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PATENTS IN GENOMICS AND BASIC RESEARCH

ISSUES FOR DEVELOPING WORLD HEALTH

1. INTRODUCTION

The patent system is now reaching into the tools of basic medical research. This poses important questions for the future of medical research for the benefit of the developing world. It is genomics that has received the greatest attention, because of the fact that many people have ethical concerns that genes should not be patented. The genomics issue is not just one of genes, but one of other types of genomic information — for example of expressed sequence tags (ESTs), single nucleotide polymorphisms (SNPs), or receptors that lack therapeutic properties. Most of those closely associated with medical and pharmaceutical research in the developed world believe it essential to permit effective patent coverage of protein products (and perhaps therefore of the corresponding gene sequences), in order to encourage private sector investment in the research and clinical trials needed to bring such products to the market. Even these people, however are often opposed to patents on ESTs and SNPs, because they see these partial sequences as likely to be useful in therapeutic discovery. In general, the patentability of such partial sequences is defended by genomics firms that are developing them and seeking to market information derived from them to pharmaceutical firms, but their patentability is opposed by the pharmaceutical firms themselves. And there is a still newer generation of questions coming in this area, involving efforts to obtain patent rights over computer programs for the analysis of genomic information, the "annotation" of the genome, the conditions of expression of the different genes, and the structures and roles of the various proteins encoded by the genes. The law may become confused, because the concept of gene and protein patents may have to change with the new revelations that one gene may be transcribed in a number of ways, so that the link between a sequence and the associated proteins may be much more complex than previously realized.[1]

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[1] Venter et al, The Sequence of the Human Genome, *Science* **291**: 1304 (16 Feb. 2001).

The immediate pragmatic issue posed by such patents is their impact on research. In this respect, they are like patents on many other inventions and products that can serve as research tools.[2] Patents are now available on research technologies as fundamental as cell fusion procedures, cell separation procedures, animal models of particular diseases, and the use of particular kinds of diagnostic information. Although these have received much less public attention, they may be just as important for developing world health, and are therefore considered in this paper.

2. THE RELEVANT INTELLECTUAL PROPERTY RIGHTS

It is useful to begin by examining some of the actual forms of patent, looking especially at United States practice. Although United States practice is the most expansive in this area, similar positions are often taken in other patent law systems. Patents were granted quite early for naturally-occurring proteins, and the genes that coded for them. Not long ago, the sequencing of genes was difficult, and often took place together with the identification and purification of the protein. The patents typically included claims (which are the formal descriptions of the precise legal area of exclusive rights) for the genetic sequences in isolated form, for various vectors that included the gene and are used for inserting the sequences into cloning organisms, for the cloning organisms used for mass production of the protein, and for the proteins themselves. The patent law's requirement of "novelty," that the patented invention be new and not anticipated in previous literature or in nature, was met by the theory that the product had never before existed in isolated (concentrated) form, and that the gene sequence had never before been isolated. Although protection of the protein (which is essential to the pharmaceutical industry) does not necessarily imply protection of the sequence, sequence claims were regularly granted, and, in one case, sequences were described as essential to protection of the protein under contemporary law, *Fiers v. Revel*, 984 F.2d 1164 (CAFC 1993).

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[2] Report of the National Institutes of Health Working Group on Research Tools (June 4, 1998), available at http://www.nih.gov/news/researchtools/index.htm.

The public and private human genome programs completely changed the research pattern that underlay this early body of law. Genome sequences now became available on a large scale, often without full understanding of the functions of the sequences. This led to new legal issues. One group of issues involves sequences which are believed to code for a protein whose function may be unknown or only estimated from homology to known sequences. In the new *Utility Examination Guidelines*, 66 *Fed. Reg.* 1092 (Jan. 5, 2001), the United States Patent and Trademark Office (PTO) has indicated that it will require a "specific and substantial utility that is credible." Its *Revised Interim Utility Guidelines Training Materials* imply that a sequence for a protein whose function is unknown is unpatentable, as is one identified as able to bind with another specific protein where the further protein has no known utility. Patents will, however, be available for sequences whose function is biologically significant although known only from homology, and the PTO has issued one patent on partial sequences whose function is known from homology.[3] These guidelines are not binding on the Court of Appeals for the Federal Circuit (CAFC), which has sometimes declared patentable types of inventions, e.g. business methods, that the PTO had declared unpatentable. But, assuming that the guidelines hold up, it can be anticipated that genomic patents will be available only for genes whose function is known. The same pattern is likely to prevail in Europe under *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.*[4]

For ESTs (expressed sequence tags, i.e. shorter sequences that are parts of genes being expressed in particular circumstances), the key legal issues are whether the discoverer of a EST should have a right (1) to no patent at all, (2) to a patent covering only the use of that EST as a probe to help in identifying the entire gene or (3) to a patent that would also be infringed by the entire sequence or protein, regardless of whether the EST is used to identify the protein. In technical patent law, the question of whether the latter scope should be available is that of whether a "comprising" claim should be granted — a claim to a sequence "comprising" the identified EST sequence would be infringed by the entire gene that included the patented sequence. The implications of this difference are extremely important: a firm that holds the first kind of patent can block use of one specific way to identify a gene (and is likely to be motivated to market that method to other firms), while a firm that holds the broader "comprising" style of patent can keep any other firm from using the gene at all. Here, as just noted, one patent has been granted; it includes certain "comprising" claims. The new utility guidelines strongly suggest that no further EST patents will be granted, with either narrow or broad claims, unless there is

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[3] Au-Young et al, (Incyte), 5,817,479, *Human kinase homologs*, Oct 6, 1998. Note that this patent involved partial sequences, not the entire gene sequences.

[4] Article 5 states, in part, that "An element isolated from the human body . . . including the sequence or partial sequence of a gene, may constitute a patentable invention . . ." The section goes on to say that "The industrial application of a sequence or partial sequence of a gene must be disclosed in the patent application."

reason to believe that the protein which they may assist in identifying will itself be useful.[5]

[5] It is certainly possible that "comprising" claims will be granted in contexts where the partial sequence has a known function and is likely to be used as a building block, as when the sequence codes for a promoter or a protein region with specific binding properties or transmembrane features.

SNPs (single nucleotide polymorphisms) are points in the genetic sequence in which one person's DNA differs from another's and present a much different issue. Because these sequences can be used to identify particular genetic conditions, they obviously have greater utility than do ESTs, assuming that the implications of the specific SNP have been identified. There has been a number of patents covering, for example, the BRCA1 and BRCA2 mutations predisposing to breast cancer.[6] These were based on early research and extensive use of genetic linkages. And there has been one patent for SNPs, in which the value of the polymorphisms was unspecified other than that they could be used for forensic identification purposes.[7] Although this patent does not seem to have the specific utility needed under the new guidelines, SNPs that have a clear diagnostic role seem likely to be patentable. The principles go further; it is essentially certain that there will be U.S. patents on all kinds of genotypic-phenotypic linkages, completely covering the use of particular genomic information to infer characteristics of the organism.

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[6] E.g., Skolnick et al, (Myriad), 5,710,001, *17q-linked breast and ovarian cancer susceptibility gene*, Jan 20, 1998. These patents typically include claims covering comparison of a person's gene sequence with the identified mutation. There is also a patent on the "consensus sequence," Murphy et al (OncorMed), 5,654,155, *Consensus sequence of the human BRCA1 gene*, Aug. 5, 1997. Litigation between the two firms was settled in 1998. Another example of claim scope is Tsuchihashi, (Mercator Genetics), 5,712,098, *Hereditary hemochromatosis diagnostic markers and diagnostic methods*, Jan. 27, 1998. The key claim speaks broadly of assessing DNA or RNA from the individual for the presence or absence of the identified mutation.

[7] Chee & Fan, (Affymetrix), 5,856,104, *Polymorphisms in the glucose-6 phosphate dehydrogenase locus* (Jan 5, 1999).

The post-genome era of biological research raises further patent issues. Patents in which the invention consists of new software or statistical or other analytic approaches, have been granted and are likely to continue to be granted. Such patents will certainly cover particular approaches to the development of annotations describing the functions or characteristics of a part of the genome, to the analysis of genomic data or gene expression data, or to protein structure calculation. Whether there will be other efforts to protect annotations themselves (other that through contractual restrictions on access to databases) is not yet clear, but at least one of the software-oriented patents has very broad claims on use of databases that include protein functions and may therefore indirectly restrict annotation.[8] There is also an important new line of applications, seeking claims that would control the use of genomic information in machine readable form.[9] One even seeks to restrict use of the information for comparison purposes in order to search for homologies.[10] Such patent claims seem absolutely inimical to the very concept of the patent system, and are unlikely to be issued outside the United States — but they will be very hard to avoid under contemporary U.S. patent principles, as will be noted below.

Genomic information is not the only kind of basic information being patented. For example, it is now possible to obtain a patent on the use of a particular receptor (a molecule on the surface of a cell that leads to a particular response when it is contacted by another particular molecule) as a drug target. Similarly, it is possible to obtain a patent on the portion of a protein that triggers a receptor or an immune response. Such patents may preempt large areas of medical research and lay down a legal barrier to the development of a broad category of products by firms other than those which hold the patent

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[8] Seilhamer et al, (Incyte), 6,023,659, *Database system employing protein function hierarchies for viewing biomolecular sequence data*, Feb. 8, 2000.

[9] E.g. Kunsch et al, (Human Genome Sciences), EPO App. 786,519, filed July 30, 1997, *Staphylococcus aureus polynucleotides and sequences.*

[10] The Institute for Genomic Research, European Patent Office Application 756,006, January 29, 1997, *Nucleotide sequence of the mycoplasma-genitalium genome, fragments thereof, and uses thereof.* Among the claims sought are:

> 1. Computer readable medium having recorded thereon a nucleic acid sequence selected from the group consisting of . . .
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> 14. A method for identifying commercially important nucleic acid fragments of the Mycoplasma genome comprising the step of comparing a database comprising a nucleotide sequence as described in claim 1 with a target sequence to obtain a nucleic acid molecule comprised of a complementary nucleotide sequence to said target sequence, wherein said target sequence is not randomly selected.

Another category of broad patents are those on procedures that may be used in medical research. Few would argue against patents that cover new devices or methods for medical research, e.g. new cell sorting technologies or cell fusion procedures. However, some of the patents go much further than this, to reach, for example, a suspension containing a particular level of concentration of particular types of stem cells, regardless of how that concentration was achieved.[11] And, there are patents on laboratory animals and disease models themselves. The initial case was the Harvard "Oncomouse," genetically engineered to be susceptible to cancer, but there are now much newer ones.[12]

3. IMPLICATIONS FOR RESEARCH

[11] Tsukamoto et al (SyStemix), 5,061,620, *Human hematopoietic stem cell* (Oct. 29, 1991).

[12] E.g. Jolicoeur et al, 6,184,436, *Transgenic mice expressing HIV-1 in immune cells* (Feb. 6, 2001).

For some researchers and institutions, these patents create an important incentive; for others, they are an important legal barrier to research. Indeed, these research tool patents have created an economic division in the research community, between those who benefit from such patents and those who are hindered by such patents. The first group, those who benefit, consists of universities and certain biotechnology firms. Universities often conduct quite basic research, typically funded by governments and foundations -- and this basic research is likely to lead to fundamental discoveries and inventions. Now that the Bayh-Dole Act [13] and a variety of parallel laws in other nations encourage such recipients of public funds to file for patents on their inventions, they will often seek such patents on their fundamental innovations, and then seek to exercise these patents against those who may use the technologies in research. The biotechnology firms which support research tool patents are those who own such patents (either as a result of making the inventions themselves or by taking a license from universities), and then seek strategic alliances with pharmaceutical firms to help the firms by using the particular research tools. This is the business plan of a number of firms in genomic research, who offer to make their data bases and proprietary analytic tools available to pharmaceutical firms on a contract basis. Firms with similar business plans have emerged to offer such services as use of genomic array chips (which permit, for example, easy screening of a large number of expressed sequences in a tissue or an organism under particular conditions), procedures for producing a large variety of candidate drug compounds, and use of proprietary cell culture or identification techniques. The opposing side, that more doubtful about the wisdom of certain genomic and research tool patents, is the pharmaceutical industry itself. This industry would like to have full freedom to use all available research tools to identify possible products. It sees many of the research tool patents as creating significant barriers to its own research (but, of course, wants patent protection on its final products).

The differences between these two wings of the research community have, so far, been barriers to any change in the law. Rather, firms and universities are living with the conflict, typically through license agreements containing "reach-through" royalties, i.e., royalties on use of a patented research tool, measured as a percentage of the sales of the final product produced through use of the research tool. This puts the risk that no product will be forthcoming on the holder of the research tool patent; it probably also leads to a bigger net payment than any lump sum likely to be agreed upon at the beginning. And when a university is a user of a research tool (which is very common), it gives the university a way to avoid making a significant initial payment for use of the technology. (Funding for such payments is rarely found in a research grant.)

These patents will sometimes be solid encouragement for innovations. And it is often the experience of university licensing officers that simply publishing or broadly and reasonably licensing a research tool will not lead to its use, while giving an exclusive license to a venture-capital funded startup will create a group that aggressively applies the technology and ends up serving society through its

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[13] P.L. 96-517, December 12, 1980.

arrangements with pharmaceutical firms (which will normally conduct the tests and clinical trials needed for product approval, and also produce and market the product). But sometimes these patents may hurt more than they help. The extensive time and energy needed to avoid infringing patents and to obtain licenses, even when the licenses are readily available, lead to significant costs and delays in conducting research, even in universities. And the task of assembling all the legal rights necessary to market a product may be so great as to discourage a firm from proceeding. Even if the total license fees can be kept low, there are enormous negotiation costs, and even one "hold-out" may be enough to lead to project cancellation.

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4. IMPLICATIONS FOR DEVELOPING-WORLD HEALTH

Probably the most important implication for developing-world health is the possible slowing of global medical research that has just been described. This is, of course, still a matter of judgment; the patents will both encourage and accelerate important research, as they probably have in the sequencing of the human genome, and at the same time slow and complicate the application of that research. To the extent that these patents do create a slowing, they weaken the contribution of the global research community to the creation and application of medical technology for developing nations. [14]

But it should be recognized that patents are territorial, and that few research tools are likely to be patented in developing nations, either because those nations' laws won't allow such patents to be issued, or because inventors have concluded that economic benefits of patenting the research tools in

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[14] To the extent that the patents increase costs, either through royalties or through negotiation costs, they might conceivably also raise prices for all including the developing world. The optimal price for a pharmaceutical firm, however, is not affected by such long-since-sunk economic costs but rather by current market conditions. Hence, the more likely problem is that these patents will lead to decisions not to undertake particular projects in advance, because of fear that the costs of royalties and negotiations will make the projects uneconomic.

those nations are not big enough to justify the cost of patenting. The research tool firm or university seems likely to look to large developed world firms for its return rather than to those researchers in developing nations. Thus, researchers in developing nations will often be legally free to use the patented research tool or genomic technologies, without having to worry about the patents or possible royalties. Sometimes, this will provide a way to undercut any limitations associated with research tool or genomic patents; where, however, the research must be done in a developed world university or pharmaceutical firm, the researchers will have to observe the limitations of the patents.[15]

5. RESPONSES

[15] There is also an international patent law issue of whether (or when) products developed in the developing world by use of research tools patented in the developed world can be exported back to the developed world. This may be an issue for agriculture; it is probably not one for medicine.

Three kinds of responses are plausible. One is develop a *cross-license* to permit the patented technologies to be used freely for important developing world applications. This is the pattern pioneered by the "SNP consortium," a consortium of pharmaceutical firms, created by the Wellcome Trust.[16] The consortium funded the identification of a large number of SNPs, important in certain drug and genetic research, and placed the information in the public domain so that it would be freely usable. This reflects the pharmaceutical industry's interest in having free access to such research tools. The firms are willing to give one another the technology, because they would rather compete on their products and marketing than through patent battles. (Note that the motivations of universities, which hope to gain income from their technology, are quite different from those of the pharmaceutical firms who want freedom to investigate products, from which they will then make income.)

Although the exact scope and details of such an arrangement cannot be set without substantial discussion, it seems possible that the existing pharmaceutical industry, and possibly the biotechnology industry and universities, would be willing to provide a broad license to permit research by developing-world entities and by one another on some or all of the diseases of the developing world. The chances are that such an arrangement would cost the industry little or nothing; it would, of course, have enormous benefits for the developing world as well as for public relations. It would be easier for diseases found primarily in the developing world, e.g. malaria, than for diseases for which there is a developed world market as well, e.g. HIV. And some of the participants would probably demand safeguards to ensure that the license applied only to use of research tools for developing nation applications and not to use for developed world products.

A second approach is to *change patent law utility and research exemption doctrines*. Such changes could be implemented in developed or developing nations, and can be done in ways consistent with TRIPS. There is an unavoidable tension in the patent law governing research tools and technologies. Basic science is in fact valuable, and patent law seems like a good way to encourage it. But there is a risk, as noted above, that a patent holder can then gain "power to block off whole areas of scientific development, without compensating benefit to the public."[17] Every nation's patent system has evolved a number of doctrines to maintain a reasonable balance in this situation. One is to define a doctrine of "utility" or "industrial applicability." to ensure that abstract ideas are not patented in a way that would give a discoverer an undue monopoly. The doctrine itself is quite abstract and is difficult to define well and apply well in a situation in which much innovation is, in fact, somewhat intangible or abstract, as in basic biology or computer software. But it can be used to shift the balance somewhat in favor of those seeking to apply prior basic and genomic inventions.

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[16] The SNP Consortium Limited, home page at http://snp.cshl.org/.

[17] *Brenner v. Manson*, 383 U.S. 519 (1966).

Another doctrine allows inventions to be used for academic-type research without infringing the patent.[18] The United States courts have recently given this doctrine a very narrow reading, and one of the judges argued in concurrence that there is no such exemption.[19] But many other nations include such a doctrine in their statutes. Usually, however, the research exemption allows experimentation to understand or improve on the patented product or process, but not experimentation to use it. This responds to the perceived need to allow patents for developing new research tools and instrumentation. Thus, a patented approach to making an analytic balance might be used in an attempt to design an improved balance, but not to weigh things, even in research. This is the pattern emerging in Europe, where, in some cases, the research exemption applies to industrial research as well as academic research.[20] Although this exemption would help in many aspects of medical research, many research applications would, in fact, be experimentation to use the technology and would not be permitted.

But there is still a further patent law approach, which would be very wise for many developing nations (and probably developed nations as well) to enact — this is the "dependency license," found in French law.[21] Under this approach, anyone can improve on an invention and, if the improvement is genuinely substantial, obtain a reasonable royalty license to use the invention. By applying an analogous approach in the research tool context, a researcher could be guaranteed that it would not be blocked from applying the technology; at the same time, the research tool inventor would obtain a reasonable return.

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[18] See R. Eisenberg, Patents and the Progress of Science: Exclusive Rights and Experimental Use, 56 *U. Chi. L. Rev.* 1017 (1989).

[19] *Embrex, Inc. v. Service Engineering Corp.*, Case 99-1064 (CAFC, June 28, 2000).

[20] Klinische Versuche (Clinical Trials) I and II, [1998] RPC 423 and [1999} RPC 623 (Federal Supreme Court of Germany, 1995 and 1998).

[21] Code de la Propriété Intellectuelle, Loi 92-597, art. L. 613-15 (July 1, 1992).

The final approach is to narrow the scope of *patentable subject matter* and to restore principles (which once existed) restricting the patentability of abstract concepts, of information, or of principles of nature. This can be done nationally or internationally. Such narrowing might protect, for example, against control of genomic information or of the information that a specific SNP is associated with a specific genetic characteristic, or against patent-based controls on use of genomic information in computer programs. Such a change is consistent with many patent law traditions, which frequently oppose patents on such abstract innovations as software, business methods, and algorithms.[22] Almost certainly, this approach would receive significant support from the scientific community, from significant parts of the medical research community, and, depending on the context, from those members of the business community who believe that software patents are more a nuisance than an incentive. It would be opposed, of course, by the research tool and genomics communities. It is, in a sense, an effort to take the Blair-Clinton statement of March 2000 that " . . . raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere" and to apply it more broadly. It may be better to deal together with genomic and software and business method issues and thus gain from the support of communities that oppose software patents, or alternatively it may be better to restrict the focus to the more narow focus of genomics; this is an important political question.

[22] Again, there are serious difficulties in the careful definition of such a principle, for innovation is becoming more abstract. A measure of the difficulty is *IBM/Computer programs*, [2000] E.P.O.R. 219, in which the European Patent Office's Technical Board of Appeal greatly weakened the provision of European Patent Law which prohibits patents on computer software. The computer program involved was to help deal with resource recovery within a computer. There will be many such difficult borderline cases.