Intellectual Property & Ownership Issues in Genetic Research

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Overview

- Gene patents
- Use of patented gene sequences and related technologies in research
- Ownership of patented gene sequences and related inventions

Criteria for Patentability

- Patentable subject matter (35 U.S.C. § 101)
  - Process
  - Machine
  - Article of manufacture
  - Composition of matter
  - Improvements thereof
- Utility (35 U.S.C. § 101)
- Novelty (35 U.S.C. § 102)
- Nonobviousness (35 U.S.C. § 103)
- Enablement (35 U.S.C. § 112, ¶ 1)
- Description of invention (35 U.S.C. § 112, ¶ 2)

Limits on Patentability

- The following are not patentable:
  - Laws of nature
  - Physical phenomena
  - Abstract ideas

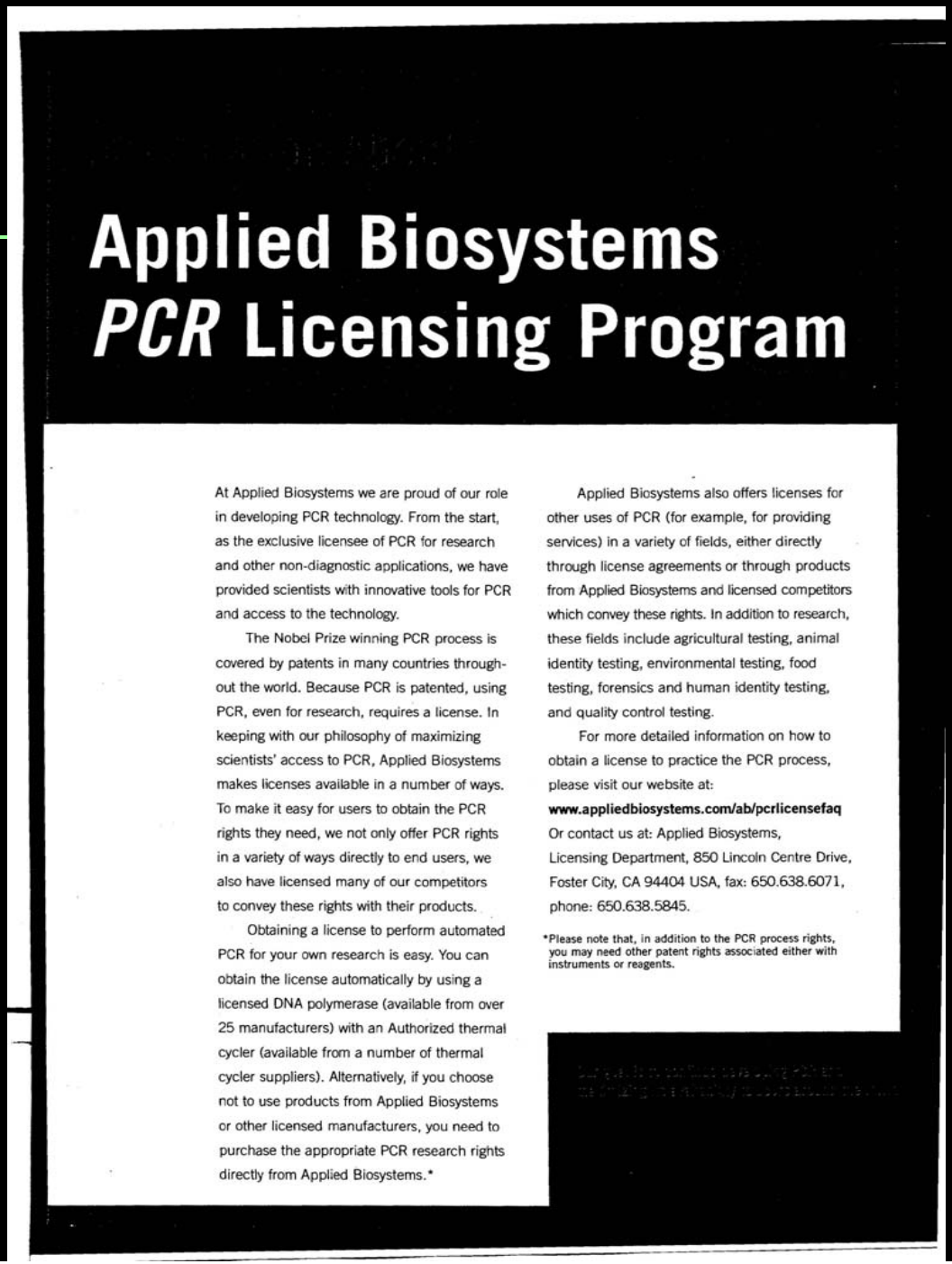
  See, e.g., Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948) (holding claims to naturally-occurring *Rhizobium* bacteria capable of fixing nitrogen unpatentable as "manifestation of laws of nature").
- Patentable subject matter includes anything under the sun that is *made by man.*

Biotechnology Patent Milestones

- In 1980, the Supreme Court held that a genetically-engineered bacterium was a patentable composition of matter because it was not naturally occurring. Diamond v. Chakrabarty, 447 U.S. 303 (1980)
- The first of three recombinant DNA cloning patents ("the Cohen-Boyer patents") issued in late 1980. U.S. Patent No. 4,237,224 (issued Dec. 2, 1980)
- In 1980, Congress passed the Bayh-Dole Act, which encourages federal grantees to patent inventions made with federal funds. 35 U.S.C. §§ 200-212 (2004).
- Patents on nucleic acid sequences have been issued at steadily increasing rates since the 1980s.

Biotechnology Patents

302 (5645) SCIENCE 539 (Oct. 2003).



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www.appliedbiosystems.com/ab/pcrlicensefaq
Or contact us at: Applied Biosystems, Licensing Department, 850 Lincoln Centre Drive, Foster City, CA 94404 USA, fax: 650.638.6071, phone: 650.638.5845.

*Please note that, in addition to the PCR process rights, you may need other patent rights associated either with instruments or reagents.

Criteria for Gene Patents I

- Isolated or purified nucleic acid molecule

  Chakrabarty, 447 U.S. 303; Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

- Specific, substantial, and credible utility for the nucleic acid molecule, such as:
  - Function
  - Hybridization properties
  - Gene regulation properties

  Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001)

Criteria for Gene Patents II

- Previously unknown nucleic acid molecule
- Nonobvious nucleic acid molecule
  - This is a highly fact-specific determination.
  - Prior disclosure of an amino acid sequence may not render the underlying nucleic acid sequence obvious due to the redundancy of the genetic code *unless* knowledge in the field would lead to a particular nucleic acid sequence.
    In re Deuel, 51 F.3d 1552, 1558-59 (Fed. Cir. 1995)

Criteria for Gene Patents III

- Method of isolating the nucleic acid molecule.
  Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991)
- Precise definition of the nucleic acid molecule, such as by structure, formula, or physical properties.
  Id.; Regents of the Univ. of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).
  - *E.g.*, "A mammalian insulin cDNA" without more structural information (*e.g.*, sequence or defining features) is insufficient *unless* the function is known in the field to be correlated to a particular, known structure.
    Enzo Biochem v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002).

Gene Patent Claims

- "1. An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO:2."

- "2. The isolated DNA molecule of claim 1, wherein said DNA molecule comprises the nucleotide sequence set forth in SEQ ID NO:1."

U.S. Patent No. 5,837,492 (issued Nov. 17, 1998)

Gene Patent Claims

- "9. Isolated DNA or RNA comprising:
  a. a nucleic acid which comprises SEQ ID NO:2; or
  b. a nucleic acid which is fully complementary to and of the same length as the nucleic acid of (a)."

- "10. An isolated nucleic acid which exhibits at least 98% nucleotide sequence identity to the isolated DNA or RNA of claim 9."

U.S. Patent No. 6,683,165 (issued Jan. 27, 2004)

What Does a Gene Patent Mean?

- A gene patent entitles the owner to exclude all others from making, using, selling, offering for sale, or importing the *claimed* nucleic acid molecule.
  35 U.S.C. § 271.
  - Tests and other procedures that require use of the nucleic acid molecule are necessarily subject to exclusion.
- This right of exclusion is generally limited in duration to twenty years from the date on which the patent application was filed. 35 U.S.C. § 154(a)(2).
- *But note:* A patent does not guarantee its owner the right to practice the claimed invention.

Debate Surrounding Gene Patents

- Human body parts should not be commodified.

  See, e.g., D. Nelkin & L. Andrews, *Homo Economicus: Commercialization of Body Tissue in the Age of Biotechnology*, 28 HASTINGS CTR. REP. 30 (1998).

  - Continuum of societal attitudes regarding commodification of the human body:
    - Sales banned, donation only (*e.g.*, organs)
    - Free market approach (*e.g.*, blood, gametes)
    - Ongoing debates re: "property" status (*e.g.*, frozen embryos)

    See Robert F. Weir & Robert S. Olick, THE STORED TISSUE ISSUE: BIOMEDICAL RESEARCH, ETHICS, AND LAW IN THE ERA OF GENOMIC MEDICINE 171-76 (2004).

- The prospect of commercialization jeopardizes the physician-patient relationship. *See* Nelkin & Andrews.

Debate Surrounding Gene Patents

- Gene patents impede scientific research and data sharing among scientists.

  See M.A. Heller & R.S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280(5364) SCIENCE 698 (1998); Eric G. Campbell *et al.*, *Data Withholding in Academic Genetics: Evidence From a National Survey*, 287(4) JAMA 473 (2002).

- Gene patents increase the cost of patient care and, in some cases, prevent access to necessary treatments.

  See D. Butler & S. Goodman, *French Researchers Take a Stand Against Cancer Gene Patent*, 413 NATURE 95 (2001) (limited availability and high cost of Myriad Genetics' BRCA1 gene test); Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064 (S.D. Fla. 2003) (patentee limits access to Canavan disease gene test).

Use of Patented Genes and Technologies in Research

- Once a gene or fundamental scientific technique ("research tool") has been patented, what is the impact on researchers who want to use the patented gene or technique in their own *research*?

Use of Patented Genes and Technologies in Research

- At least one survey suggests that scientists engaged in research routinely use patented research tools without obtaining a license from the patent owner.

  See John P. Walsh *et al.*, *Research Tool Patenting and Licensing and Biomedical Innovation, in* PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285-340 (S. Merrill *et al.* eds., 2003).

  - "Research exemption"
  - Patent invalidity, *i.e.*, the patented technology was previously well-known in the scientific community
  - Widely-held belief that corporations will not sue university researchers due to lack of monetary damages and bad publicity

The Research Exemption

- However, a recent Federal Circuit decision clearly indicates that the "research exemption" is very narrow and strictly limited in application.

  See Madey v. Duke, 307 F.3d 1351 (Fed. Cir. 2003)

- The exemption applies only to research undertaken "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." *See* id. at 1362.

The Research Exemption

- "Our precedent clearly does not immunize use that is in any way commercial in nature. Similarly, our precedent does not immunize any conduct that is in keeping with the alleged infringer's legitimate business, regardless of commercial implications. For example, major research universities, such as Duke, often sanction and fund research projects with arguably no commercial application whatsoever. However, *these projects unmistakably further the institution's legitimate business objectives*, including educating and enlightening students and faculty participating in these projects. These projects also serve, for example, to increase the status of the institution and lure lucrative research grants, students and faculty." Id. (emphasis added).

Reflections on Madey v. Duke

- Madey v. Duke is an implicit recognition of the increasingly commercial nature of academic institutions under the Bayh-Dole Act.
- Justified reliance upon extra-legal solutions to protect and preserve university research?

  See, e.g., Cristina Weschler, *The Informal Experimental Use Exception: University Research After Madey v. Duke University*, 79 N.Y.U. L. REV. 1536 (2004).

Consequences of Madey v. Duke

- The “research exemption” is not a viable defense to patent infringement by university researchers.
- Patent invalidation is a fact-intensive, expensive, and risky strategy.
- While patent owners may not pursue infringing researchers, they are likely to initiate lawsuits once successful products are developed and monetary damages become available.

Ownership of Gene Patents and Related Inventions

- Under the United States patent system, patents are awarded to inventors.
  - An "inventor" is any person who contributes to the conception of the invention.
    Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456 (Fed. Cir. 1998).
  - In the context of gene patents, conception requires knowledge of (a) the structure of the nucleic acid or characteristics sufficient to distinguish it from other nucleic acids ("precise definition") *and* (b) a method for obtaining the isolated or purified nucleic acid.
    See Amgen, Inc., 927 F.2d at 1206.
- Multiple inventors may be named on a single patent.

Ownership of Gene Patents and Related Inventions

- **Inventorship ≠ Ownership**
- The majority of inventors are required to assign their inventions to their employers as a condition of employment.
  - Thus, most patents are owned by corporations or universities.
  - Inventors may receive royalties on sales of patented products.
- Patent owners may commercialize patented technologies themselves or license their patents to others for commercialization and further development.

Ownership of Gene Patents and Related Inventions

- What happens when a patented invention is derived from body fluids or tissue samples taken from one or more individuals?
  - Do those individuals own the patent?
  - Are those individuals entitled to share in the financial benefits the patent yields?
  - Can those individuals control the extent to which the patent is asserted against potential infringers?
  - Do individuals have a right to prevent the use of their body fluids or tissues in the development of patented inventions and/or commercialized products?

Moore v. Regents of the University of California, 793 P.2d 479 (Cal. 1990).

- John Moore underwent treatment for hairy-cell leukemia at UCLA Medical Center in 1976.
  - This treatment included the withdrawal and testing of numerous bodily fluids, as well as the removal of Moore's spleen upon his doctor's recommendation.
- Moore's doctor instructed him to return to UCLA Medical Center numerous times for additional testing over the next 7 years.

Moore, cont.

- Unbeknownst to Moore, his doctor was conducting research using the cells obtained during his testing and treatment.
- In 1981, Moore's doctor applied for a patent on a cell line established from Moore's T-lymphocytes.
- U.S. Patent No. 4,438,032 issued on March 20, 1984.
- UCLA licensed the patent to Genetics Institute (GI), and Moore's doctor received 75,000 shares of GI stock and more than $400,000 in compensation pursuant to the license.

Moore, cont.

- Upon learning his cells had been patented and commercialized, Moore sued his doctor and UCLA claiming:
  - Violation of the doctor-patient relationship ("breach of fiduciary duty") and lack of informed consent; and
  - Interference with his possessory and ownership interests in his personal property ("conversion").

Moore, cont.

- The Court held that Moore's doctor had violated the doctor-patient relationship and failed to obtain Moore's informed consent.
  - A doctor must disclose personal interests in medical procedures if those interests are unrelated to the patient's health and may affect the doctor's medical judgment. *See* Moore, 793 P.2d at 485.
  - These personal interests may be research-related or economic.

Moore, cont.

- However, the Court concluded that Moore retained neither a possessory nor an ownership interest in his cells after they were removed. *See* id. at 487-89.
  - The threat of liability will chill downstream medical research.
  - The patented cell line is distinct from the cells removed from Moore's body.
  - Commodification of the human body is immoral. *See* id. at 497-98 (Arabian, J., concurring).

Ethical Implications of Moore

- A patient may opt-out of research with commercial implications or opt-in without sharing in the financial benefits, but a patient may not opt-in *and* share in the financial benefits.
  - Ownership of source materials v. ownership of patented invention
  - This distinction may enable patients to negotiate contractual agreements in which they are assured some control over decisions regarding commercialization of gene patents and related technologies.
    See Paul Smaglik, *Tissue Donors Use Their Influence in Deal Over Gene Patent Terms*, 407 NATURE 821 (2000).

Ethical Implications of Moore

- What protections exist when the researcher and the tissue donor are not in a doctor-patient relationship?

Greenberg v. Miami Children's Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

- In 1987, families of persons suffering from Canavan disease formed a collaboration with Dr. Reuben Matalon to identify the disease gene.
  - The families, in association with several nonprofit organizations, located other Canavan families throughout the world and convinced those families to provide tissue samples, familial pedigrees, and financial support.
  - Using these resources, Dr. Matalon isolated the Canavan gene in 1993.

Greenberg, cont.

- In 1994, Dr. Matalon filed a patent application on the Canavan disease gene without informing the families.
- U.S. Patent No. 5,679,635 issued in October 1997.
- In 1998, Dr. Matalon and his employer, Miami Children's Hospital (MCH), initiated an aggressive campaign to restrict use of the Canavan test through lucrative exclusive licensing agreements.

Greenberg, cont.

- Upon learning of the patent and licensing scheme, the families sued Dr. Matalon and MCH on numerous grounds, including:
  - Violation of a fiduciary duty and lack of informed consent;
  - Interference with their possessory and ownership interests in their personal property ("conversion"); and
  - Unjust enrichment.

Greenberg, cont.

- The Court concluded that medical researchers have no duty to disclose their economic interests in research to research subjects.
  See Greenberg, 264 F. Supp. 2d at 1069-70.
  - Imposition of such a duty would chill downstream medical research.
  - *But note:* The Court found that "in certain circumstances a medical researcher does have a duty of informed consent" with respect to non-economic interests. *See* id. at 1070.
- Citing Moore, the Court concluded that the families retained neither a possessory nor an ownership interest in their donated tissues.
  See id. at 1074-76.

Greenberg, cont.

- However, the Court held that a trial was need to determine whether Dr. Matalon and MCH had unjustly obtained a financial benefit using the resources provided by the families.
  See id. at 1072-73.
  - The Court noted that, in certain circumstances, the procurement and enforcement of a gene patent may give rise to an unjust enrichment claim. *See* id. at 1072.
- Following this decision, the case settled.

Ethical Implications of Greenberg

- Researchers who are not in a doctor-patient relationship with their research subjects have no legal duty to disclose their economic interests in the research, although they may have a duty to disclose non-economic interests.
- However, ethical principles and the inability of subjects to control commercialization of downstream technologies suggest disclosure of *all* interests may be appropriate.

Ethical Implications of Greenberg

- Genetic researchers should expect savvy research subjects to condition the provision of their bodily fluids and tissue samples upon the execution of contractual agreements that assure the subjects some control over the commercialization of derivative products.
  - *E.g.*, PXE International
  - Limited to coherent advocacy groups and well-informed subjects
  - What about individuals without such leverage?