. The longest of the three sequences disclosed in the Progenitor patent application encodes a total of 958 amino acids, including a cytoplasmic domain of 97 amino acids[49]. Progenitor has noted that the final 66 amino acids in the intracellular domain have a coding sequence that is virtually identical to a human retrotransposon[49,50], suggesting a splicing error. Studies of obese mice expressing a short form of the leptin receptor suggest that the longer form of the cytoplasmic domain identified by Millennium may be crucial for initiating intracellular signal transduction[51–53].

Progenitor's patent rights

The implications of these distinctions for the respective patent positions of Progenitor and Millennium have been particularly critical because the conflict came to light in a year when both firms were approaching the market with initial public offerings of their common stock[46,54]. Although Progenitor ultimately decided to postpone its stock offering due to adverse market conditions[55], as this commentary goes to press Progenitor and Amgen have announced the signing of an agreement giving Amgen an exclusive license to develop commercial products out of Progenitor's leptin receptor technology in exchange for a $500,000 license fee plus milestone payments that could total as much as $22 million in the event of successful development of a commercial product[56]. These developments highlight the importance of patent rights in attracting funding for biotechnology companies, whether through the capital markets or through license agreements with other firms.

An important threshold question that has been analysed elsewhere[57] is whether Progenitor's patent application will satisfy the mercurial standards of the PTO for utility[25]. That Progenitor did not identify its sequence as encoding a leptin receptor would not prevent it from obtaining product patent rights covering any and all uses of the sequence, but the law requires at a minimum a specific assertion of a practical utility for the claimed invention[25]. Progenitor's utility disclosure is vague and circular. It asserts, without data or elaboration, that the invention may be used for "the diagnosis of cancer" and "the marking of fetal tissues," as well as for "the screening of ligands and compounds that bind the receptor molecule," "for the diagnosis of diseases resulting from aberrant expression of Hu-B1.219," or in "gene therapy to treat conditions in which the cells do not proliferate or differentiate normally due to underexpression of normal Hu-B1.219" (ref. 49).

Assuming Progenitor is able to meet the basic patent law requirements of novelty, utility and nonobviousness, the next issue will be the breadth of patent rights they may obtain. Will their patent rights be limited to the specific sequences that they have identified and disclosed, or will they be able to claim their invention more broadly so as to cover other similar sequences, including the longer forms identified by Millennium and Roche? If the specific sequences disclosed by Progenitor in fact lack portions of the intracellular domain that are necessary for effective signal transduction, claim breadth could be a very significant issue.

So far the courts have been hostile to broadly worded patent claims to DNA sequences, particularly when they define their scope in terms of the desirable biological activity of the gene product. For example, in the case of *Amgen v. Chugai Pharmaceutical*[1] the Federal Circuit affirmed a lower court decision holding invalid a broad generic claim covering all DNA sequences that encode any polypeptide having an amino acid sequence sufficiently duplicative of erythropoietin to possess the property of increasing production of red blood cells. The Federal Circuit took a similarly parsimonious approach toward claim scope in the case of *Genentech v. The Wellcome Foundation*[58]. In that case the court construed patent claims to a DNA sequence encoding human tissue plasminogen activator (t-PA) as covering only those sequences that encode a product having the same structure as natural t-PA, rejecting as "hopelessly overbroad" other suggested interpretations that would extend to all sequences encoding products that cover the essential or enzymatically active portions of the protein, or that are capable of catalysing the conversion of plasminogen to plasmin. These and other cases suggest that Progenitor might be limited to patent claims covering the specific sequences they have disclosed — claims that would not be infringed by the longer Millennium sequence.

On the other hand, the PTO has issued relatively broad patents on DNA sequences that use structurally based rather than functionally based claim language. For example, the PTO recently issued several patents to Human Genome Sciences with claims covering "an isolated polynucleotide *comprising*" a particular disclosed sequence, a term that is ordinarily understood in chemical patent practice to mean "including but not limited to"[59], as well as other sequences that hybridize to the disclosed sequence and are at least 95% complementary thereto[60–62]. The validity of these patent claims has not yet been tested in the courts; they may be vulnerable to challenge on a number of grounds, including that the scope of the claim language exceeds the scope of the supporting disclosure. If the PTO issues a patent with similar claim language to Progenitor, Progenitor would hold a dominant patent position in the leptin receptor field, requiring Millennium and others to obtain a license from Progenitor if they use any sequence covered by the claims.

Millennium's patent rights

The patentability of Millennium's sequence presents a separate question from the scope of patent rights to which Progenitor is entitled. Even if Progenitor obtains broad patent claims that cover Millennium's sequence, Millennium might still obtain patent rights of its own, although it might be unable to exploit them without a license from Progenitor under its dominant patent. Conversely, even if Progenitor obtains narrow patent rights that do not cover Millennium's form of the sequence, or, for that matter, obtains no patent rights at all, Progenitor's activities could create prior art that would constrain Millennium in its pursuit of its own patent rights. The EST in the public domain database will also be included in the prior art in assessing the patentability of Millennium's invention, and it is entirely possible that the owners of private cDNA sequence databases have also tagged the same gene and have their own patent applications pending that will be included in the prior art.

Will the Millennium sequence be considered obvious in light of these sequences? Recall that the courts, borrowing from the chemical patent cases, consider a new chemical to be *prima facie* obvious when it is structurally similar to a known chemical. Although some commentators have expressed concerns, in light of the practice of the PTO, that disclosure of ESTs will render the corresponding full-length genes unpatentable on grounds of obviousness[63,64], court decisions provide little support for this position. Indeed, if the courts continue to focus on structural similarity rather than method of identification as the primary consideration in determining the obviousness of DNA sequences, it seems unlikely that disclosure of a small fragment would make a full-length gene obvious. Following *In re Deuel*, if disclosure of a partial amino acid sequence does not make the corresponding DNA sequence obvious in the understanding of the courts, it is unlikely that disclosure of a fragment of the gene itself would do so.

It is much more likely, however, that a prior art sequence encoding a protein of 958 amino acids would be deemed structurally similar to a very similar sequence encoding a somewhat longer

protein of 1,165 amino acids. But even disclosure of a structurally similar sequence only makes the subsequently claimed sequence *prima facie* obvious; the patent applicant may rebut the *prima facie* case by showing surprising properties for the new product not possessed by the prior art product. The case law suggests, however, that Progenitor's failure to identify its claimed sequence as encoding a leptin receptor will not prevent it from rendering Millennium's similar sequence obvious if the Progenitor sequence in fact had the properties of a leptin receptor all along[37].

At this point, functional differences between the forms of the receptor disclosed by Progenitor and Millennium become critical. If Millennium can demonstrate that the receptor encoded by the Progenitor sequence is incapable of leptin-mediated signal transduction because of its truncated intracellular domain, this difference would allow Millennium to overcome the *prima facie* case of obviousness by showing that its sequence, although structurally similar to the Progenitor sequence, possesses surprising properties not present in the prior art sequence. But even if Millennium is able to obtain a product patent on its sequence, the claims will have to be drafted so as not to cover any sequence in the prior art, including the Progenitor sequence.

Apart from any product patent claims on DNA sequences, Millennium may be able to obtain a patent on various process claims related to its discovery that its sequence encodes a leptin receptor. Such process claims might include method-of-treatment claims to the use of the receptor in the treatment of diseases requiring control of weight or appetite. It is possible, for example, that the leptin receptor might be administered in soluble form to treat wasting disorders by intercepting leptin before it binds its receptor. But treatments for obesity are likely to be more commercially significant than treatments for wasting disorders. The most commercially significant use of the leptin receptor in the near future is therefore likely to be as a screening tool to find molecules that will bind the receptor and might therefore be developed into drugs for treating obesity.

Can Millennium obtain a process patent on the use of the receptor for such screening purposes? There is abundant authority in the case law for the proposition that one may patent a new use for an old product as a process[28, 65]. Since Progenitor's patent application makes no reference to leptin or obesity, it would not seem to make this process obvious. On the other hand, Progenitor's patent application does teach the use of the disclosed Hu-B1.219 sequences for "the screening of ligands and compounds that bind the receptor molecule encoded by Hu-B1.219," (ref. 49), raising the possibility that Millennium's screening process is unpatentable for lack of novelty. Although Progenitor does not identify the purpose of this process as identifying potential products for the treatment of obesity, it could be argued that Millennium has merely discovered a hitherto unappreciated reason for performing a previously disclosed (and therefore unpatentable) process, rather than inventing a new process.

As a practical matter, it is unlikely that Millennium's process claims would ultimately fail the test of novelty. Rejections for lack of novelty are highly technical, requiring that a single reference disclose each and every element of the claimed invention, and can therefore often be avoided by careful claim drafting to avoid covering the previously disclosed process. Millennium might, for example, avoid the prior art by restricting its claims to a screening process that uses its own distinct form of the receptor with the long intracellular domain rather than Progenitor's shorter forms. But these strategies limit the scope of the resulting patent rights: if Millennium's claims are drafted so as to avoid Progenitor's disclosed process, Progenitor's process would not infringe the claims. The significance of this limitation depends on the relative technical value of Millennium's claimed process compared to Progenitor's disclosed process. In this case, given that the extracellular binding domains are virtually identical for both the Progenitor and Millennium forms of the sequence, the process disclosed by Progenitor is likely to be adequate for purposes of identifying molecules that bind the receptor. But the longer form identified by Millennium might allow it to claim a more specific cellular assay that permits identification of compounds that trigger signal transduction pathways important in weight modulation.

The fact that this particular dispute involves rights to a receptor that is likely to be useful primarily as a screen for potential products, rather than as an end product to be sold for diagnostic or therapeutic purposes, limits the significance of the patent rights at stake. Even if Millennium is ultimately able to obtain broad U.S. patent claims on the use of the leptin receptor to screen for drugs that modulate weight and appetite, such a patent would confer no rights until it is issued. Meanwhile, anyone is free to make and use the sequence for any purpose whatsoever without any obligation to Millennium under the U.S. patent laws. By the time Millennium's patent is issued, its competitors may already have succeeded, by using the receptor as a screen, in identifying candidate products that they may thereafter develop and sell during the patent term without infringing the claims of Millennium's patent. Progenitor's patent application has been pending longer, and may ripen into an issued patent sooner, but the commercial significance of any patent rights it obtains is still likely to be limited because the receptor is primarily a research tool rather than an end product.

Significance for the future

The importance of this dispute transcends the commercial significance of the leptin receptor. In all likelihood this case is a harbinger of future conflicts over the allocation of patent rights when a gene is sequenced by one firm, and then subsequently related to a biological function or disease by another firm. And in future cases the sequences at issue may be more closely related to diagnostic and therapeutic proteins, making the allocation of patent rights more crucial to the profitability of product development. Indeed, the strength of patent rights accruing to firms that identify new DNA sequences, on one hand, and firms that discover biological functions or disease relevance of genes, on the other, may determine what type of firm is able to command the resources for product development.

If patent law systematically allocates stronger rights to those who identify novel DNA sequences while withholding effective patent protection from those who elucidate gene function, it stands to reason that the business of elucidating gene function will be less lucrative than the business of identifying novel DNA sequences. It does not follow, however, that no firms would be motivated to investigate gene function under such an allocation of rights. The firms that own intellectual property rights in DNA sequences would have an interest in learning about the functions of the genes they had patented, whether on their own or in collaboration with research partners, to maximize the commercial value of their prior discoveries. But starting from a large set of 'orphan' genes and working to understand their functions may not always be the most efficient way to learn about the genetic components of disease.

On the other hand, a patent system that gives stronger rewards to those who discover the functions of previously identified genes might encourage a different model of research that proceeds in the direction followed by Millennium, beginning with a particular set of disorders and working to understand their genetic basis. Moreover, effective patent protection for the discovery of gene function may be increasingly important as the Human Genome Project yields new DNA sequence information in the public domain. In a few short years, it is likely that the entire human genome will have been

publicly disclosed, making it difficult to obtain product patent rights in DNA sequences themselves. In this environment patent rights in discoveries related to gene function may be critical in motivating commercial investment in the development of products that emerge from knowledge of the genome.

Meanwhile, firms that identify novel genes may be able to obtain strong product patent rights on the basis of very preliminary identification of gene function. Such an allocation of rights encourages a model for research and development that parallels a traditional pharmaceutical approach, in which firms initially create proprietary molecules and then screen them in search of uses. Does this model make sense as a way of structuring genomics research? Or are we likely to make more diagnostic and therapeutic products available more promptly by structuring patent incentives to encourage a different approach in which firms focus on a particular disease and seek to identify its genetic causes? It is difficult to generalize in advance. In all likelihood each approach will have its winners and losers, and it would be a shame to allocate patent rights in a manner that stacks the deck by making one approach decidedly more profitable than the other for reasons unrelated to technological achievement and promise.

Acknowledgements

I gratefully acknowledge the helpful comments and suggestions of M. Adelman, F. Collins, B. Cook-Deegan, H. Feldman, S. Holtzman, S. Suter, H. Wagner and C. Whitman. This research has been supported by the Office of Health and Environmental Research of the U.S. Department of Energy and the Cook Fund of the University of Michigan Law School. Copyright 1997 Rebecca S. Eisenberg.

1. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir.), *cert. denied sub nom.* Genetics Institute v. Amgen, 502 U.S. 856 (1991).
2. In re Papesch, 315 F.2d 381 (CCPA 1963).
3. U.S. Patent Act, 35 U.S. Code § 103(a).
4. Final act embodying the results of the uruguay round of multilateral trade negotiations, Apr. 15, 1994, Annex IC: Agreement on Trade-Related Aspects of Intellectual Property Rights §§ 27–34, 33I.L.M.81, *reprinted in* The Results of the Uruguay Round of Multilateral Trade Negotiations—The Legal Texts (ed. GATT Secretariat)1–19, 365–403 (1994).
5. Convention on the Grant of European Patents § 53, opened for signature October 5, 13 I.L.M. 290 (1973).
6. Dickson, D. Europe tries to untangle laws on patenting life. *Science* **243** 1002–1003 (1989).
7. Kass, L.R. Patenting Life. *Commentary* at p.56.(December, 1981).
8. Dresser, R. Ethical and legal issues in patenting new animal life. *Jurimet. J.* **28** 399–435 (1988).
9. 35 U.S. Code § 101.
10. 35 U.S. Code § 102.
11. 35 U.S. Code §§ 101, 112.
12. 35 U.S. Code § 103.
13. 35 U.S. Code § 112.
14. Funk Bros. Seed Co. v. Kalo Inoculant Co., 33 U.S. 127 (1948).
15. *Amgen Inc. v. Chugai Pharmaceutical Co.*, 13 USPQ2d (BNA) 1737, 1759 (D. Mass. 1989).
16. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
17. Parke-Davis & Co. v. H.K. Mulford & Co., 189 F. 95 (S.D.N.Y. 1911).
18. *Kuehmsted v. Farbenfabriken*, 179 F. 701 (7th Cir. 1910), *cert. denied*, 220 U.S. 622 (1911).
19. *Merck & Co. v. Olin Mathieson Corp.*, 253 F.2d 156 (4th Cir. 1958).
20. *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970).
21. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).
22. *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).
23. *Brenner v. Manson*, 383 U.S. 519 (1966).
24. Eisenberg, R. & Merges, R. Opinion letter as to the patentability of certain inventions associated with the identification of partial cDNA sequences. *Amer. Intell. Prop. L. Ass'n Q. J.* **23**, 1–52 (1995).
25. U.S. Pat. & Trademark Off. PTO Utility examination guidelines *Fed. Reg.* **60**, 36,263 (1995).
26. *In re Spada*, 911 F.2d 705 (Fed. Cir. 1990).
27. *In re Thuau*, 135 F.2d 344 (CCPA 1943).
28. *In re May*, 574 F.2d 1082 (CCPA 1978).
29. U.S. Patent No. 4,724,232 (Feb. 9, 1988).
30. U.S. Patent No. 4,833,130 (May 23, 1989).
31. U.S. Patent No. 4,837,208 (June 6, 1989).
32. U.S. Patent No. 4,818,750 (Apr. 4, 1989).
33. U.S. Patent No. 4,828,838 (May 9, 1989).
34. U.S. Patent No. 4,818,538 (Apr. 4, 1989).
35. *Ex parte Novitski*, 26 USPQ2d (BNA) 1389 (Bd. Pat. App. & Interf. 1993).
36. *In re Hoch*, 428 F.2d 1341 (1970).
37. 919 F.2d 688 (Fed. Cir. 1990), *cert. denied sub nom. Dillon v. Manbeck*, 500 U.S. 904 (1991).
38. 566 F.2d 81, 195 USPQ (BNA) 753 (CCPA 1977).
39. Zhang, Y. *et al.* Positional cloning of the mouse *obese* gene and its human homologue. *Nature* **372**, 425–431 (1994).
40. Hamilton, J. *et al.* Is this 'fat gene' worth its fat tab? *Business Week* (March 20, 1995).
41. Lönnqvist, F., Arner, P., Norfors, L. & Schalling, M. Overexpression of the obese (*ob*) gene in adipose tissue of human obese subjects. *Nature Med.* **1**, 950–953 (1995).
42. Hamilton, B.S., Paglia, D., Kwan, A.T.M. & Deitel, M. Increased obese mRNA expression in developmental fat cells from massively obese humans. *Nature Med.* **1**, 953–956 (1995).
43. Maffei, M. *et al.* Leptin levels in human and rodent: measurement of plasma leptin and OB RNA in obese and weight reduced subjects. *Nature Med.* **1**, 1155–1161 (1995).
44. Considine, R.V. *et al.* Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *New Engl. J. Med.* **334**, 292–295 (1996).
45. Tartaglia, L.A. *et al.* Identification and expression cloning of a leptin receptor, OB-R. *Cell* **83**, 1263–71 (1995).
46. Millennium Pharmaceuticals, Inc., Common Stock Prospectus at p.11 (May 6, 1996).
47. Progenitor, Inc., Progenitor announces publication of patent application for leptin receptor (Press Release, March 22, 1996).
48. Patent Cooperation Treaty June 19, 1970, 28U.S.T.7645, as amended, Art. 21.
49. Progenitor, Inc., International Patent Application No. WO 96/08510 (March, 21 1996).
50. Cioffi, J.A. *et al.* Novel B219/OB receptor isoforms: possible role of leptin in hematopoiesis and reproduction. *Nature Med.* **2**, 585–589 (1996).
51. Chen, H. *et al.* Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in *db/db* mice. *Cell* **84**, 491–495 (1996).
52. Lee, G-H. *et al.* Abnormal splicing of the leptin receptor in *diabetic* mice. *Nature* **379**, 632–635 (1996).
53. Vaisse, C. *et al.* Leptin activation of Stat3 in the hypothalamus of wild-type and *ob/ob* mice but not *db/db* mice. *Nature Genet.* **14**, 85–96 (1996).
54. Progenitor, Inc., Common stock prospectus (subject to completion, dated July 11, 1996)
55. Reuters Financial Service. Progenitor Inc. postpones IPO, cites market. (Aug. 30, 1996) (available in LEXIS, News Library, Wires File).
56. Business Wire. Amgen and Progenitor sign leptin receptor agreement. (Jan. 6, 1997) (available in LEXIS, News Library, Wires File).
57. Sherwood, P. Owning genes vs. cloning genes. *Bioventure View* 15–16 (June, 1996).
58. 29 F.3d 1555 (1994).
59. Greer, T.J., Jr. *Writing and Understanding U.S. Patent Claims* (Michie, Charlottesville, VA, 1979).
60. U.S. Pat. No. 5,506,133 (Apr. 9, 1996).
61. U.S. Pat. No. 5,504,003 (Apr. 2, 1996).
62. U.S. Pat. No. 5,501,969 (Mar. 26, 1996).
63. Goldstein, J. & McConathy, E. Patent applications on partial cDNA sequences. *J. NIH Res.* **7**, 58–61 (1995).
64. Steffe, E. & Covert, J. Expressed sequence tags: any prior art effect? *Biotechnol. Law Report.* **14**, 947–952 (1995).
65. *In re Hack*, 245 F.2d 246, 248 (CCPA 1957).