Post-1980 world of biotechnology patents in the US

Rajendra K. Bera

Till 1980 the US patent laws did not anticipate that one day such exotic objects as living things would become patentable. In the absence of laws tailored for biotechnology patents, the courts and the USPTO have tried to work within the existing legal framework. Their unease stems from the products of recombinant DNA technology which they treat as compositions of matter. Is life merely a patentable composition of matter? Post-1980, as DNA sequences, protein structures and disease pathways became patentable, the biotechnology sector has found a new unexpected commercial ally in the research university.

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THE year 1980 was a momentous one in the US for the nascent biotechnology sector. Three notable events in that year have had a profound impact on the future development of the sector. The first event was the Supreme Court's ruling in *Diamond* v. *Chakrabarty*[1] that Congress intended 'manufacture' to mean 'anything under the sun that is made by man' to be eligible for patenting. Accordingly, it interpreted the statute to cover a 'nonnaturally occurring manufacture or composition of matter – a product of human ingenuity' and in June 1980, in a 5–4 majority, ruled in favour of Chakrabarty. It held that Chakrabarty's genetically engineered bacteria met the statutory definition of patentable subject matter. The mere fact that Chakrabarty's invention happened to be alive was deemed immaterial. Chief Justice Warren Burger, delivering the majority opinion declared that, 'the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions'. Chakrabarty's bugs were new compositions of matter, the product of his ingenuity, not of nature's. They were thus innovative manufacturers, and hence, patentable. The United States Patent and Trademark Office (USPTO) granted the patent (No. 4,259,444) in March 1981.

In the same judgment the Supreme Court did invite Congress to address the issue of patent protection of organisms produced by genetic engineering and exclude, if desired, living organisms not contemplated by the Plant Patent Act[2] or the Plant Variety Protection Act[3] from patent law. It said: 'Our task, rather, is the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted. Congress is free to amend §101 so as to exclude from patent protection organisms produced by genetic engineering'.

Rajendra K. Bera is in the International Institute of Information Technology, 26/C, Electronics City, Hosur Road, Bangalore 560 100, India. e-mail: rbera@iiitb.ac.in

Congress has remained silent

The Supreme Court's decision subsequently allowed the patenting of plants, transgenic animals, and biological material that make up man, if not man himself. By now a number of patents have been granted for transgenic animals, gene sequences and stem cells. These include mice (in the hundreds), rats, rabbits, sheep, pigs, cows (in the tens), etc. Researchers have created mice with brains that contain about 1% human tissue[4].

The second notable event of 1980 was a piece of legislation[5] known as the Bayh–Dole Act of 1980. This along with the Stevenson–Wydler Technology Innovation Act[6] of 1980 codified the explicit US policy of allowing grantees to seek patent rights to federally funded research results. This policy further augmented by the Federal Technology Transfer Act of 1986, which amended the Stevenson–Wydler Technology Innovation Act of 1980, made technology transfer the responsibility of every Federal laboratory. Indeed, it went further and mandated that technology transfer be considered part of employee performance evaluations. The law now requires Federal laboratories to actively seek opportunities to transfer technology to industry, universities, and state and local governments. The result is that universities – the major recipients of federal grants – have become significant players in the biotechnology patenting arena.

The third notable event was the US patent (No. 4,237,224) granted to university researchers Stanley Cohen and Herbert Boyer in December 1980. This patent protected a method of gene splicing that revolutionized biological research and launched the biotechnology industry.

The patent was granted ten days before the Bayh–Dole Act was enacted, and six months after the Supreme Court's ruling in *Diamond* v. *Chakrabarty*; that ruling had finally paved the way for the grant of the patent after some six years from the time the original patent application had been filed in 1974.

Freedom to patent

Prior to 1980, patenting by universities was rare. The biotechnology industry was nascent, and government research sponsors, especially the National Institutes of Health (NIH), frowned on patent protection. This impeded development of new products and collaborations between academic and commercial investigators. Under the Bayh–Dole Act, grantees suddenly discovered that they have unfettered discretion in determining when seeking intellectual property rights is appropriate and how these rights may be licensed[7]. Furthermore, the Act does not distinguish between downstream inventions that lead to commercial products and basic research discoveries that broadly enable further scientific investigation, such as research tools. Thus, grantees were free to file patent applications on basic research discoveries, such as new DNA sequences, protein structures and disease pathways that are valuable precursors to further research. The ability of the grantees to convey exclusive licenses of their inventions to private firms motivated firms to transform new discoveries into commercial products[7]. The seeds were sown for the spectacular growth of the biotechnology sector.

Over the years discernible observers have noted that the courts and the USPTO consider the skills of the man of ordinary skill in biotechnology to be quite low compared to other technology areas. The Court of Appeals for the Federal Circuit is further seen to use relaxed standards for patent protection, such as for utility (compare *Brenner* v. *Manson*, 383 U.S. 519 (1966) with In re Brana, 51 F.3d 1560 (Fed. Cir. 1995)) and non-obviousness (compare *Graham* v. *John Deere*, 383 U.S. 1 (1966) with *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995)) that might have otherwise prevented the patenting of incremental advances in biomedical research[7]. This has led to the granting of narrow patents, making it difficult for firms to garner all the patent licenses they need, say, for assembling and screening new molecules. Also, the cumulative cost of acquiring licenses to use the required patents (sometimes called 'royalty stacking') raises product development cost. These assorted developments created an opportunity for gutsy venture capitalists to bankroll a breed of new firms, the biotechnology firms, to develop, market and protect through patents proprietary research that lies in between traditional academic research and end-product drug development.

Interestingly, while researchers see the DNA both as a molecule and as an information string, US courts tend to conceptualize DNA as molecules rather than as information products. This, in some cases, allows patent rights to be evaded by simply paraphrasing the information covered by the patent[8]. Such paraphrasing is possible because it is possible to alter protected nucleotide sequences while generating a functionally similar product[9]. If intelligently done, one could avoid infringement under the doctrine of equivalents.

NIH and the Bayh–Dole Act

As a government agency the NIH would like to see the free and unencumbered dissemination of broadly enabling research tools such as stem cell lines for use across the broad spectrum of biomedical research. However, the Bayh–Dole Act gets in the way. Only under exceptional circumstances (such as 'to alleviate public health or safety needs or requirements for public use specified by Federal regulations') can NIH exercise 'march-in rights' *ex post* to compel licensing of patents on inventions made in the course of previously funded federal research. However, the process is cumbersome, time-consuming and subject to exhaustion of court appeals. It has never been tried.

With the gap between academic and industrial biomedical research narrowing and the universities aggressively pursuing patents, commercial firms now perceive academics as potential commercial rivals, as they may join or work with rival firms. This has led to increased restrictions on the transfer of research tools, even when unpatented, among the players. Universities seek cash payments or reach-through royalties on sales of future products. On the other hand, private firms typically require the scientist and the university to sign a material transfer agreement. Such an agreement may include grant-back provisions calling for an option to license patent rights to subsequent discoveries made through use of the tools[7]. Such arrangements are reported to stifle basic research and escalate healthcare costs.

Genetic engineering

Ironically, most products produced using biotechnology do not qualify for a product patent because of the existence of prior art. New drugs created by biotechnology are often highly purified proteins that have been previously discovered in their naturally occurring forms. The mere mention of their discovery or isolation in the scientific literature is enough to qualify them as prior art and prevent the biotechnology-derived, highly purified version from receiving a product patent. Since genetic engineering is the only commercially feasible method for manufacturing human proteins, a patent on the recombinant manufacturing process can be tantamount to a product patent for biotechnology products, and many have been granted. But there are subtle problems.

Patentable talking chimpanzees?

The technique of recombinant DNA pioneered by Cohen and Boyer has led to advances in biotechnology that are beginning to make yesterday's science fiction today's reality. On 8 May 2007, Chinese scientists reported identifying a transversion mutation in human KLK8 gene[10]. In essence, they found a striking example of a single nucleotide polymorphism (SNP) that alters gene expression and gene product function in a human gene encoding KLK8, a gene expressed in the human brain and known to be associated with speech and memory. It was known earlier that of the two types of human neurospin cDNAs found in the brain, type I is homologous to the mouse counterpart, but type II is absent in mouse. Both transcripts include six exons and differ only in their exon 3 sequences. Type II includes an extra 45 amino acids at the N-terminus of exon 3 due to alternative splicing. The new result found by the researchers was that the long form variant (type II) is not expressed in other primates (or any other mammalian species studied), but that the capacity of producing this alternatively spliced transcript was due to a T to A mutation in the intervening sequence between coding exons 2 and 3. Other primates do not have this mutation; only humans do (and there is no polymorphism detected among different human racial groups, implying that this mutation is perhaps 'fixed' in the human genome), and it can be traced to an event that occurred about 5 million years ago. The mutation creates a 'splicing enhancer' sequence that creates the type II transcript for the first time in primate evolution.

Given that the genomic DNA differences between human and chimpanzee are only about 1.2%, there is considerable difference in their respective mental and linguistic capabilities. There are, of course, several possible reasons for the divergence, including gross alterations in cytogenetic architecture, local chromosomal rearrangements, segmental genomic duplications, single-gene creation or loss, and differences in gene transcription and alternative splicing of mRNA. The discovery of the *KLK*8 mutation and recombinant DNA technology seems to suggest the tantalizing possibility of creating a transgenic talking chimpanzee, and to make it legally exciting, a transgenic, patentable talking chimpanzee using alternative splicing. Such a chimpanzee might actually be able to speak and be capable of making connections between human words, objects and even emotions. For the first time we may be able to establish verbal communication with another species. But will the USPTO allow the patenting of a talking chimpanzee?

USPTO's stand on human–animal chimeras

In June 1999, the USPTO had announced that creatures created from a mixture of human and animal cells (human–animal chimeras) cannot be patented. That decision followed from its examination of a patent application (08/993563) filed on 18 December 1997 by Stuart Newman, a cell biologist and professor at the New York Medical College, and Jeremy Rifkin, a well-known biotechnology activist. The invention was[11]: a mammalian embryo developed from a mixture of embryo cells, embryo cells and embryonic stem cells, or embryonic stem cells exclusively, in which at least one of the cells is derived from a human embryo, a human embryonic stem cell line, or any other type of human cell, and any cell line, developed embryo, or animal derived from such an embryo.

Essentially the inventors claimed a method for combining human and animal embryo cells to produce a single embryo, which could then be implanted in a human or animal surrogate mother, resulting in the birth of a 'chimera'. The patent application specifically mentioned chimeras made in part from mice, chimpanzees, baboons and pigs. The invention, though never made, is a theoretical possibility. The unusual objective of the inventors was to secure the patent and then restrict the application of this technology for the life of the patent, during which they hoped to foster a social debate about moral boundaries in relation to biotechnology patents. The USPTO rejected the patent claim as being directed to nonstatutory subject matter because it 'embraces a human being'. (That ruling, if legally valid, could undermine thousands of patents on organisms carrying human genes.) Newman and Rifkin filed an appeal to the patent office because they believed that contemporary applications on cloned cells (including human cell DNA transplanted into denucleated cow's eggs) came under the same rule and so should also be outlawed. After seven years, during which Newman split his patent application for tactical reasons into two (one involving primates and the other focused on other animals), the USPTO on August 2004 turned down both his patent applications, *inter alia*, on the ground that his creatures would be too close to humans. The inventors did not further contest the USPTO's decision in the subsequent 6-month appeal period. In February 2005, both patent applications lapsed. Yet, Newman and Rifkin saw the rejections as a victory of sorts in the belief that other human–animal chimeras ought to be turned down. Newman believes the USPTO ruling may affect stem-cell researchers too, who attempt to obtain patents on genetic material they create using mixtures of human and animal cells[4].

Some see the protest patent applications of Newman and Rifkin as an attempt to block science. For example, the role that the Harvard mouse and the SCID mouse have played in cancer and immunology research and in the development of therapies respectively is well established. Other instances include insertion of human genes into *Escherichia coli* for manufacturing insulin for the treatment of diabetes, and pigs have been produced that express the gene for human growth hormone. For the

future there is optimism that animals such as pigs would be used to successfully create human transplantable organs tailored to an individual's unique genetic profile. It is doubtful that, in the larger interest of human welfare, one would now attempt to block the development of therapies by denying patent protection on such inventions in the future without which new therapies are unlikely to be developed or consider making existing successful therapies illegal. Chimeric animals and patents are crucial to the ability of the biotechnology sector to develop cures for human diseases. Yet there are genuine moral concerns in such experiments.

Impact of patents on upstream basic research

Basic genetic research requires many technologies and other research inputs that are now the subject of patents. These include animal and human gene sequences, bacterial and viral cultures, cell lines, chemical reagents, computerized instruments, data processing software, diagnostic equipment and materials, gene-marking chemicals, gene-splicing methods, and laboratory containers and equipment. Consequently basic researchers now face restricted access to these inputs.

There is no explicit research exemption in the Patent Act of 1952, but judicial decisions have allowed the 'experimental use' of a patented invention as a defence to an allegation of infringement. However, in *Madey* v. *Duke University* (October 2002)[12], the Federal Circuit tempered that by cautioning: '[R]egardless of whether a particular institution or entity is engaged in an endeavor for commercial gain, so long as the act is in furtherance of the alleged infringer's legitimate business and is not solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry, the act does not qualify for the very narrow and strictly limited experimental use defense. Moreover, the profit or non-profit status of the user is not determinative.'

This has substantially eliminated the experimental use defence to patent infringement, especially where university–industry collaborative research is concerned. Now, most organizations carrying out research or experimental work involving patented inventions could find themselves liable for patent infringement.

A possible means of mitigating such access-related problems in research is to amend the patent laws by, say, reinvigorating the 'products of nature' limitation on patent eligibility so as to exclude purified DNA sequences and proteins, and biochemical mechanisms from patent protection, or fortifying the utility standard to limit the patenting of broadly enabling research tools. Another possible measure is to provide an exemption from infringement liability for research, particularly non-commercial research. However, these changes require thoughtful consideration of consequential side-effects. Patents are crucial to the biotechnology industry and undue restrictions on patent protection may dry up private investment (including risk capital) in research and product development. Changes in patent laws that exclude research tools from protection or exempt research activities from infringement liability could have a significant effect on the ability of biotechnology firms to raise funds for research. Given that private funding of biotechnology R&D well exceeds federal funding, caution is needed[13].

Too many upstream patents pose the danger of over-fragmentation of rights, increase the fear of debilitating injunctions, and decrease the efficiency of downstream product development. Open collaboration, on the other hand, enhances access and leads to efficient pooling of resources. Too much openness, however, inhibits the ability to generate healthy returns and drives out further investment. The SNP Consortium and the Alliance for Cell Signaling are two examples where a considered emphasis on openness has shown that collaboration around the shared knowledge infrastructure of an industry can yield large collective benefits. Another example is the BLAST algorithm[14]. In this case, one may speculate where modern biology would be if broad patents covering the BLAST algorithm had been obtained by a for-profit company that was unwilling to license them widely. Would it have led to more effective workarounds or even better methods, relocation of bioinformatics activity to jurisdictions that did not recognize the patent, etc.[15]?

Scientific research depends on global collaborative efforts, which in turn depend on the norms of the scientific community and the policies of granting agencies and academic journals (such as *Nature* and *Science*), which enforce prompt and regular deposits of data. However, without major Government financial support these initiatives are hard to sustain. For example, after the Swiss Government dropped its support, the Swiss-PROT database struggled to find a commercial business model that covered both maintenance and distribution costs and also satisfied the demands for open access by the public sector researchers who largely created the data[15]. Swiss-Prot has now been merged with the UniProt database.

Impact of exclusive licenses

While the proliferation of narrow, fragmented patents has created problems, there is also a growing number of patents on genes and certain proteins that are so broad that they can effectively block a wide range of research activities of a competitor[8]. Now that universities have begun to aggressively commercialize their patents, we find that the Bayh–Dole Act does little to ensure that a university holding patents on a broadly enabling technology will license them non-exclusively. In fact, the Bayh–Dole Act and subsequent legislations have given universities considerable discretion in granting exclusive licenses in the

belief that such licenses would attract private investment necessary to develop preliminary research discoveries into commercial products. One only hopes that universities, on their own volition and in the best interest of all, would license non-exclusively their patents on broadly enabling upstream research technologies that do not require further development as products and are ready for dissemination to researchers. An example worthy of emulation is the pre-Bayh–Dole Cohen–Boyer patent (U.S. Patent No. 4,237,224) granted in December 1980 based on their November 1973 paper[16] for combining DNA from different organisms (recombinant DNA technology). It is widely believed that the rapid progress of the biotechnology industry occurred due to this technology being widely and cheaply licensed non-exclusively. It went on to garner more than 450 licensees and generated US$ 255 million in licensing revenues from US$ 35 billion in worldwide product sales[17]. Because this invention was readily licensed and available, innovative products such as insulin for the treatment of diabetes, growth hormone for children with growth deficiencies and interferon for cancer patients were created.

Of course, there are discoveries, including some important research tools and enabling technologies, which require substantial commercial investment before they can be reliably mass-produced for widespread distribution. An example is the suite of technologies and machines for DNA sequencing and analysis, which although initially developed in academic laboratories, later required substantial follow-on investment by private firms to convert them into reliable and commercially viable laboratory equipment. Patents and exclusive licenses may be crucial to motivate this sort of investment[7].

University-centred research is now enormously valuable in the biotechnology sector given that drug discovery, once largely a matter of trial-and-error and luck, is now critically dependent on basic knowledge of genes, proteins and associated biochemical pathways. However, when transferring an innovation to a for-profit company, the university usually relinquishes control over the subsequent development and marketing of the innovation. This sometimes puts a medicine out of reach of many patients in poor countries, either through high pricing or restricted access. To mitigate such situations and bring in a humanitarian touch to an otherwise for-profit activity, the Universities Allied for Essential Medicines (UAEM) has embarked on a goal 'to improve access to medicines in poor countries through university action'. The UAEM suggests that 'universities should adopt licensing provisions that facilitate access to their health-related innovations in poor countries'. It also proposes a set of humanitarian licensing provisions known as 'equitable access licensing' under which, for example, a generic pharmaceutical company in a poor country can request that patent barriers be lifted for an overpriced key medicine in the country[18].

Concluding remarks

Rapid and unexpected advances in biotechnology and the Bayh–Dole Act have created new markets for biotechnology products, and have fostered university–industry R&D collaboration at levels never seen before. In the process, the ideals of open science have come into conflict with the monopoly rights granted through patents. There are genuine fears that patents may be 'locking up' significant portions of molecular biology, thereby raising R&D costs for both for-profit and not-for-profit players. There are additional fears of litigation rising to unsustainable levels. Then there are unsettled questions, which include the rights and responsibilities related to the ownership of engineered life forms, the ethics of genetic testing and the utilization of new medical procedures. Complex legal issues are likely to arise when living matter extracted from humans, such as hospitalized patients, is used in biotechnology inventions. The John Moore hairy cell leukaemia case[19] decided by the Supreme Court of California in July 1990 is an indicator of the complexities involved.

Owners of genomic patents need to be sensitive in their licensing and other technology transfer practices, so that in some sense the greater good of mankind is not lost. The dominance of the Cohen–Boyer patent during its term did not stifle research, but served instead to spur innovation. On the other hand, the exclusive license granted to DuPont by Harvard University on the oncomouse patents has created a lot of heartburn[20].

Biotechnology patents are seldom susceptible to challenges based on undiscovered prior art because of the scientific community's tradition of open documentation, but may suffer from enablement problems because the patent specification really does not allow an independent party to recreate the process described in the patent. This sometimes provides opportunities to challenge a biotechnology patent if it is asserted against an alleged infringer.

Finally, there is an intriguing question. Since biological molecules such as the DNA are also information carriers, can man-made information carrying biological molecules be copyrighted?

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