Genomics and intellectual property rights

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Issues that concern intellectual property (IP) rights in biotechnology have become increasingly focused on genomics. IP protection in genomics often involves patenting DNA and it is on this aspect that much of the complexity and controversy has centred. Genomics has also stimulated the development of new technologies crucial to the exploitation of the large volume of information that genomics is beginning to generate. IP rights for some of these technologies are being vigorously pursued. Because the structural and functional analysis of human and other genomes has central significance to many areas of the life sciences and to developments in healthcare, questions over accessibility and appropriability of genomic information are being widely debated. In this article the factors shaping IP rights in genomics are explored together with the probable implications. The patenting strategies of industry, including the multinational pharmaceutical firms and the small, specialized firms, are considered together with those of the public sector.

The application of genomics to the life sciences will be enormously influential. The development of automated DNA sequencing techniques in the early 1990s initiated what will become the transformation of the life sciences. The emphasis has shifted from small-scale to large-scale research and from small units of discrete knowledge to the generation of enormous amounts of information. Continual improvements in DNA sequencing and new approaches to functional analysis using DNA chip technology have the potential to enhance healthcare through the identification of disease genes and new drug targets. Parallel DNA sequencing and functional analysis in a range of organisms has also allowed the development of *in silico* methodologies. Functional DNA sequence homologies in yeast and *Caenorhabditis elegans* present an extremely powerful tool for understanding human gene structure and function.

The development of genomics and its application is approached from different perspectives by the public sector, where some of the techniques were initiated, and the private sector. For the public sector researchers based in universities and research institutes, research that involves genomics is essentially risk free. Gene identification and functional analysis in human and other organisms offer new ways of applying the molecular approach to physiology and development. The application of genomics in the private sector is a completely different matter. The potential value of identifying disease genes and designing new drugs to act on specific targets is difficult to predict. It is, moreover, expensive and as we shall see, there are major uncertainties associated with intellectual property (IP) rights. Despite these uncertainties, the pharmaceutical multinationals and many small companies continue to make major investments in the field of genomics. This is because understanding the role of genes in disease offers the most rational approach to elucidate the underlying pathology and to develop drugs that act on those processes.

In broad terms, the main outputs of genomics will be:

- Identification of disease genes that have applications in clinical diagnostic and predictive testing

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- Identification of genes that influence behavioural characteristics and that will improve our understanding of human behaviour and psychology
- Improved understanding of disease processes, patient genotyping in relation to drug metabolism, and a greatly enhanced understanding of biological processes

How do IP rights align with the expanding field of genomics? The application of IP rights to biotechnology has been shaped over the past 20 years by existing patent laws, new patent laws, patent office decisions on patent applications, case law and to some extent technology 'push'. The development of IP rights in the broad area of biotechnology has been widely reviewed (for example, see Ref. 1). In this article, we are concerned with the impact of genomics on the broadly based public policy framework established for IP in biotechnology. In the next section we briefly consider the existing framework for patenting in the area of biotechnology that is relevant to genomics and then consider how this is likely to be influenced by current development.

Intellectual property framework for genomics

DNA sequences were patented some years before the concept of the human genome project was developed. Early on in the development of recombinant DNA therapeutics, researchers became aware that the success of these drugs would be dependent on patenting the gene sequence itself. In the early 1980s, patenting pharmaceuticals was the norm and therefore patenting the biological template for the drug was an obvious step. Many of these early patents were for interferons, interleukins and similar molecules based on human genes. Examination of claims within these patents has shown that many are overlapping and it is likely that some of the patents would have been declared invalid if challenged. Few of these early patents have translated into marketable drugs. The most important example is erythropoietin (EPO). Amgen (Boulder, CO, USA) was able to claim the rights to this recombinant drug because it had shown 'reduction to practice' by including the DNA sequence in its patent claims[2]. As the quality and speed of DNA sequencing improved, so the concept of genomics emerged. It became obvious to the leading pharmaceutical companies that gene identification would be highly informative in providing new drug targets. The development of the EST (expressed sequence tag) approach, whereby partial sequences could be isolated from mRNA in different tissues, has played a major role in this respect. Once a partial sequence is located, identifying the full sequence is a relatively simple process.

The attempt by Craig Venter [a National Institutes of Health (NIH, Bethesda, MD, USA) researcher] to patent 1350 partial gene sequences of unknown function created an international furore. Although the US Patent and Trademark Office (PTO) rejected the application, the approach led to the establishment of the first genome company: Human Genome Sciences (Rockville, MD, USA). Since then, ~25 genome companies have been founded, nearly all of them in the USA and involved in mapping and sequencing genes associated with human disease. Two of these also have significant involvement with plant genome analysis. Multinational pharmaceutical companies have invested over $1.8 billion in these small firms to help apply genomics to their drug discovery programmes. For example, Millennium (Cambridge, MA, USA) has collaborations with nine corporate partners including Bristol-Myers Squibb, Eli Lilly, Roche and Pfizer. It also has a new agreement with Monsanto (St Louis, MO, USA) worth $200 million. The agreements underlying these collaborations are strongly tied to IP rights.

Intellectual property strategy in the private sector

There are two parallel strands that are important in private sector genomics. First, patents for inventions that are based on key disease genes continue to be central to IP strategy. Second, there is increased emphasis on the production of information. For example, the role of particular receptors in a disease pathway may not be clear when identified at the outset, but their probable importance as drug targets means that the corporate approach will be to patent them regardless. As the metabolic pathways involved in many common diseases will be complex, the main approach can be summarized as 'if in doubt, patent it'. This strategy means that companies can always allow patents to lapse if, in due course, a particular receptor or enzyme proves not to be relevant to the proposed therapeutic approach. Because the scale of genetic information production is so large and many thousands of ESTs can be sequenced in a particular set of disease tissues, owning the rights to molecules of possible importance becomes critical at the outset of drug discovery programmes. As in the 1980s, many pharmaceutical companies will be pursuing the same information for the same diseases.

Potential for over-patenting

A major disadvantage of the emphasis on the high throughput of information being produced both in-house by pharmaceutical companies and by small genomics companies is that it may lead to a trend towards over-patenting. It is not always obvious which gene mutations, receptors or enzymes

may be important in the disease process, and so the temptation is to patent all possible candidates. This effect will be even further exaggerated if ESTs are considered to be patentable inventions by patent offices. Although the US PTO rejected the initial attempt by Venter in 1991, recent signals from the US PTO suggest that ESTs may be patentable if they fulfil the utility requirement by having utility, for example, as a probe. The US PTO has pointed out that the utility of an EST as a probe may be small but it is nevertheless valid. Whether the recent granting of a patent for ESTs to Incyte (Palo Alto, CA, USA) is the start of a trend or an exception remains to be seen. It will not be clear until more time has elapsed as to whether early claims on partial DNA sequences will have (reach-through) effects on complete gene sequences. Thus a company or public sector researcher may file for a patent on an EST sequence suspected of having an important role in a disease process and be awarded a patent. Another researcher who subsequently locates the full sequence and elucidates its function may be denied a patent on the basis of the priority awarded to the patent holder on the claims to the partial fragment. There has been speculation about such scenarios but unfortunately no guidance is forthcoming in this area of public policy because such decisions are largely shaped by case law. Those involved are filing for patents on both full and partial gene sequences in the hope that some of these will afford the protection needed in bringing diagnostics and drugs to market. R.S. Eisenberg in particular has pointed out that the prospect of over-patenting may lead to under-exploitation of an important resource[3]. The possibility of large numbers of patents on fragments of human DNA raises a relatively unmanageable and sub-optimal situation.

A further step down towards the direction of over-patenting may also be imposed by patenting of single nucleotide polymorphisms (SNPs). SNPs are point mutations in the genome that are thought to have potential in pharmacogenomics and in locating disease genes, although there is debate about their utility in association studies[4]. It is likely that SNPs will be patented even though they are only a few bases long. If these mutations are claimed in the context of locating a particular gene, then it seems probable that they will indeed be patentable. One company, Genset (Paris, France), which has a large SNP programme for human genome mapping has already made it clear that it will be filing patents on SNPs. As SNPs are distributed throughout the genome it seems likely that complications may occur in future licensing.

A recent comparative study of genomic patents filed by small biotechnology companies in Europe and the USA revealed that while the overall number of filed patents per company was similar, because of the sheer size of the small firm sector in the USA, the total number held in the US sector was fivefold that of Europeans[5]. In particular, the very substantial contribution from companies such as Human Genome Sciences (HGS) and Genentech (South San Francisco, CA, USA) is unmatched in Europe. For example, a total of 98 patents applications from HGS were divided into four main groups: G-protein-coupled receptor patents, patents claiming other receptors, channels and transporters, and genome patents. A substantial proportion of the HGS PCT patents are in the area of cytokines and chemokines [Patent Convention Treaty patents are processed by the World Intellectual Property Organization (WIPO)]. At least one complete genome sequence has been claimed in an HGS patent. This is the patent for the entire sequence of the *Haemophilus influenzae* genome, which has claims for diagnostics in the context of the complete sequence. Also claimed is the use of the sequence in database searches to enable allocation of function to related organisms.

Shotgun sequencing the human genome

No review of IP rights in genomics can ignore the recent initiatives to accelerate sequencing of the human genome. The loosely collaborative international Human Genome Project had aimed to complete the sequencing of the entire human genome by 2005. However, the recent announcement of Celera (Rockville, MD, USA), a joint venture between the multinational Perkin-Elmer and Craig Venter, formerly of The Institute for Genomic Research (TIGR, Rockville, MD, USA) aims to use the shotgun technique to sequence the human genome within two years. The aim of this commercial sequencing project is to harvest what the company sees as the most valuable information and to make the sequence data available to those who wish to have access to it. Venter has suggested that the company will only be patenting 200–300 genes, which seems a modest estimate. Reaction to this initiative has been mixed. Some genome researchers have welcomed the additional resources and the more rapid achievement of a common goal. Others have taken the view that the project will not be particularly helpful as it will not produce a complete sequence, and they doubt the value of Celera's intention to put DNA sequence in the public domain. Although Celera is committed to depositing the sequencing information at quarterly intervals it seems likely that this information will only be really useful if the user subscribes to a processing service for which he or she will have to pay. Another genomics company, Incyte, has announced that it is also setting up a new project to sequence

the genome within two years. Sponsors of the public sector international project have agreed to put further funds into the project to bring forward their own efforts. Both the NIH in the USA and the Wellcome Trust (London, UK) have committed additional funds to try and achieve new sequencing goals by 2003.

Patenting strategies in the public sector

Public sector approaches to IP rights in genomics have been varied. There has been a major commitment to public access to sequence data by the major genome sequencing centres such as the Sanger Centre (Hinxton, UK), the Washington University Genome Sequencing Centre (St Louis, MO, USA) and other genome consortia. This commitment has been particularly evident in the *C. elegans* project, yeast and in human DNA sequencing research. The approach was most clearly exemplified by the international collaborative yeast-sequencing project that involved more than a hundred laboratories. In April 1996 the complete DNA sequence of bakers yeast (*Saccharomyces cerevisiae*) was deposited in public databases[6]. This was a landmark event in genomics for two reasons. First, it was the first entire new eukaryotic genome to be sequenced. Second, it was the first genomic sequence that represented a tractable experimental system with a large constituency of active researchers around the world ready and willing to exploit the sequence data[7].

In terms of IP rights issues, the yeast DNA sequencing project illustrates several interesting points. First, the absolute commitment to the rapid dissemination of DNA sequence data to the global scientific community by the European Union Network set the standards for those publicly funded projects that followed. This approach was taken mainly because those leading the project viewed DNA sequences as discoveries not inventions. For the funding agencies such as the European Commission, the benefits for European industrial competitiveness were not measured in terms of short-term commercial benefits but in the longer-term building of research capabilities. Now that functional analysis in yeast is under way in the EUROFAN project, there has been a deliberate shift in policy towards commercial development. Genes in a functional, rather than just a structural, context are highly patentable if they meet the necessary criteria. Corporate members of the Yeast Industry Platform are allowed prior access to functional data arising from EUROFAN and, unlike individual research groups within the network, may file for patents. Any royalties will be paid into a trust fund that operates on behalf of the yeast research community. There is the same public commitment to early public release of DNA sequence in *C. elegans* as yeast, which means that the sequence cannot be patented once released. The emphasis in these large-scale public sector projects is on public domain deposition and publication. Industry, by contrast, publishes very little in the genomics field, makes little use of resource centres and deposits few sequences in public domain databases[8]. There are relatively few patented gene sequences in model organisms and the patents that do exist have almost exclusively been filed by researchers working on projects external to the large-scale sequencing projects. For example, between 1980 and mid-1997, 102 patents were filed for *S. cerevisiae* (bakers yeast), 302 for *Escherichia coli* and 582 for mouse (for a full analysis of patent data on these model organisms, see Ref. 5).

A recent study of filed patent applications on human DNA sequences reveals, however, that US researchers in the public sector in particular are patenting at relatively high levels[9]. Public sector researchers filed ~40% of such patent applications. Most of these patent applications are from the USA and appear to come from researchers funded by the public sector based in universities or research institutes but not the large genome centres. Although the proportion of human DNA sequence patents filed in this study from the public sector was approaching that of the private sector, growth in the latter over the next few years is likely to expand considerably.

Future developments in genomics

The past eight years in genomics have been influenced by three key developments.

- The emergence of large-scale collaborative mapping and sequencing programmes in the public sector
- The development of in-house genome programmes by multinational companies in the pharmaceutical and agrofood sectors
- The emergence of a small group of genomics companies

The next five years will be increasingly dominated by functional analysis of genomes, particularly in model plants, yeast and human. Complex public and private sector commitments to genomics and their interaction are likely to intensify over the next few years. The increasing availability of functional information will make IP rights easier to secure and recent trends in the patenting of human DNA sequences can lead us to expect interest in IP from public and private sector scientists alike. However, it is in the private sector that we can expect to see the most intense activity and greatest gains.

In the USA a strong, vibrant, innovative small firm genomic sector has evolved which has been unmatched in Europe. European multinationals in particular have moved swiftly to form strategic alliances with these US firms, primarily to gain access to their private DNA sequence databases. It is unclear what the long-term future goals of these genomics companies, which essentially build databases and sell information, will be. Once companies have most of the structural information when the genome is sequenced in a few years time, emphasis will be switched to functional analysis technologies where there is already a separate and rapidly growing number of firms[10].

Although the framework for patents in genomics is broadly the same as for all other technologies, the real difficulty for the pharmaceutical and diagnostic industries is the unknown dependency between different categories of DNA sequences. What is the dependency between an EST diagnostic marker or an EST probe patent and a later patent on the full-length sequence in which the patented EST resides? The real issues over ESTs and SNPs concern the utility and scope of the claims. In general, partial DNA sequences reveal little information about gene function. The broad strategy that appears to be emerging is that patent applicants are being advised to seek the broadest patent scope possible and to place considerable emphasis on the use of comprising language to maximize the reach-through claims of partial sequences[11].

What are the implications of the recent award of the first US patent for ESTs to Incyte? One view is that this patent has essentially 'slipped through' the patent examination process and there is doubt as to whether the US PTO even considered these inventions to be ESTs (Ref. 12). The US patent granted to Incyte is for a single full-length gene together with polynucleotides that code in excess of 40 protein kinases. One reason for the granting of the patent may be that the full-length gene and the fragments were highly characterized in contrast to the virtually random DNA sequences that were part of the controversial NIH patent application for ESTs in the early 1990s. Draft guidelines published by the US PTO indicate that examiners will be looking for correspondence between what the applicant describes and what the applicant claims. Some commentators are predicting that only a few EST patent applications will actually be granted. A major limiting factor is likely to be the lack of time and funds to pursue and defend patents on gene fragments. Meanwhile, it seems likely that companies, large and small, will file applications in the hope that whatever is granted, at least some will gain strategic advantage. The implications downstream for product development will depend to a considerable extent on the industry, namely, as to what kind of licensing strategies it is prepared to adopt.

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In short…

Pfizer (New York, USA) has announced that barring unusual circumstances its Board of Directors will vote on a three-for-one split of Pfizer common stock in the form of a stock dividend on 22 April 1999.

A stock split requires an increase in the number of authorized Pfizer shares, and shareholders will vote on a proposal to increase the number of authorized shares of Pfizer common stock at the annual meeting on 22 April. If shareholders approve the increase, the board will act on the proposal in a session that follows the annual meeting. Information about the proposal will be included in a proxy mailing to stockholders scheduled for mid-March.