Research-tool patents: issues for health in the developing world*

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Abstract The patent system is now reaching into the tools of medical research, including gene sequences themselves. Many of the new patents can potentially preempt large areas of medical research and lay down legal barriers to the development of a broad category of products. Researchers must therefore consider redesigning their research to avoid use of patented techniques, or expending the effort to obtain licences from those who hold the patents. Even if total licence fees can be kept low, there are enormous negotiation costs, and one ''hold-out'' may be enough to lead to project cancellation. This is making it more difficult to conduct research within the developed world, and poses important questions for the future of medical research for the benefit of the developing world. Probably the most important implication for health in the developing world is the possible general slowing down and complication of medical research. To the extent that these patents do slow down research, they weaken the contribution of the global research community to the creation and application of medical technology for the benefit of developing nations. The patents may also complicate the granting of concessional prices to developing nations — for pharmaceutical firms that seek to offer a concessional price may have to negotiate arrangements with research-tool firms, which may lose royalties as a result. Three kinds of response are plausible. One is to develop a broad or global licence to permit the patented technologies to be used for important applications in the developing world. The second is to change technical patent law doctrines. Such changes could be implemented in developed and developing nations and could be quite helpful while remaining consistent with TRIPS. The third is to negotiate specific licence arrangements, under which specific research tools are used on an agreed basis for specific applications. These negotiations are difficult and expensive, requiring both scientific and legal skills. But they will be an unavoidable part of international medical research.

Keywords Research; Patents; Licensure; Molecular sequence data; Drug industry; Developing countries (*source: MeSH, NLM*).

Mots clés Recherche; Brevet; Autorisation exercer; Données séquence moléculaire; Industrie pharmaceutique; Pays en développement (*source: MeSH, INSERM*).

Palabras clave Investigación; Patentes; Licencias; (Molecular sequence data); Industria farmacéutica; Países en desarrollo (*fuente: DeCS, BIREME*).

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The relevant intellectual property rights

The patent system is now reaching into the tools of medical research, including gene sequences themselves. This is making it more difficult to conduct research within the developed world, and poses important questions for the future of medical research for the benefit of the developing world (*1, 2*).

Patents on genes have received the greatest attention. Many people think that for ethical reasons genes should not be patented. At the same time, however, most of those closely associated with pharmaceutical research believe it is 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.

Patents were therefore granted quite early on for naturally occurring proteins and the genes that coded for them. Not long ago, the sequencing of genes was difficult and often took place at the same time as the identification and purification of the protein. Typically, the patents included claims (which are the formal descriptions of the precise legal area of exclusive rights) for genetic sequences in isolated form, for various vectors that included the gene and might be used for inserting the sequences into cloning organisms, for cloning organisms used in the mass production of the protein, and for the proteins themselves. The need to meet the "novelty" requirement in patent law — that the patented invention should be new and not anticipated in previous literature or in nature — was met by the theory that the product or gene sequence had never before existed in isolated form.

The public and private human genome programmes 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 a legal debate over the patentability of sequences which are believed to code for a protein whose function may be unknown or only estimated from homology to known sequences. In its new *Utility Examination Guidelines*, the United States Patent and Trademark Office (PTO) indicated

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that it would require a "specific and substantial utility that is credible" (*3*). The same pattern is likely to prevail in Europe under the Biotechnology Patent Directive (*4*).

Patents have been sought for expressed sequence tags (ESTs), which are sequences of parts of genes that are expressed in particular circumstances, and which are relatively easy to identify and sequence. The new utility guidelines strongly suggest that EST patents will only be granted if applicants show they have reason to believe that the protein which they may assist in identifying will in itself be useful. If this utility is present, the question still remains: whether the patent should cover only the use of the EST as a probe to help in identifying the entire gene or whether it should also cover the entire protein containing the sequence, regardless of whether the EST is used to identify the protein. The implications of this choice are extremely important: a firm that holds the "probe" kind of patent can block the use of one specific way of identifying a gene (and is likely to be motivated to market that method to other firms), while a firm that holds the broader style of patent can prevent other firms from using the gene altogether.

SNPs (single nucleotide polymorphisms) present different problems. They are points in the genetic sequence in which one person's DNA differs from that of another. Because these sequences can be used to identify particular genetic conditions, they obviously have greater utility than ESTs, assuming that the implications of the specific SNP have been identified. Thus, there are patents covering the breast and ovarian cancer-predisposing genes (*BRCA*1 and *BRCA*2) which were based on early research and extensive use of genetic linkages (e.g. *5*). It is almost certain that there will be United States patents not only on SNPs with a clear diagnostic role, but also on all kinds of genotypic-phenotypic linkages, completely covering the use of particular genomic information to infer characteristics of the organism.

The post-genomic era is here, and efforts are being made to obtain patent rights over computer programs for the analysis of genomic information, the "annotation" of the genome and the conditions of expression of the different genes, and the structures and roles of the various proteins encoded by the genes. In the United States, patents have long been granted in cases where the invention consists of new software or statistical or other analytic approaches. Such patents will certainly cover particular approaches to the development of annotations describing the functions or characteristics of a part of the genome, the analysis of genomic data or gene expression data, and protein structure calculation. There is also an important new line in patent applications, namely, seeking claims that would control the use of genomic information in machine-readable form (e.g. *6*).

It is now possible to obtain a patent on the use of a particular receptor which may serve 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. Patents have also been granted on protein structures, with claims covering the use, in computers, of the coordinates in calculations to identify compounds that might bind to the protein (e.g. *7*). Patents have long been available on fundamental research technologies such as PCR (polymerase chain reaction) for amplifying gene sequences or Cre-Lox for excising particular sequences. Few would argue against patents that cover new devices or methods for medical research, for example, new cell sorting technologies or cell fusion procedures. However, some of the patents go much further, even covering, for example, a suspension containing a particular level of concentration of certain types of stem cells, regardless of how that concentration was achieved (*8*). There are also patents on laboratory animals and the disease models themselves. The first case of this type was the Harvard "Oncomouse", which had been genetically engineered to be susceptible to cancer, but there are much newer cases, too.

Implications for medical research generally

Some of these patents can preempt large areas of medical research and lay down a legal barrier to the development of a broad category of products. The possibility is particularly strong in biotechnology for several reasons: there are so many broadly relevant patents; research builds on the use of so many prior discoveries; and solid and clear title to a product is so important to the pharmaceutical industry. A researcher must therefore sometimes consider either redesigning a research programme in order to avoid using patented techniques, or expending the effort to obtain licences from the patent holders. 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 licence fees can be kept low, there are enormous negotiation costs, and one "hold-out" may be enough to cause the project to be cancelled.

Indeed, 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 them. Those who benefit include universities and certain biotechnology firms. Now that universities and public institutions are encouraged to file for patents on their inventions, they often seek such patents on their fundamental innovations, and may seek to exercise these patents against those who might use the technologies in their research. Many biotechnology firms also support research-tool patents. These firms acquire such patents, either through their own research or by taking licences from universities. They then seek strategic alliances with pharmaceutical firms which they help by using the relevant research tools. These firms serve an important function — university licensing officers have often said that simply publishing or broadly and reasonably licensing a research tool will not lead to its use, whereas giving an exclusive licence to a venture-capital funded start-up company will create a group that aggressively applies the technology and ends up serving society through its arrangements with pharmaceutical firms. This is the business plan of genomics firms that make their databases and proprietary analytical tools available to pharmaceutical firms on a contract basis. Firms with similar business plans offer services such as the use of genomic array chips, procedures for producing a large variety of candidate drug compounds, and use of proprietary cell culture or identification techniques.

The opposing side, which includes many scientists and the pharmaceutical industry itself, is more doubtful about the wisdom of certain genomic and research-tool patents. This section of the industry would like to have complete freedom to use all the available research tools in order to be able to identify possible products. It sees many of the research-tool patents as creating significant barriers to its own research, but, of course, it would like patent protection on its final products. (In economic terms, the return from the product has to cover the costs of the pharmaceutical firms, including clinical trials, as well as any return to the research tool patentees.)

We are still learning whether, in general, these conflicts will really harm medical research. According to a recent survey, projects have only rarely, if ever, been stopped, but they have been delayed and made more expensive (*9*). Firms and universities are having to live with the effects of the conflict. The licence agreements often include "reach-through" royalties, that is, royalties on the use of a patented research tool, measured as a percentage of the sales of the final product produced through use of the research tool. The pharmaceutical firms protect themselves in return by seeking "anti-stacking clauses", in which the firms and universities that supply the research tools agree to accept a reduction in their reach-through royalty if the total level of royalties derived from different research tools embodied in a single final product becomes too large (*10*). However, some firms, instead of acquiring rights, are simply using the technology in the laboratory, either ignoring the patent rights altogether, or hoping to be covered by a research exemption to the patent laws. Consideration is even being given to moving research off-shore to regions where fewer broad patents have been issued (*9*).

Implications for health in the developing world

What will the impact of all this be on medicine in the developing world? We really do not know yet, although there is a strong basis for concern that the difficulties just described will also affect research on diseases in developing nations. Such concern already exists over the analogous issue in agriculture (*11*). Probably the most important implication for health in the developing world is the possible general slowing and complication of medical research. Such slowing and complication weaken the contribution of the global research community to the creation and application of medical technology for the benefit of developing nations. The patents may also complicate the grant of concessional prices to developing nations — for pharmaceutical firms that seek to offer a concessional price may have to negotiate arrangements with research-tool firms, which may lose royalties as a result.

It ought to be recognized that the private sector has relatively little interest in patenting the special tools that are important specifically to medicine in the developing world, for example, the genomes of tropical pathogens. Moreover, patents are territorial. Few research tools are therefore likely to be patented in developing nations, either because their laws will not allow such patents to be issued, or because inventors have concluded that the economic benefits of patenting the research tools in those countries are not big enough to justify the cost of patenting. Thus, researchers in developing nations will often be legally free to use the patented research tool without having to worry about the patents or possible royalties (and this may even be an incentive to carrying out research in developing nations).

Sometimes, however, part of the research will have to be done in a university or pharmaceutical firm in a developed country where the technology is patented; in that case, the researchers will have to observe the limitations of the patents. The same is true where a product is to be marketed in the developed world (e.g., for travellers), as well as in the developing world. And for important immune system or vaccine components, there may soon also be important patents in developing countries, especially in the larger ones such as Brazil, China, and India. An additional problem that scientists in developing nations often face is that they do not have the easy access to legal advice that is available in the developed world.

Responses

Three kinds of response are plausible. One is to develop a broad or global licence to permit the patented technologies to be used for important applications anywhere in the world, including in developing countries. This is the pattern pioneered by the SNP Consortium, a consortium of pharmaceutical firms created by the Wellcome Trust (*12*), which funded the identification of a large number of the SNPs needed for certain drug and genetic research — and placed the information in the public domain so that it would be freely usable. The United States Patent Office has prepared a discussion paper on such approaches (*13*).

It seems that a large section of the pharmaceutical industry, if not all of it, and perhaps the biotechnology industry and universities as well, would be willing to provide a broad licence to facilitate research on some or all the diseases of the developing world. The chances are that such an arrangement would cost the industry little or nothing and would, of course, have enormous benefits for the developing world as well as for its own public relations. It would work better for diseases found primarily in the developing world, for example, malaria, than for diseases for which there is also a market in the developed world, for example, HIV. And grantor policies, such as those already issued by the United States National Institutes of Health to encourage reasonable sharing of research tools, could be used to persuade entities that receive public research support to be more cooperative (*14*).

A second way of responding is to change technical patent law doctrines. Such changes could help avoid delays and complications in developed and developing nations that adopted the reforms. 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, as the United States Supreme Court noted in 1966, there is a risk that a patent holder may thereby gain "power to block off whole areas of scientific development, without compensating benefit to the public" (*15*).

Every nation's patent system has evolved a number of doctrines to enable a reasonable balance to be maintained in such a situation, and these doctrines could be modified — and still remain consistent with TRIPS — to shift the balance in favour of the user of the technology. A case in point is the doctrine of "utility" or "industrial applicability", which ensures that abstract ideas are not patented in a way that would give the discoverer an undue monopoly. The doctrine could be strengthened to shift the balance slightly in favour of those seeking to apply prior basic inventions.

Another doctrine allows inventions to be used for academic-type research without infringing the patent. Usually, this exemption allows experimentation for the purpose of understanding or improving the patented product or process, but not to enable it to be used. This responds to the perceived need for patents in order to develop new research tools and instrumentation. Thus, a patented approach to making an analytical balance might be used in an attempt to design an improved balance, but not for

weighing things, not even in research. This exemption could help in some aspects of medical research, but many research applications of patented technology would, in fact, be experimentation to use the technology and would therefore not be permitted.

A further patent law approach to this problem is the "dependency licence", which exists in the law of a number of countries (e.g. *16*). A dependency licence allows a researcher to improve on an invention and, if the improvement is genuinely substantial, to obtain a reasonable royalty licence to use the invention. Researchers could be given a guarantee that they would not be blocked from applying the technology; at the same time, the inventor of the research tool would obtain a reasonable return. Such an approach seems to be especially desirable for developing countries.

Alternatively, the law could be used to restore principles (which once existed) restricting the patentability of abstract concepts, information or principles of nature. Such restrictions might provide protection, for example, against control of genomic information or information linking a specific SNP with a specific genetic characteristic, or against patent-based restrictions on the use of genomic information in computer programs. Some of these patent claims seem absolutely inimical to the very concept of the patent system and are unlikely to be issued outside the United States. Almost certainly, some restriction would receive significant support from the scientific community and from significant parts of the medical research community. This is, in a sense, an effort to broaden 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".

The third way of responding to current problems posed by patenting is to negotiate specific licence arrangements, by which specific research tools are used on an agreed basis for specific applications. This is already a familiar process in the agricultural sector, where a number of specific partnerships have been formed between research institutions in developed and developing countries to provide technology that may be covered by patents (*11*). Careful management of patent rights is one of the issues being tackled by the new research partnerships on diseases that are prevalent in the developing world, such as malaria (*17*). Negotiating such arrangements is difficult and expensive since legal as well as scientific skills are required, but it will be an unavoidable part of international medical research. ■

Conflicts of interest: none declared.

Résumé

La protection par brevet des outils de recherche : conséquences pour la santé dans le monde en développement

Le régime des brevets s'étend maintenant aux outils de la recherche médicale, y compris les séquences géniques elles-mêmes. Beaucoup des nouveaux brevets délivrés peuvent potentiellement bloquer de larges secteurs de la recherche médicale et placer des obstacles juridiques au développement de catégories entières de produits. Aussi les chercheurs devraient-ils étudier la possibilité de revoir leurs méthodes de recherche pour éviter d'utiliser des techniques brevetées ou renforcer leurs efforts pour obtenir des licences de ceux qui détiennent les brevets. Même si le total des redevances de licences reste d'un niveau raisonnable, le coût des négociations est énorme et un seul point de blocage peut suffire à entraîner l'annulation de tout un projet. Les recherches menées dans les pays développés sont rendues d'autant plus difficiles, ce qui pose d'importants problèmes pour l'avenir de la recherche médicale au profit du tiers-monde. L'incidence probablement la plus importante pour la santé dans les pays en développement est la possibilité d'un ralentissement général possible et de la complication de la recherche médicale. Dans la mesure où ces brevets ralentiront effectivement les choses, ils affaibliront la contribution de la communauté mondiale des chercheurs à la création et à l'application de technologies médicales au profit des pays en développement. Les brevets peuvent aussi rendre plus difficile l'octroi de prix de faveur aux pays en développement, car les firmes pharmaceutiques qui essaient de leur offrir ces prix plus intéressants peuvent avoir à négocier des arrangements avec les sociétés qui détiennent les outils de recherche, lesquelles peuvent subir un manque à gagner dans l'opération. Trois types de réponses à ce problème sont envisageables. L'un consisterait à imaginer un système de licences élargies ou mondiales permettant d'utiliser les technologies brevetées pour d'importantes applications dans les pays en développement. Le deuxième consisterait à modifier la doctrine juridique concernant les brevets techniques. Ces changements pourraient être mis en œuvre à la fois dans les pays développés et dans les pays en développement et pourraient être très utiles tout en demeurant compatibles avec l'Accord de l'OMC sur les ADPIC. La troisième solution consisterait à négocier des arrangements de *licences spécifiques*, dans le cadre desquelles certains outils de recherche pourraient être utilisés sur une base convenue pour des applications déterminées. Ces négociations sont délicates et coûteuses, car elles nécessitent à la fois des compétences scientifiques et des compétences juridiques, mais elles constitueront un aspect incontournable de la recherche médicale internationale.

Resumen

Patentes sobre instrumentos de investigación: repercusión para la salud en el mundo en desarrollo

El sistema de patentes está extendiéndose a los instrumentos de investigación médica, incluidas las secuencias genéticas. Muchas de las nuevas patentes pueden llegar a proteger grandes áreas de la investigación médica e imponer obstáculos jurídicos al desarrollo de una amplia categoría de productos. En consecuencia, los investigadores se ven obligados a rediseñar sus investigaciones para sortear las técnicas patentadas, o a invertir las sumas necesarias para obtener las licencias de los titulares de las patentes. Aunque los derechos de licencia sean bajos, el costo de las negociaciones es enorme, y una sola negativa puede bastar para

anular el proyecto. Todo esto hace más difíciles las investigaciones en el mundo desarrollado, y ensombrece con graves interrogantes el futuro de las investigaciones médicas beneficiosas para el mundo en desarrollo. La consecuencia probablemente más importante para la salud en el mundo en desarrollo es el posible retraso y entorpecimiento general de las investigaciones médicas. En la medida en que efectivamente retrasan los avances, estas patentes debilitan la contribución de la comunidad investigadora mundial a la producción y aplicación de tecnologías médicas beneficiosas para los países en desarrollo. Las patentes pueden dificultar además la concesión de precios de favor a los países en desarrollo, toda vez que muchas de las empresas farmacéuticas interesadas en ofrecer tales precios tienen que negociar acuerdos con firmas de instrumentos de investigación, que como resultado de ello pueden perder regalías. Ante esta situación, cabe imaginar tres posibles respuestas. Una consiste en desarrollar una licencia general o mundial que permita usar las tecnologías patentadas para aplicaciones importantes en el mundo en desarrollo. La segunda es modificar las doctrinas que sustentan el derecho de patentes técnicas; esos cambios podrían aplicarse en los países desarrollados y en los países en desarrollo y podrían ser de gran ayuda aun asegurando la compatibilidad con los ADPIC. Y la tercera, por último, consiste en negociar acuerdos de concesión de *licencias específicas*, que permitan emplear instrumentos de investigación específicos según lo convenido para aplicaciones específicas. Estas negociaciones son difíciles y onerosas, y exigen gran preparación tanto científica como jurídica, pero serán un componente inevitable de la investigación médica internacional.

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