# US Perspective

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The quantum leap taken by molecular biology over the last 20 years has engaged the efforts of a substantial portion of the research industry and has produced results that have raised social and economic concerns. These concerns have elevated the patenting of inventions to a much higher profile than that previously enjoyed. This may have obscured the fact that *ownership* issues are not substantially affected by this progress. Because ownership is substantially independent of patent protection and because there is relatively little recent decisional law on this aspect, ownership issues will be discussed first.

## Ownership

Apart from the recently proposed legislation in San Francisco that pet owners be labelled 'guardians' rather than owners, there has been little question that society sanctions the ownership of non-human animals by humans or human institutions. People have been considered to own various life forms for centuries. In most of the world, it is considered improper for human beings to own one another; the ownership of life forms generally by humans, however, is reasonably universally recognized.

Perhaps less straightforward is the ownership of 'body parts' which may include, in addition to whole organs, cells and components of cells, such as genetic material. The only decide case of which this author is aware wherein the misappropriation of a body part by another has been alleged was *Moore v Regents of the University of California*.[1]

Also named as defendants were the attending physician, the Genetics Institute and Sandoz.

In that case, Mr. Morre, who was under treatment for cancer at UCLA, was subjected to a treatment involving a splenectomy and repeated removal of blood which, of course, contained some of his cells. These cells were established as a cell line which was a high cytokine producer. Patent protection was sought and obtained for the cell line. Mr. Moore brought action for conversion, and thus sought to assert an ownership right in the resulting cell line and a share of any profits that would be made.

The decision in *Moore* declined to find such a property interest. It did hold that Mr. Moore had a cause of action against his physician based on lack of informed consent. The Court refused to extend liability beyond the physician himself. It cited the interest of the public in having the research community free from the obligation to make inquiry regarding the materials it routinely uses. As the Court stated, an important policy consideration is that 'we not threaten with disabling civil liability innocent parties who are engaged in socially useful activities, such as researchers who have no reason to believe that their use of a particular cell sample is, or may be, against a donor's wishes'.

Ownership of the physical embodiments of genes and life forms has thus been, in reality, not a particularly controversial topic. What is controversial, apparently, is the ownership of 'intellectual property' associated with these materials. It will be remembered, of course, that 'intellectual property' at least in the form of patent protection, only permits the owner to exclude others from making, using, offering to sell, selling or importing the patented subject-matter. It does not permit the 'owner' free reign to carry out any of these acts.

**Patenting**

The above-mentioned research over the last 20 years has created a great deal of intellectual property subject to patent protection. The availability of such protection has offered the patentee opportunity to have a significant impact both on the progress of research and on the marketplace. It is this influence of the patentee that is of real concern.

An excellent, and perhaps overworked, example of perceived adverse economic impact is the controversy over patenting of express sequence tags (ESTs). Theses are small fragments of genetic material obtained by reverse transcription of messenger RNA (mRNA) from expressed genes. Thus, the ESTs may contain portions of the coding sequence for a particular protein or may represent untranslated regions of the mRNA. More recently, genomic DNA has been subjected to 'shotgun' sequencing resulting in small sequences which may or may not be part of an expressed gene. The patent issues arising with respect to these sequences, however, are similar to those with respect to ESTs.

The problem foreseen is as follows: because ESTs represent only portions of genes, and because the 'inventor' of the EST will attempt to use open language to claim the entire gene of which the EST is a part, it may be that multiple patentees will have rights to the same gene, requiring the subsequent developer of the gene or gene product to obtain a multiplicity of licenses from multiple patentees. This is far from reality, at least in the United States and at least at this time.

The patent stated to be the first issued 'EST' patent in the US is US Patent No 5,817,479 issued to Incyte Pharmaceuticals on 6 October 1998. The claims are directed to nucleotide sequences putatively encoding kinases. Claim 1 reads: 'A purified polynucleotide having a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2… and SEQ ID NO:44'.

It is apparent from the prosecution history that the examiner interpreted the word 'having' as closed language, ie the purified polynucleotide contains only the nucleotide sequence specified and does not contain any additional sequence. However, claim 2 reads: 'An expression vector comprising the polynucleotide of claim 1'.

In US practice, 'comprising' is clearly open language; thus, the expression 'vector' presumably could contain the entire gene.

The issuance of patents covering putative ESTs has, since this patent, slowed considerably. Later issued patents form Incyte and other groups engaged in this activity seem to cover only one or two genes, more in line with the tradition of focusing on individual genes. It should be noted that there are earlier patents issued which could be considered in line with the approach taken by the Incyte applicants whose contribution is simply the retrieval of a previously undisclosed nucleotide sequence. The usual manner of satisfying the utility requirement (and that used, apparently, in the above-cited Patent No 5,817,479) is to compare the retrieved sequences with those in publicly available databases such as GenBank and then to hypothesise an activity based on sequence similarity. This procedure is an interesting one in that analogous sequences might be presumed to patentably obvious over publicly known sequences; nevertheless, it is the sequence similarity that serves to identify the nature of the gene. In US Patent No 5,114,923, a similar approach was used although the rubric surrounding this patent is more in line with 'traditional' gene patenting. The human genome was probed for sequences with similarity to those encoding peptides of known natriuretic activity. A sequence was found having sufficient similarity in the essential features to convince the applicants that the protein encoded would itself have natriuretic activity. On the basis of this similarity, a patent was applied for and obtained, not only for the encoding nucleotide sequence, but also for the resulting encoded peptide.

In addition, utility can be predicated on use as a marker by virtue of tissue of origin. An earlier issued US Patent No 5,552,281 claimed an isolated osteoclast specific or related DNA sequence or its complement listing simply several SEQ ID Nos. The utility of the nucleotide sequences (which were claimed in open 'comprising' language) is as markers for osteoclast cells.

It should be apparent form the foregoing that patent protection for partial gene sequences is only a logical extension of the well established practice in the US of providing patent protection for complete genes. This reflects the traditional approach of starting with a known activity and obtaining the gene encoding the protein which exhibits this activity. Over 700 patents have been issued in the US on such subject-matter including such commercially important genes as tissue plasminogen activator, erythropoietin, granulocyte colony stimulating factor, Factor VIII and hepatitis B surface antigen. The inherent information value contained in the nucleotide sequences of such genes has been repeatedly recognized by the US courts.[2]

While the patentability of entire genes encoding proteins of known activity is very well established indeed, the efficiency of modern sequencing techniques does raise additional concerns. Currently, the amount of sequence information obtainable by a single organization is of the order of millions of sequences per day. Fears have been expressed that a few companies will thus control the entire genome not only of humans, but also of other organisms subject to such sequencing such as rice and corn. Of course, those organizations that are carrying out the sequencing activity would like this to be the case. It would be in their interest, in their view, to obtain patent protection for all of the sequence information obtained.

This prospect appears quite unlikely. First, in order to establish some kind of credible utility, a retrieved sequence must find some counterpart in a database that allows at least a high probability hypothesis of its significance to be formulated. Only a small proportion of those sequences obtained will show up as such matches, especially when the genome is the sequenced substrate. However, if millions of sequences are obtained, surely thousands will be matched. On the other hand, if the US Patent and Trademark Office continues its stated policy of examining only ten unrelated sequences in an application, the number of applications required to be filed, ultimately, to protect thousands of sequences becomes a prohibitive expense. Even at the modest filing fee of US$760, the costs soon mount up to an impractical level. And even grouping sequences in categories, as did Incyte in seeking protection for genes encoding 'kinases', may not play out to provide an economical solution to obtaining patent protection.

Where it has been possible to obtain the complete genomic sequence for an organism (as has been the case for a number of micro-organisms so far) an additional approach might be to claim the entire genomic sequence or a 'fragment thereof'. Whether this would get by a reasonably alert examiner is questionable since the utility of any particular (unidentified) fragment is clearly not predictable.

Thus the nightmare scenario whereby only a few multinational corporations control the entire genome for any particular organism, including humans, seems at this point unlikely.

With respect to plants and animals, following the decision in *Diamond v Chakrabarty* in 1980,[3] the Patent Office felt sufficiently confident in the Supreme Court position (although *Chakrabarty* was a five-to-four decision) to decide on its own that higher plants and animals are patentable subject-matter.[4] A fair number of patents on animals and plants have been issued since these decisions were rendered and the patentable subject-matter status of these organisms (other than humans) does not appear to be in jeopardy.

Further comments on the ability to detect a multiplicity of nucleotide sequences resulting from high throughput techniques are in order since the type of activity associated with obtaining these sequences is fundamentally different form that required to obtain a gene encoding a desired protein. Typically, the DNA samples are prepared using standard techniques, subjected to automated sequencing and printout, announced with the aid of software and their biological role evaluated. All of these activities would be performed by several different people, often at a level that is well within ordinary skill. Who, in the circumstances of such projects, qualifies as and inventor? It is a critical question in the US since incorrect inventorship invalidates and issued patent.

Difficulties with respect to ascertaining inventorship are not, of course, confined to biotechnology patents, but they are exacerbated by the collaborative nature of biotechnological research and by what some perceive as lack of 'invention' at all (only 'discovery'). Perhaps the most germane to biotechnology *per se* is the instance of

*Burroughs Wellcome Co v Barr Laboratories Inc*,[5] involving the invention of the use of AZT for treating AIDS. In a contested proceeding, the Federal Circuit decided that the inventorship was confined to those who did the initial screening of compounds in murine cells and constructively reduced to practice by preparing a draft patent application. Inventorship was held not to include National Institutes of Health (NIH) personnel who verified the results in human cells and in clinical studies.

Inventorhip is of importance, as, indeed, in the foregoing case, not only with respect to patent validity but also with respect to ownership. In the US, all inventors have an undivided interest in the entire patent even if contributions were not made to all the claims. A seemingly trivial inventive addition to a more overarching concept may result in considerable economic power with respect to the thereby included inventor.[6]

Turning, then, to the economic implications of the patentability considerations discussed above, there is no denying that the availability of patent protection is not neutral from a socioeconomic viewpoint. The right to exclude others n the US is almost absolute. There are some exceptions-the US Government has a right to a compulsory licence, the recent decision in *Florida Prepaid Post-Secondary Education Expense Board v College Savings Bank,* [7] has immunized states against liability for patent infringement and there is some history in the courts of requiring a licence at a reasonable royalty if an invention is of great social benefit (such as the cell sorting technique for which Cellpro had obtained regulatory approval even though the technique infringed a Johns Hopkins patent. [8] But as a general proposition, there is no compulsory licensing in the United States.

One interesting example is the ability of Genentech to eliminate competition in the production of tissue plasminogen activator (tPA) by virtue of its patent position, even though the competitor's product was held ultimately not to infringe. A lower court decision held that a version of tPA intended to be marketed by Wellcome infringed Genentech's patent under the Doctrine of Equivalents. This essentially drove Wellcome out of the tPA business, even though, several years later, the Federal Circuit reversed that holding.[9] Amgen's ability to control the market in erythropoietin has also been a result of its patent position *(Amegen Inc v Chugai, supra)* and biotechnology companies in general rely on the exclusivity guaranteed by patent protection to safeguard their market position in their products. Perhaps the company with the highest profile in this regard is Monsanto whose attempts to track down farmers assertedly illegally using 'Roundup ready' crops have attracted a great deal of publicity in the general press.

The availability of patents on materials and methods that are essentially research tools has also attracted attention. A number of companies and individuals have established licensing programmes on, for example, assay methods and receptors needed to screen candidate drugs. This has raised sufficient concern that the NIH established a committee to formulate policy to regulate patenting and availability of research tolls developed under NIH grants. The concern is that the cost of doing research will become prohibitive. Because much research requires a multiplicity of such research tools, the stacking of royalties required greatly escalates research costs.

In short, there is no doubt that a patent holder with respect to a valuable invention has a substantial economic asset which necessarily works to the economic detriment of those who need access to the patented invention.

## Conclusion

As stated in Article 8 of the US Constitution, the patent system is supposed to be designed to advance the progress of the useful arts. The availability of patent protection, without much doubt, does encourage investment in research. Whether this benefit is or is not outweighed by the limited period in which others can be exclude from using the invention for further progress, or in competition with the patent owner, is an ongoing issue for any technology. It is acute with respect to patents on genes and life forms because of the immediate importance to society of the protected products and because of the relevance of many patented materials to further research.

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[1] 249 Cal Rptr 494 (Cal Ct App 1988), *aff'd in part, rev'd in part,* 793 P2d 479, 15 USPQ 2d 1753 (Cal 1990), *cert denied,* 499 US 936 (1991).

[2] *Amgen Inc v Chugai Pharmaceutical Co,* 18 USPQ 2d 1016 (Fed Cir 1991) *cert denied,* 502 US 856 (1991), *Fiers v Sugano,*984 F2d 1164, 25 USPQ 2d 1601 (Fred Cir 1993), *In re Bell,* 999 F2d 781,26 USPQ 2d 1529 (Fed Cir 1993), *In re Deuel,* 34 USPQ 2d 1210 (Fed Cir 1995), and *Regents of the University of California v Eli Lilly,* 43USPQ 2d 1398 (Fed Cir 1997).

[3] 447 US 303, 206 USPQ 1993 (1980).

[4] *Ex parte Allen,* 2 USPQ 2d 1425 (Bd Pat Apps & Int 1987) (animals) and *Ex parte Hibberd,* 227 USOQ 443 (Bd Pat Apps & Int 1985) (plants).

[5] 40 F3d 1223, 32 USPQ 2d 1915 (Fed Cir 1994), *cert denied,* 115 S Ct 2553 (1995).

[6] *Ethicon Inc v US Surgical Corp,* 135 F3d 1456, 1460, 45 USPQ 2d 1545, 1548 (Fred Cir 1998).

[7] 51 USPQ 2d 1081 (S Ct 1999).

[8] *Johns Hopkins University v Cellpro,* 894 F Supp 819, 34 USPQ 2d 1276 (D Del 1995).

[9] *Genentech Inc v The Wellcome Foundation Ltd et al,* 29 F3d 1555, 31 USPQ 2d 1161 (Fed Cir 1994).