PATENTS AND GENE SEQUENCES

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The international project to map and sequence the human genome has stimulated a debate about patents involving gene sequences. Recent developments such as the announcement of a 'first draft' of the genome have served to intensify the issue.

This briefing outlines the progress to date of sequencing efforts and examines the intellectual property rights (IPR) issues that arise.

BACKGROUND

For more than 10 years researchers in the publicly funded human genome project (HGP) have been attempting to read the sequence of 3.1 billion bases that comprise the human DNA code[1]. The recent (September 1999) involvement of a privately funded American company (Celera) has served to accelerate the process. In a joint statement on 26th June 2000, scientists announced that they had obtained:

- a 'first draft' of ~85% of the total human genome;
- a finished sequence for ~24% of the genome.

Work to 'fill the gaps' and check the accuracy of the first draft should produce the finished version by 2003. The draft sequence covers virtually all of the bits of most interest – the 100,000 or so genes, each of which contains the recipe for making one of the proteins that control biological processes. The challenge facing researchers now is to understand what the code means. For instance, how are genes involved in certain types of common disease such as cancer, heart disease or diabetes? How do subtle variations between genomes contribute towards predisposition to particular diseases, reactions to certain types of drugs, etc? Better understanding of these questions, and of the role of genes in controlling basic biological processes will lead to improved diagnostic tools and therapies.

ISSUES

At some point between raw sequence data becoming available and the marketing of a gene-based invention, researchers will seek IPR to protect their research investment. There is a near universal consensus against patenting raw sequence data. Indeed under patent law a gene is not patentable *per se* without the knowledge of its function, role in disease, etc. However, as discussed below, there is debate over how much such knowledge is required, and over the scope of some patents already allowed.

BOX 1 PATENT LEGISLATION

The UK Patents Act (1977) – UK patents are based on a 'first-to-file' system. An inventor files an initial application for a patent describing details of the invention. If granted, a patent may last up to 20 years from the date of this initial filing. The Act requires an Examiner to decide whether an invention fulfills three criteria:

- novelty – the invention must be new and not previously disclosed in the public domain;
- inventive – it must also be non-obvious (i.e. to someone skilled in the art who is aware of relevant publicly available material);
- industrial application – can it be used for a practical purpose?

The Directive for the legal protection of biotechnological inventions was approved by the European Parliament in May 1998 and entered into European law in July 1998. It must be implemented into national law by July 30 2000 and harmonises national patent laws throughout the EU by specifying what can (and cannot) be patented:

- cloning human beings, genetic modification of the human germ line, commercial uses of human embryos **cannot** be patented because their commercial exploitation is contrary to morality.
- genetic modification likely to cause suffering to animals **cannot** be patented unless there is substantial medical benefit to man or animal.
- genes or other body parts in their natural state **cannot** be patented.
- Inventions concerning isolated genes that are identical to those found in nature **can** be patented provided they fulfil the three usual criteria for patentability (see above).

Novel, inventive and useful?

Although details vary, most patent systems require an invention to fulfil three main criteria (**Box 1**): novelty; inventiveness; and usefulness ('industrial application' under UK and European patent law and 'utility' in the US). Under current UK law (and the EU Directive - Box 1) genes as they exist in cells in the human body cannot be patented; the sequence itself is a discovery, **not** an invention. However, the act of isolating a sequence from a cell and cloning it **may** represent a sufficient technical contribution to allow a patent claim. This will depend on:

- the means used to isolate the sequence (would it have been obvious to skilled researchers in the area at the time?);
- whether the isolated sequence is novel (has it been previously described?);
- whether the claim describes a practical use for the sequence (see below).

Establishing whether an invention is useful is more difficult. One of the problems here is that DNA is an 'inherently useful' molecule – even a relatively short length of sequence can be used as a 'probe' to find the gene from which it originated. In the past, this particular use has formed the basis of utility claims made for hundreds of thousands of partial sequences from genes of unknown function (**Box 2**).

[1] **See POST report 142 Human Genome Research for more details.**

To date, no such claims have been allowed by agencies such as the UK Patent Office, European Patent Office or US Patent and Trademarks Office (USPTO). Of these, the USPTO has had to deal with the largest number of gene-based claims. It has granted several thousand such patents, mostly involving whole gene sequences (Box 2); in each case the function of the gene was known and the claimed utility (whether therapeutic or diagnostic) backed up with experimental evidence. There are also a large number of provisional applications involving partial sequences from genes of unknown function. Recent revisions to USPTO examination guidelines that effectively tighten up the utility requirements mean that companies are unlikely to pursue these. Under the new guidelines, applicants must describe uses for their inventions that are specific, credible and substantial (i.e. that define a 'real world' use).

Patent scope

A closely related issue is that of patent scope. In order to maximise their intellectual property portfolio, applicants often frame their claims in the broadest possible terms – for instance, claiming that the invention can be used for therapeutic and/or diagnostic purposes in humans and other species. Concerns have been raised that, if granted, such claims may effectively award the patent holder a monopoly on all possible future uses of the sequence in question.

The example of the CCR5 receptor gene, isolated by an American company (HGS) in the mid-1990s, illustrates some of the issues that arise. Research initially implicated the gene in inflammatory diseases such as arthritis. On this basis, HGS sought a patent (granted in January 1999) containing a broad claim to "*medical uses of CCR5 such as therapies to block or enhance the receptor function*". Further research – much of it publicly funded - has subsequently shown that the CCR5 receptor is also one of the co-factors involved in the infection of cells of the immune system by HIV. Although HGS had no inkling of the role of CCR5 in HIV infection when it applied for its patent, the broad scope of the claim means that it may well cover such applications of the gene. This is currently being contested by the scientists that discovered the role of CCR5 in HIV/AIDS. They argue that the scope of the HGS patent should be limited to those applications described (and supported by research evidence) in the original claim. They are currently seeking their own patent covering therapeutic applications of the CCR5 gene in HIV/AIDS treatments.

BOX 2 SEQUENCE-BASED PATENTS

Partial gene sequences. The first attempt to claim ownership of gene sequences on a large scale came in the early 1990s, when the US National Institutes of Health (NIH) filed patent applications for nearly 7,000 partial sequences from genes of unknown function with the USPTO. All the other HGP collaborators opposed these applications, although the Medical Research Council (MRC) also applied for patents on some 1,100 partial gene sequences in a defensive measure designed to protect UK interests if the US applications were granted. NIH withdrew the applications in August 1992; MRC decided not to pursue its applications shortly thereafter. More recently, at least one US company (Incyte) has filed provisional patent applications on more than 1.3 million partial gene sequences from genes of unknown function.

Whole genes. Several US Companies are currently seeking patents on large amounts of sequence data. Among the bigger players are:

- Celera – intends to publish all of its human genome sequence on the Internet, but will first seek patents on any sequences identified by its pharmaceutical partners as being medically interesting. By October 1999, Celera had made provisional applications for patents on some 6,500 gene sequences (the company had previously stated to the US congress that it expected to obtain patents on 100 to 300 gene sequences).
- Human Genome Sciences Inc. (HGS) – as of January 2000, HGS had filed patents describing the medical use of more than 7,400 human genes (153 of which have been allowed to date).
- Incyte – in addition to claims relating to partial gene sequences (see above), Incyte is also seeking patents involving over 5,300 full length genes. Of these, around 250 patents on pharmaceutically important genes have already been issued. Under the terms of its agreements with its subscribers, Incyte could receive future payments and royalties on sales of products developed with Incyte technology and database information.

Polymorphisms are chromosomal locations where DNA sequence varies within a population. There is currently much interest in identifying such sites, and several large companies are seeking IPR on databases of polymorphisms. In the UK, a consortium consisting of the Wellcome Trust and 10 drug companies is compiling a publicly accessible database of around 300,000 polymorphisms.

Overview

A recent joint statement from President Clinton and Prime Minister Blair reiterated that:

- raw sequence data should be released "*rapidly into the public domain*" but that;
- patents for gene-based inventions will "*play an important role in stimulating the development of important new healthcare products*".

This puts the emphasis on patents that describe a gene-based procedure rather than those that attempt to claim a gene itself. Under such an approach, it would be possible for different patents to be awarded describing different uses of the same gene. Detailed questions on scope, novelty, inventiveness and usefulness will only be resolved over time, as a jurisprudence emerges from the application of patent law and challenges to it through the courts.