POLICY: BIOTECHNOLOGY

The Patenting of DNA

John J. Doll

In the past two decades, there has been an explosion of innovative growth in the field of biotechnology. This growth has resulted in many new products and methodologies that are useful in agriculture, environmental biotechnology, food technology, and the diagnostics and pharmaceutical industries. Other results are new areas of research and development in genomics and bioinformatics. The Human Genome Project is a global coordinated effort to characterize human genetic material and provide a complete human DNA sequence library by 2005. Even though the project is not yet complete, a vast amount of useful DNA sequence information has already been gathered, including sequences of genes and their regulatory regions and genome markers such as expressed sequence tags (ESTs) and single nucleotide polymorphisms (SNPs) (*1*).

The United States Patent and Trademark Office (USPTO) recognizes that many people in the biotechnology community are concerned with the possible impact of patents granted for DNA-related inventions (*2*) on research and innovation in biomedical research and technology. Some in the biotechnology community are concerned that patents on ESTs or SNPs may impede cooperation among laboratories and limit the ready availability of data and materials to researchers. Public access to such sequence data has been the subject of much debate. Several bioinformatics companies are building proprietary sequence databases. On the other hand, some pharmaceutical companies, as well as the National Institutes of Health (NIH), are creating public databases of sequence information to ensure public access to such information. Some critics have even suggested that patents should not be granted for these new discoveries and that a new form of intellectual property protection is needed.

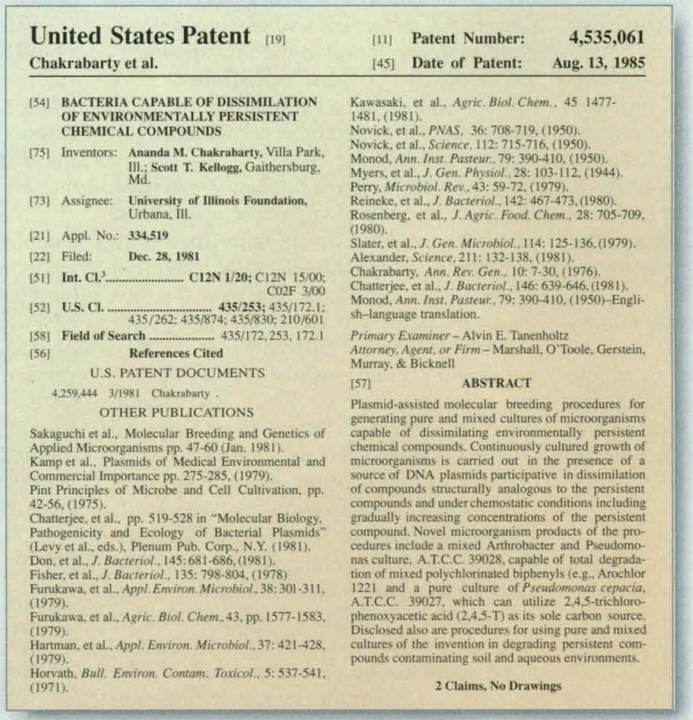
However, in the USPTO's view, new areas of technology do not create the need for a whole new specialized patent law. In many ways, the arguments currently being used for DNA sequence technology resemble those voiced 30 to 40 years ago when polymer chemistry was an emerging technology. At that time, people argued that if broad generic claims were granted on the building blocks of basic polymers, it would devastate the industry. In fact, no such disaster occurred. For example, the issuing in 1965 of a basic patent broadly claiming a vulcanizable copolymer of aliphatic mono-olefins and unsaturated bridged-ring hydrocarbons (*3*) did not preclude the later issuing of patents to different inventors for several copolymers of this type (*4*). These patents represent early examples of ethylene-propylene-diene monomer (EPDM) rubbers, which are highly weather- and ozone-resistant, stable to thermal aging, and have good electrical insulating properties. These EPDM rubbers have been commercially important as components in tires, weather stripping, radiator hoses, wire insulation, impact modifiers, and roofing.

EPDM copolymers were assembled from three basic building blocks that could be combined in many different ways and, as such, generic and specific claims to these copolymers are analogous to claims that may be issued to DNA inventions. Just as the issuing of broad product claims at the early stages of this technology did not deter development of other new vulcanizable copolymers, the issuing of relatively broad claims in genomic technology should not deter inventions in genomics. Two relevant examples of this in the field of biotechnology are the polymerase chain reaction (PCR) and the human immunodeficiency virus (HIV) protease, which were patented and then widely licensed to permit the biotech industry to continue to grow and benefit from these inventions.

The same patentability analysis is conducted for every patent application, regardless of whether the application is for a computer chip, a mechanical apparatus, a pharmaceutical, or a piece of DNA. In every field of technology—whether emerging, complex, or competitive—all the conditions for patentability (such as statutory subject matter utility, enablement, written description, novelty, and nonobviousness) must be met before a claim is allowed (*5*).

In applying existing patent law to DNA sequence inventions, a first area of concern is whether such inventions constitute patentable subject matter. As DNA sequences are typically isolated and purified manufactures or compositions of matter under U.S. law; in other words, products of human ingenuity "having a distinctive name, character, [and] use" (*6*) (see Figure), they are patentable subject matter in the United States. In order for DNA sequences to be distinguished from their naturally occurring counterparts, which cannot be patented, the patent application must state that the invention has been purified or isolated or is part of a recombinant molecule or is now part of a vector.

Although some SNPs and ESTs may not directly identify genes, they may still be extremely useful and thus satisfy the utility re-



United States Patent [19]
Chakrabarty et al.

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[54] **BACTERIA CAPABLE OF DISSIMILATION OF ENVIRONMENTALLY PERSISTENT CHEMICAL COMPOUNDS**

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[52] **U.S. Cl.** **435/253**; 435/172.1; 435/262; 435/874; 435/830; 210/601

[58] **Field of Search** 435/172, 253, 172.1

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,259,444 3/1981 Chakrabarty .

OTHER PUBLICATIONS

Sakaguchi et al., Molecular Breeding and Genetics of Applied Microorganisms pp. 47-60 (Jan. 1981).
Kamp et al., Plasmids of Medical Environmental and Commercial Importance pp. 275-285, (1979).
Pint Principles of Microbe and Cell Cultivation, pp. 42-56, (1975).
Chatterjee, et al., pp. 519-528 in "Molecular Biology, Pathogenicity and Ecology of Bacterial Plasmids" (Levy et al., eds.), Plenum Pub. Corp., N.Y. (1981).
Don, et al., *J. Bacteriol.*, 145: 681-686, (1981).
Fisher, et al., *J. Bacteriol.*, 135: 798-804, (1978)
Furukawa, et al., *Appl. Environ. Microbiol.*, 38: 301-311, (1979).
Furukawa, et al., *Agric. Biol. Chem.*, 43, pp. 1577-1583, (1979).
Hartman, et al., *Appl. Environ. Microbiol.*, 37: 421-428, (1979).
Horvath, *Bull. Environ. Contam. Toxicol.*, 5: 537-541, (1971).
Kawasaki, et al., *Agric. Biol. Chem.*, 45 1477-1481, (1981).
Novick, et al., *PNAS*, 36: 708-719, (1950).
Novick, et al., *Science*, 112: 715-716, (1950).
Monod, *Ann. Inst. Pasteur.*, 79: 390-410, (1950).
Myers, et al., *J. Gen. Physiol.*, 28: 103-112, (1944).
Perry, *Microbiol. Rev.*, 43: 59-72, (1979).
Reineke, et al., *J. Bacteriol.*, 142: 467-473, (1980).
Rosenberg, et al., *J. Agric. Food. Chem.*, 28: 705-709, (1980).
Slater, et al., *J. Gen. Microbiol.*, 114: 125-136, (1979).
Alexander, *Science*, 211: 132-138, (1981).
Chakrabarty, *Ann. Rev. Gen.*, 10: 7-30, (1976).
Chatterjee, et al., *J. Bacteriol.*, 146: 639-646, (1981).
Monod, *Ann. Inst. Pasteur.*, 79: 390-410, (1950)–English–language translation.

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[57] **ABSTRACT**

Plasmid-assisted molecular breeding procedures for generating pure and mixed cultures of microorganisms capable of dissimilating environmentally persistent chemical compounds. Continuously cultured growth of microorganisms is carried out in the presence of a source of DNA plasmids participative in dissimilation of compounds structurally analogous to the persistent compounds and under chemostatic conditions including gradually increasing concentrations of the persistent compound. Novel microorganism products of the procedures include a mixed Arthrobacter and Pseudomonas culture, A.T.C.C. 39028, capable of total degradation of mixed polychlorinated biphenyls (e.g., Arochlor 1221 and a pure culture of *Pseudomonas cepacia*, A.T.C.C. 39027, which can utilize 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) as its sole carbon source. Disclosed also are procedures for using pure and mixed cultures of the invention in degrading persistent compounds contaminating soil and aqueous environments.

2 Claims, No Drawings

Product of Human Ingenuity. This patent was issued to Chakrabarty following the Supreme Court decision, *Diamond* v. *Chakrabarty* (*6*), in which the patentability of a living bacterium, genetically engineered to break down crude oil, was affirmed.

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quirement. SNPs and ESTs may have specific utilities that are separate and distinct from the genes to which they correspond. For example, SNPs can be used to trace ancestry or parentage. ESTs can be used for chromosome identification and gene mapping. Both can be used to identify genes that contribute to predisposition to disease.

Claims to DNA elements useful for forensic identification, the identification of tissue type or origin, chromosome mapping, chromosome identification, or tagging of a gene of known and useful function must fulfill the enablement requirement. For any invention, enablement is satisfied when, by reading the patent application, an individual who has skill in the technology would have been able to make and use the invention as intended without undue experimentation.

In fact, it is common for the patentability of DNA elements to hinge on whether sufficient information has been given to enable at least one credible or specific utility. Examples of potentially non-enabled utilities for a DNA sequence fragment include its use to locate disease-associated genes when the disease has no known genetic origin; as an antisense reagent when the corresponding protein to be suppressed is unknown; as a triplex probe to inhibit expression of a protein when the protein and its function are unknown; and to locate and identify genes of unknown utility.

An area of patent law that is still developing relates to the kind of information that must be included in the patent application of a biotechnology-related invention in order to sufficiently identify and distinguish its characteristics from other subject matter (in other words, satisfaction of the written description requirement). In the case of the *Regents of the University of California* v. *Eli Lilly* (7), the court held that in order to claim a specific DNA sequence, such as the human DNA encoding insulin, more is required than a mere statement that it is part of the invention, plus a fragment of the claimed nucleic acid, plus a reference to a potential method of isolating the entire sequence. As a result of the Lilly case and several earlier cases (8), the USPTO is preparing interim examination guidelines for determining compliance with the written description requirement that should be made available for public comment within the next 3 months.

There has been considerable debate and discussion over how the issuance of a patent on DNA fragments of a gene will affect the patenting of full-length genes. The USPTO views this situation as analogous to having a patent on a picture tube. The picture tube patent does not preclude someone else from obtaining a patent on a television set. However, the holder of the picture tube patent could sue the television set makers for patent infringement if they use the patented picture tube without obtaining a license.

In a second example, a patent might be granted for compound X, which is disclosed to have a specific use (such as a headache remedy). If other investigators find that X has a new and unexpected use, perhaps in combination with compound Y, for treatment of heart arrhythmias, they may have to obtain a license from the individual who first patented compound X in order to sell XY.

In summary, once a product is patented, that patent extends to any use, even those that have not been disclosed in the patent. A future nonobvious method of using that product may be patentable, but the first patent would have been dominant.

For DNA to be patentable, it must be novel and nonobvious in light of structurally related DNA or RNA information taught in nonpatent literature or suggested by prior patents. To be considered nonobvious, the invention must have been compared to what was known previously and be judged not to be obvious to someone of ordinary skill working in the field. Because of this, patent claims limited in scope to a specific novel and nonobvious SNP or EST (for example, for forensic identification) would not necessarily preclude the future patenting of the corresponding full-length gene of known function discovered later. The granting of comprehensive claims to downstream DNA products such as full-length genes or to ultimate proteins is unlikely in the absence of a significant amount of information about the gene and protein being disclosed in the patent application.

Two specific examples may be helpful. A patent is granted to a large fragment of DNA, within which exists a gene of great medical interest, even though the location of the open reading frame with the fragment has not been determined. The person who actually discovers and isolates the gene may also be able to receive a patent. Alternatively, many patented DNA fragments such as ESTs or SNPs may be isolated that turn out to be part of the same gene. In both cases, the second patent holder may have to obtain licenses from or pay fees to the primary patent holder but is not prevented from obtaining the second patent.

If the invention has been described in a patent or printed publication anywhere in the world, or if it has been in public use or on sale in the United States for more than 1 year before the date on which an application for patent is filed in the United States, a patent cannot be obtained. Thus, any SNPs or ESTs that have been available in a public database for more than 1 year prior to the filing date of the application cannot be patented. If an SNP is published less than a year before the patent application is filed and the inventor (who was not one of the authors) can show that he or she invented the SNP before the publication date, the SNP may still be patentable.

Without the incentive of patents, there would be less investment in DNA research, and scientists might not disclose their new DNA products to the public. Issuance of patents to such products not only results in the dissemination of technological information to the scientific community for use as a basis for further research but also stimulates investment in the research, development, and commercialization of new biologics. It is only with the patenting of DNA technology that some companies, particularly small ones, can raise sufficient venture capital to bring beneficial products to the marketplace or fund further research. A strong U.S. patent system is critical for the continued development and dissemination to the public of information on DNA sequence elements.

References and Notes

1. An EST is a short sequence of the complementary DNA that was expressed by the full-length gene. A polymorphism, such as an SNP, is a variation in the DNA sequence of some members of a species.
2. F. S. Collins, M.S. Guyer, A. Chakravarti, *Science* **278**, 1580 (1997).
3. U.S. Patent No. 3,211,709, filed 14 July 1958 by Adamek *et al.* and assigned to Hercules Powder Company.
4. U.S Patent No. 3,527,739, issued 8 September 1970 to Valvassori *et al.* and assigned to Montecatini Edison; U.S. Patent No. 3,531,447, issued 29 September 1970 to Gumboldt *et al.* and assigned to Farbwerke Hoechst Aktiengesellschraft.
5. Title 35 of the United States Code, sections 101, 102, 103, and 112.
6. *Diamond* v. *Chakrabarty*, 447 U.S. 303, 310, 206 USPQ 193, 197 (1980).
7. *Regents of the University of California* v. *Eli Lilly and Co.*, 119 F.3 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).
8. *Fiers* v. *Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993); *Amgen Inc.* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

9. The author acknowledges the contributions of S. G. Kunin, N. J. Linck, R. A. Schwartz, M. M. Parr, R. J. Hill, and S. A. Chambers.