Bio-Technology Development and Patents

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Abstract

Concerns over potential impediments to biochemical patenting derive from the significance of biotechnology to the future of medicine. From a medical perspective, developments in genetics could hardly be more consequential. (10) The legal revolution referenced above began with a scientific breakthrough--the development in 1972 of recombinant DNA technology. This invention spawned further advancements in genetic research, including the discovery in 1983 of a generally applicable method for cloning genes for polypeptides where the amino acid, DNA, and mRNA sequences were not completely known; the availability beginning in 1986 of computer controlled sequencing machines for the DNA base pairs that form genes; and the development of polymerase chain reaction technology the same year.

These advancements have powerfully boosted the ability of scientists to locate and sequence genes. As the president of one major biotechnology company noted, a few decades ago it might have taken ten years to find a particular gene, but, with modern gene maps, a gene can now often be found with a fifteen second computer search. Sequencing has also become far less laborious. The ability of scientists to rapidly sequence DNA has resulted in an explosion of discoveries of DNA sequences--both meaningful and meaningless scientifically--that, in turn, has caused a

deluge of patent applications claiming DNA sequences and the proteins and other biochemicals for which these sequences code.

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Chapter I

Introduction

A quiet revolution has taken place during the past two decades in the federal law governing property rights in the biological and chemical constituents of living organisms. The Patent and Trademark Office (PTO) now routinely grants, and federal courts consistently uphold, patents on newly discovered, naturally occurring genes, DNA fragments, proteins, and other biochemicals (1) in contravention of long established principles of patent law. The PTO's position is reflected in an essay by John J. Doll, the PTO's Director of Biotechnology Examination, published in Science magazine. In the essay, Doll asserts that DNA sequences "isolated and purified" from their natural state are "products of human ingenuity" (2) and must be patentable because 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. (3)

Doll's statement reflects PTO policy more generally. In July 2000, Todd Dickinson, the Director of the PTO, declared to the Subcommittee on Courts and Intellectual Property of the House Judiciary Committee:

“There are so many chemicals in the human body that, if we ruled them all off limits to patenting, we would rule out an extraordinary number of valuable and important inventions.... Without the funding and incentives that are provided by the patent system, research into the basis of genetic diseases and the development of tools for the diagnosis and treatment of such diseases would be significantly curtailed.” (4)

Neither Doll nor Dickinson has offered an explanation as to how chemicals found in the human body can be "inventions" under the positive law of patents; their comments instead present policy rationales for the PTO's treatment of newly discovered biochemicals and organic tissues. (5) The vast majority of commentators have adopted the same perspective, acclaiming the patentability of naturally occurring biochemicals after "isolation and purification." To illustrate, two members of the patent bar have written: "There is little dispute that defined,

functional DNA sequences obtained through research in the human genome project will be, and should be, patented." (6) Other authors have opined that a patent on a purified, naturally occurring biochemical is consistent with patent law if the purification was difficult. (7) Yet another asserts: "Virtually cost-free to the public fisc, making patents slightly easier to get will satisfy the policy needs of the biotechnology industry and will be logically defensible." (8) Still others insist that DNA and other natural products should be patentable "lest we eliminate patent incentives for the development of important medicines." (9)

Researchers have now sought and obtained patents on human DNA sequences that play an important role in understanding and diagnosing, and perhaps some day treating, the most common and serious of human diseases, including: tuberculosis, diabetes, cancer, multiple sclerosis, Alzheimer's disease, (16) and even immune system maldevelopment. (17) Researchers have also patented the entire genomes of important pathogenic bacteria affecting public health, including Streptococcus pneumoniae, the leading cause of bacterial pneumonia and meningitis. (18) In March 2001, the drug company Geron Corp. obtained a patent covering genes coding for human embryonic stem cells. (19) There is currently a similar race for the discovery of genes relating to less medically critical but equally profitable DNA sequences,

such as those affecting baldness and snoring, and, under the current trend, this may be expected to continue for remaining DNA sequences and other components or derivatives of the human body, (20) particularly proteins and hormones. (21) Researchers are now scouring the human genome and the genomes of other species with powerful computers in the hope of finding and monopolizing DNA sequences that may someday be used in product development.

Research on DNA sequences and their corresponding proteins is considered to represent the future of diagnostic and therapeutic medicine. Genetic research has led to the mass production of human pharmaceuticals, biologics, and vaccines that previously could be obtained only by the laborious process of extracting them from the natural tissues or secretions of living beings. Increasingly, such therapeutics and vaccines are made available through plants, bacteria, yeasts, and animals genetically engineered to produce the desired protein, hormone, or other substance like a living factory. (22) A patent on the critical genes or the entire genome of these organisms may confer a significant advantage on the patentee in producing biochemicals compared with competitors who obtain the same or similar chemicals through more traditional processes.

Ownership (23) of rights to a single gene or, in some cases, a single brief DNA sequence could also result in a near monopoly

on diagnostic tests and treatments for widespread and serious ailments. While most disorders and diseases are caused by a combination of genetic and environmental variables, private ownership of any causative factor could create an opportunity to extract rents from those wishing to develop a diagnostic test, therapy, or pharmaceutical, resulting in higher medical costs and decreased availability to those in need. Indeed, private ownership of a DNA sequence or natural biochemical could allow a company to preclude its use in developing a diagnostic test or therapy altogether if, for example, licensing the use of the gene to develop a vaccine for a debilitating disease were less profitable than manufacturing and selling a treatment for the disease. On the opposite side are arguments, already alluded to, that patents are a precondition to the development of such diagnostics and therapies in the first place.

The ownership of preexisting genes and other biochemicals raises important questions about the scope and purpose of the patent law--what it is designed to accomplish and how biotechnology (24) fits within that design. More fundamentally, whether patent law is properly applied to products not independently created by a patent applicant implicates questions about the limits of intellectual property ownership, policy decisions about whether natural substances and processes should reside in the public or private sphere, choices about the value

placed upon publicly available knowledge, and the microeconomic effects of limiting patents to some kinds of biotechnological innovations while excluding patents on others. Are patents on naturally occurring phenomena, such as discovered DNA sequences, proteins, plasmids, and other biological chemicals, truly as uncontroversial and "simply necessary" as a matter of public policy as many legal commentators, the biotechnology industry, and the PTO Director himself have argued? Equally important, are patents on naturally occurring substances of any kind authorized by the relevant legislation and case law? The answers are far from obvious, and their importance merits a more careful and detailed examination of the legal and policy underpinnings of the patenting of genes and other biotechnological innovations than has so far been undertaken. American public figures and the media have just begun an informed debate in the last five years about the moral and policy issues raised by highly publicized biotechnological advances such as animal cloning (25) and human embryonic stem cell research. (26) Public consideration of the limits, if any, on private ownership over biochemical discoveries remains incipient. This paper provides the first comprehensive examination of this issue.

Chapter II

A Brief History Of The Patenting Of Biotechnological Innovations

Before delving into the unavoidably recondite discussion of the law and policy of gene patenting, it may be helpful to recount briefly the main patent issues historically associated with innovations in the field of biotechnology. While these early patenting issues do not always bear directly on the questions examined in this paper, they provide a matrix of information similar to what judges and PTO officials often bring when considering these issues. Having the same basic knowledge as these legal decisionmakers regarding biotechnology patenting, it is easier to understand the perspectives with which they have approached the specific issue of patenting DNA and other biochemicals. Additionally, an historical overview offers an opportunity to consider how the current interpretation of the Patent Act evolved and whether, in light of the unique--or not so unique--structure and function of the industries involved, the interpretation is the optimal one for purposes of patent policy.

The Statutory Plant Patenting Regime

The first statute on genome patents, ironically, did not mention genes at all. That statute, the Plant Patent Act (PPA) of 1930, (32) was enacted because Congress construed the patent

law then in force (the 1870 Patent Act, as amended) to forbid the patenting of living organisms. (33) None of the patent acts before the PPA mentioned explicitly the patenting of living organisms, and certainly none mentioned genes or biotechnology. Congress enacted the PPA to ensure that plant breeders were given adequate incentive, in the form of exclusive federal rights, to develop new and useful varieties of plants without fear of other breeders taking and propagating the new varieties, thereby undermining the initial breeder's intellectual and other investment. However, Congress, presumably not wishing to extend exclusive rights to breeders whose new varieties were not "inventions" within the meaning of the patent law, limited the patent rights to those varieties created by asexual reproduction.

Thus, the PPA provides for patents to issue to "[w]hoever invents or discovers and asexually reproduces" a "new and distinct" variety of plant. The PPA does not specify how "distinct" a variety must be from its naturally occurring (or, for that matter, cultivated) predecessors to be patentable. However, the legislative history of the PPA makes clear that Congress did not intend to allow the patenting of naturally occurring plants and that this exclusion was based upon Congress's understanding that plants found in nature were not and should not be patentable "discoveries" as that term is used in paper I, Section 8 of the Constitution. (34)

Following this logic, the PPA was the first U.S. patent statute to authorize the patenting of genes indirectly, in the form of a genome for a new and distinct variety of plant. It is significant that Congress saw fit to preserve the requirement that plant patents be granted only for true inventions of the cultivator by limiting such patents to new and distinct varieties of plants that were produced by human cultivation. As with patent law generally, Congress manifested no intent in either the PPA or the PVPA to extend the range of patentable subject matter to existing, unknown plants not invented by the applicant.

Patents on Monocellular Organisms

Congress's conclusion that specific laws were necessary to place plants and seeds within the realm of patentable subject matter is significant, as it implies an understanding that other living organisms are unpatentable under the principle of expressio unius est exclusio alterius. (44) Nonetheless, Congress had never authoritatively repudiated the possibility of such patents, and the patentability of living nonplant organisms (including their genes and genomes) remained, therefore, an open question throughout the nineteenth and most of the twentieth centuries. (45)

Perhaps the most surprising aspect of Chakrabarty, and the one with the most profound implications, is that the Supreme Court construed section 101 of the 1952 Patent Act to encompass living organisms. Section 101 permits patents on machines, manufactures, or compositions of matter. A living organism is, properly speaking, none of these. (52) Thus, Chakrabarty is particularly controversial and important because the Court read into the Patent Act and its legislative history support for extending patents to living organisms. (53) By virtue of this decision, the Court has created two separate paths for patentability of plants--under the PPA or PVPA on the one hand, and under section 101 of the 1952 Patent Act on the other. (54) As long as one accepts the assertion in Chakrabarty that Congress intended the terms "manufacture" or "composition of matter" to mean living organisms, the PPA and PVPA become extraneous supplements to the Patent Act and not necessary provisions for ensuring the patentability of certain living organisms (i.e., plants) that Congress believed should be an exception to the general rule of nonpatentability for whatever reasons, moral or political. Chakrabarty, then, opened the door to patenting any living organism that does not occur in nature--a door that Congress itself had declined to approach.

Patents on Complex Organisms

1. Animal Patents

Thus, beginning in 1980 with Chakrabarty, patents on living, single cell organisms (in addition to the process of creating nonplant living organisms by genetic engineering) became permissible if the organism could not be considered "naturally occurring." (55) Whether genetically engineered multicellular organisms that met the same criteria would also be patentable became the inevitable next question. The Supreme Court's opinion in Chakrabarty implied no limitation of its decision to single cell organisms. On the contrary, the Court stated that the status of the subject matter as living made no difference to its patentability, although it never said explicitly that complex organisms were patentable. Based on the logic and language of Chakrabarty, the 1952 Patent Act would seem to permit the patenting of any new, genetically engineered living organism.

And such was the PTO's interpretation when, in 1984, it granted a application sponsored by Harvard University for a patent on a mouse that is particularly prone to cancer--the so-called "oncomouse." While the patent application claimed the mouse itself or any mammal with the mouse's genetic idiosyncrasies, it arguably covered the activated oncogene sequence in the animal's germ cells and somatic cells because the scope of the claim included the offspring of any mammal having the oncogene. In other words, the claim on the mammal

entailed a claim on at least the portion of the mammal's genome that coded for its novel morphology or physiology. In spite of the significant public controversy over the patenting of a four-legged creature, the PTO granted the application. (56)

While the oncomouse application was pending, the PTO Board of Patent Appeals and Interferences (BPAI) was considering for the first time whether a multicellular animal, a polyploid oyster, was patentable subject matter. The oyster had been genetically modified to demonstrate increased growth and to be edible throughout all stages of its life cycle. The patent examiner had rejected the application for lack of subject matter jurisdiction, ruling that the oyster was a product of nature. The BPAI overturned this rejection and found that the oyster represented an invention. (57) While the examiner had observed that the oyster was "controlled by the laws of nature" and, therefore, not a patentable invention, the BPAI pointed out that the relevant test was not whether the subject matter was "controlled by the laws of nature," but whether it was naturally occurring. (58) On appeal, the Federal Circuit affirmed the BPAI's decision and, in so doing, determined that Chakrabarty had opened the door to patents on genetic codes for multicellular animals that otherwise met the patentability requirements.

The Commissioner of the PTO responded to the decision by announcing that, while it now considered "nonnaturally occurring non-human multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101," the BPAI's decision in no way altered the "principle and practice that products found in nature will not be considered patentable subject matter under 35 U.S.C. 101 and/or 102." (59) The PTO would accept applications for such "non-naturally occurring" organisms as long as the "invention" had a "new form, quality, properties or combination not present in the original paper existing in nature in accordance with existing law." (60)

2. "Human" Gene Patents

It was not long after the Chakrabarty decision that the PTO began issuing patents on human genes and gene fragments, transgenic bacteria that express human genes, and human cell lines (61) that express DNA sequences producing pharmacologically important proteins and that perform other important biological functions. (62) Human genes and gene fragments became common subjects for patents in the years following Chakrabarty. The inevitable question was whether the PTO would permit patents to issue on a complete human genome or organism and, if so, where it would draw the line between permissible and impermissible claims. If human genes were

patentable, and bacteria, plants, and animals implanted with human genes were also patentable, how many human genes would make a transgenic organism "human"?

In December 1997, a cellular biologist named Stuart Newman filed a patent application to test the limits of the patentability of human genetic modification processes. (63) The application sought a patent on a technique for combining human and animal embryonic cells to produce a single hybrid mouse-human embryo (the so-called "humouse"). The embryo could then be implanted into a human or animal surrogate mother to develop into a being of mixed human and animal composition--a not-so-mythological chimera. (64) The applicant's purpose had nothing to do with a desire to commercially exploit the humouse, it was to test what the PTO's reaction would be. The Director of the PTO appeared to understand this and declared in April 1998 that "inventions directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement." (65) The PTO then preliminarily rejected the Newman application because the invention "embraces" a human being and failed the moral utility test. (66) Moreover, any claim "directed to or including within its scope a human being" would not be considered patentable because treating a human being as exclusive property is

unconstitutional. (67) In practice, this meant that despite the PTO's purported rejection of patent applications "embracing a human being," it would begin accepting applications for engineered transgenic animals that include human genes. (68)

To summarize Parts I.A, I.B and I.C, the operative principles of patent law have been interpreted to allow the patenting of (1) the genomes and DNA sequences of plants; (2) the genomes and DNA sequences of bacteria, animals, and other living organisms; and (3) the DNA sequences of human beings, but not the entire genome of a human being or a human-like being.

The Human Genome Project and the EST Debate

A primary cause of the evolution of law is the strain caused by new technologies that challenge an extant legal paradigm. The Internet has provoked just such an evolution in intellectual property law, contract law, First Amendment law, and even real property law. The Human Genome Project, and the quantum leap in genetic and proteomic knowledge accompanying it, has similarly stressed the established patent doctrine by creating nontraditional and valuable opportunities for commercial exploitation.

1. Origins of the Human Genome Project

The patenting of bacterial and animal genes began to accelerate in the late 1980s as a result of technological advances in DNA replication. It did not take long for the possibility of recombinant DNA technology to revolutionize medical science to come to the attention of scientists in academia, the government, and businesses. In 1985, the chancellor of the University of California, Santa Cruz, convened a meeting of scientists to consider the feasibility of a cooperative effort at mapping and sequencing (69) the human genome. (70) Because sequencing in the mid-1980s was a much slower process than mapping, the scientists attending the conference concluded that mapping the human genome would be a realistic and worthy goal. Subsequent conferences sponsored by universities and the Department of Energy (DOE) reaffirmed the value and feasibility of this work and, in 1988, Congress decided to fund the DOE and the National Institutes of Health (NIH) to undertake the Human Genome Project. (71)

The DOE and NIH quickly began coordinating their efforts to map the entire genome with university research facilities and private pharmaceutical corporations. They also joined public and private research organizations in other countries to form the Human Genome Organization (HUGO), (72) which assists in coordinating the efforts of the Human Genome Project. Meanwhile, beginning in 1992, certain private corporations, such as Celera

Genomics (73) and Incyte Genomics, (74) began to create human and other genome maps for commercial purposes, offering detailed information on a subscription basis. Ultimately, both the Human Genome Project and private firms undertook to sequence the genome as well. (75)

2. The National Institutes Of Health EST Patent Applications.

NIH began using complementary DNA (cDNA) sequencing to accelerate its ability to sequence protein-coding regions of the human genome. Using this technique, researchers identify random sequences of cDNA, called expressed sequence tags (ESTs), (76) for use as probes in locating specific genes or place-markers on DNA sequences. ESTs, being random sequences of base pairs with no independent significance, have few other uses and no specific biological function. (77) Beginning in June 1991, the issue of the patentability of ESTs gained notoriety when NIH filed applications for 337 cDNA sequences and ESTs, (78) vowed to seek patents on 1000 ESTs every month , (79) and then promptly sought patents on 2750 partial cDNA sequences in subsequent months. (80) The following year, NIH submitted applications on another 4000 ESTs--short of its predictions, but still a stunningly high number compared to the rate of applications filed on other kinds of "inventions."

The patent applications were not universally supported within NIH, (81) but the main opposition came from without. (82) The American Society of Human Genetics (ASHG), which supports gene patenting generally, opposed the patenting of ESTs on the ground that they lacked utility. According to ASHG, ESTs themselves have no inherent commercial utility; any utility requires the full cDNA strand. (83) The European Directive on the Legal Protection of Biotechnological Inventions also repudiated such patents as lacking utility: "[A] mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention." (84) Both the ASHG and the European Commission believed that the "EST is, at best, a starting point for further research, and should not be patentable." (85) This position echoed broad agreement in scientific and legal circles that ESTs lacked patentable utility. (86)

The PTO's 1995 announcement of the "credible utility" standard invited a torrent of applications for ESTs claiming a trivial but credible utility. A year later, the PTO was awash in applications for patents on DNA sequences by NIH and commercial companies. (101) By October of 1996, the PTO faced 350 pending gene patent applications that collectively claimed more than 500,000 sequences. (102) The PTO estimated that it would take one patent examiner 200 years to initially examine these

applications. (103) Nonetheless, the PTO confirmed its intent to grant EST patents (104) and, in late 1998, issued the first EST patent to Incyte Pharmaceuticals, (105) which had filed applications up to that time on a total of 1.2 million partial gene fragments. (106)

3. The PTO Response: New Utility Examination Guidelines

The EST debate inspired such a profusion of academic and editorial commentary in the 1990s that it overshadowed every other biotechnology policy issue under consideration by the PTO. (107) Indeed, the subject of patent applications on ESTs became the main focus of a cottage industry of biotechnology patenting articles in law reviews and scientific journals. It is no exaggeration to say that NIH's patent applications incited the equivalent of an academic four alarm fire, drenched and redrenched every year for over a decade by a flood of articles, student notes, and symposia. (108) Sensing growing public and academic opposition to the wholesale patenting of human DNA sequences without knowledge of their biological function, the PTO issued new utility examination guidelines on December 21, 1999. (109) These "Revised Interim Utility Examination Guidelines" applied to all areas of invention, but had particular relevance to emerging technologies, such as recombinant DNA technology, in which the claimed composition of