Who Owns Life?

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PATENTING OF LIFE-FORMS
From a Concept to Reality

A. M. CHAKRABARTY

CONCEPTUAL FRAMEWORK OF AN OIL-EATING PSEUDOMONAD

Back in 1965 after completing my Ph.D. at the University of Calcutta in India, I joined the laboratory of Dr. I. C. Gunsalus at the University of Illinois at Urbana to study the nutritional versatility of a group of microorganisms called *Pseudomonas*. Many members of this genus (collectively called pseudomonads) had the ability to utilize a variety of organic compounds, some as exotic as camphor or naphthalene or various components of crude petroleum. Dr. Gunsalus's interest was to find out how the pseudomonads managed to assimilate so many organic compounds with a genome size only slightly larger than that of *Escherichia coli*, another well-studied microorganism with a limited nutritional ability. My job was to define and map the nature of the bacterial genes that allowed dissimilation of camphor, octane, and similar organic compounds. I was largely able to meet these goals and demonstrated that the genes that allowed the pseudomonads (various strains of *Pseudomonas putida*) to degrade camphor and octane resided not on the chromosome of the bacteria, but on autonomously replicating DNA elements called plasmids. At that time, bacterial plasmids were known to encode resistance to antibiotics or heavy metals and to confer fertility properties to bacteria, but not to enhance nutritional capabilities. Since plasmids are often transmissible from one bacterium to another in absence of the transfer of chromosomal DNA, our studies demonstrated the potential of the pseudomonads to transfer these plasmids (later called degradative or catabolic plasmids) to other bacteria to enhance their range of nutritional versatility.

In 1971 I moved to the Research and Development Center of the General Electric Company (GE) located in Schenectady, New York, as a staff scientist. I was assigned the task of converting cow manure to cattle feed. The manure is basically composed of undigested lignocellulosic materials that are normally resistant to microbial attack. With the help and advice of my colleague, Dr. W. Dexter Bellamy, we developed a strain of thermophilic actinomycetes that could digest the lignin and cellulose components of the manure and grow at their expense, thereby reducing the undigestible lignocellulose content of the manure and enriching it with protein, since the actinomycetes were composed of about 70 percent protein. While this was an interesting and commercially lucrative project, I missed working on the more basic aspects of biology such as an understanding of the nutritional versatility of pseudomonads, the nature and the role of plasmids, and how bacteria acquire the ability to degrade normally recalcitrant compounds.

GE had an intellectually stimulating environment where new ideas were constantly generated and discussed. During a lunch conversation with colleagues, I became aware of the fact that converting crude oil to single-cell protein (a concept very similar to the conversion of lignocellulosic material to bacterial proteins by thermophilic actinomycetes) could be a viable and commercially attractive proposition. In some parts of the world, oil was cheap, but proteins (including fish, animal meat, or plant-derived proteins) were expensive. Conversion of crude oil to bacterial biomass (about 75 to 80 percent protein) could make sense. This discussion immediately kindled my interest since I knew that the pseudomonads were able to degrade various components of crude oil and thus could be an excellent candidate for this bioconversion. However, there was a problem. Crude oil is a mixture of a large number of the hydrocarbons. Individual *Pseudomonas* strains could degrade only a limited number of the hydrocarbon components of crude oil. Growth of the crude oil with a single strain resulted in the loss of a few hydrocarbons and did not allow significant enrichment with bacterial biomass. Different strains, however, could digest different components of crude oil, and thus growth with a mixed culture allowed much more extensive utilization of different hydrocarbons that resulted in significant biomass generation. The problem with mixed-culture growth is that some strains tended to dominate over others, resulting in the survival of the fittest and, of course, overall loss of crude oil conversion. Suddenly, I had an idea. I knew that utilization of some of the crude oil components

such as octane, decane, naphthalene, and the like, in *Pseudomonas* was specified by plasmid-borne genes that could be transferred from one bacterium to another. Thus, technically I could construct a multiplasmid single strain that had a number of plasmids, each specifying a different hydrocarbon degradative pathway, so that a single pseudomonad could simultaneously degrade a number of hydrocarbon components of crude oil and grow rapidly, generating significant biomass with high protein content.

This was an attractive idea for me because it allowed me to go back to my postdoctoral days of basic research but at the same time provided me with a rationale for a potential commercial venture. During after-hours and weekends, I started tinkering with *Pseudomonas* genes in an effort to construct a multiplasmid pseudomonad. When some of the degradative plasmids appeared to be incompatible and thus could not coexist, I fused them with UV-irradiation so that they became part of a single, large plasmid. I then checked the ability of the parent strains (from which I transferred various hydrocarbon degradative plasmids) and the newly constructed multiplasmid strain to grow with crude oil as a source of carbon and energy. As expected, the multiplasmid strain grew faster and better with crude oil than the single-plasmid parent strains. This suggested that a genetically engineered pseudomonad with various degradative plasmids could have the potential to generate single-cell protein from crude petroleum in significant amounts compared to natural strains.

THE PATENTING CONTROVERSY: PRODUCT OF NATURE VERSUS COMPOSITION OF MATTER

At about the time the multiplasmid pseudomonad was being constructed, the price of crude oil was rising in the world market. It no longer made much sense to make protein from petroleum because of the high price of petroleum. However, occasional large-scale oil spills from oceangoing tankers in the late sixties and early seventies raised serious concerns regarding the pollution of coastal regions by the spilled oil. Thus the multiplasmid pseudomonad was deemed as a good candidate for oil spill cleanup because of its ability to consume oil relatively quickly. A decision was therefore made at GE to apply for a patent on the process of constructing multiplasmid

organisms as well as the organism itself. If this organism was not protected by a patent, anybody could easily isolate it and use it for oil cleanup purposes. I had some discussion with Leo I. MaLossi, the patent attorney working for GE, regarding the latter decision since microorganisms, as living matters, were considered nonpatentable by most patent lawyers working for the pharmaceutical industry. MaLossi could not quite understand why an invention, which may otherwise qualify as a patentable invention, could not be patented simply because it was living. To him, a living microorganism is nothing but a composition of matter and genetic engineering techniques that have imparted a new and useful characteristic to this organism with a consequent change in the composition of its matter. After careful investigation, he decided to include the genetically altered microorganism as a patentable invention in our patent application filed on June 7, 1972.

In late 1973 the U.S. Patent and Trademark Office (PTO) allowed the process claim, but rejected the product claim based on the fact that a microorganism is a product of nature and as such is nonpatentable. In an appeal to the PTO's board of appeals, Leo MaLossi argued that the multiplasmid pseudomonad was not a product of nature since the introduction of the plasmids, including a fusion plasmid generated from incompatible plasmids, changed the characteristics of the strain in a significant way that is very different from other pseudomonads found in nature. The board of appeals accepted this argument but rejected the products claim anyway, arguing that even though the multiplasmid pseudomonad was not a product of nature, it was nevertheless alive and therefore did not merit patent protection.

The rejection of the product claim by the patent office's board of appeals solely because of the living nature of the microbes prompted GE to appeal the decision to the United States Court of Custom and Patent Appeals (CCPA). In early 1978 Judge Giles Rich, speaking on behalf of the three judges in a three-to-two ruling, affirmed the patentability of living microorganisms, thus giving the GE claims a major boost. The CCPA considered microorganisms basically a factory of chemical reactions and various biological transformations and ruled that so long as the microorganism was useful, novel, and a product of human intervention, it merited patent protection irrespective of whether it was living or not.

During this time, another patent application filed by Upjohn Company (on behalf of Malcolm E. Bergy with claims that covered an antibiotic producing *Streptomyces* species) was also considered by the CCPA. In the *Bergy*

case, the CCPA also ruled three-to-two, in favor of Bergy. Soon thereafter, the solicitor general of the United States, on behalf of the PTO, appealed to the Supreme Court to rule on the patentability of living microorganisms. The Supreme Court, however, sent the case back to the appeals court for reconsideration in the light of another Supreme Court decision that involved a mathematical algorithm. The CCPA, however, did not see in this decision much relevance to the *Bergy* and *Chakrabarty* cases that involved the question of patentability of life-forms and reaffirmed the patentability of life-forms in 1979; this time ruling by a majority of four-to-one.

THE CASE BEFORE THE SUPREME COURT: PATENTABILITY OF LIFE-FORMS

During the appeal process, the commercial aspects of the recombinant DNA technology were gaining ground, and the proponents of the technology—particularly the pharmaceutical industry, academic institutions, and professional organizations—became deeply interested in the case involving patenting of genetically engineered microorganisms. It was also the time that a great deal of controversy was generated because of the unknown potential hazards of crossing the evolutionary barrier by recombining genes from different kingdoms. Also the PTO was under intense pressure to appeal the CCPA decision to the U.S. Supreme Court. (An excellent account of these activities has been presented by Daniel J. Kevles.)[1] Patent commissioner Sidney Diamond and the solicitor general on behalf of the PTO did just that, and in October of the same year, the Supreme Court agreed to review the case on the patentability of the life-forms. Soon thereafter, however, Upjohn Company withdrew the Bergy product claim, leaving *Diamond* v. *Chakrabarty* as the only case to be decided by the Supreme Court. A number of amicus briefs were submitted to the Court by various organizations, mostly in support of the *Chakrabarty* claim, but a few opposing it. Those who opposed it were contending that life is basically sacred and should not become a subject of the commodity marketplace. Such organizations were also worried that the patenting of a lowly life-form such as a microorganism might set a precedent for the patenting of higher forms of life (perhaps including humans), and that raised the murkiest of issues involving the morality and legality of tinkering with human genes and the ownership of human limbs, organs, or persons.

Once the Supreme Court agreed to take the case, GE hired a renowned attorney, Edward F. McKie Jr., to represent me at the Court. However, by this time, I had accepted a position as a professor of microbiology and immunology at the University of Illinois at Chicago College of Medicine and had moved to Chicago at the end of March 1979. GE offered me a consultantship to confer with McKie, and I talked with him frequently on the scientific definition of life, the biological functions characteristic of living forms, and how genetic techniques, particularly viral genome sequences and characterization of gene products, were enabling scientists to define precisely how various living functions involved a series of chemical and biological reactions. Such understandings were at the core of Judge Giles Rich's argument that there is nothing unique to the living form that can make a microorganism nonpatentable simply because it is living. In addition to his law degree, Ed McKie had a degree in engineering and used to pose sharp questions for me involving the definition (or as near a definition as one could come up with) of life or what may constitute life. In March 1980 the Supreme Court justices heard oral arguments of this case, which I was privileged to attend. The arguments centered on whether the techniques used in the construction of the oil-eating pseudomonad were or were not completely new technologies, whether they may pose unprecedented or unforeseen problems, and why patents could be issued to new chemicals but not to new bacteria even though such bacteria represented nothing more than an altered composition of matter. The broad questions of patentability of higher forms of life were set aside, and the arguments were focused on the narrow definition of the patentability of an altered form of a soulless, mindless, and lowly form of life.

On June 16, 1980, the Supreme Court delivered its verdict. In a close five-to-four decision, the Court held that the multiplasmid, oil-eating pseudomonad was not a product of nature but a man-made invention that merited patent protection. The Court brushed aside many of the scenarios that predicted calamitous consequences for allowing the patenting of life-forms. The justices affirmed that their decision was a narrow one dealing with the subject in question and not addressing bigger questions of patenting higher forms of life, which was the subject of a congressional debate and action.

BEYOND THE SUPREME COURT DECISION: PATENTING OF HIGHER LIFE-FORMS

Even though the Supreme Court based its decision in a focused manner centered on a genetically engineered bacterium, the PTO interpreted the decision in a much broader manner, granting patents on genetically altered plants, animals, human cells and tissues, disease genes, and the like. I have reviewed this area previously and will not dwell on it in detail, except to point out that granting patents on animals, birds, plants, fish, and human cells and genes (including expressed sequence tags [ESTs] and single nucleotide polymorphisms [SNPs]) represents an outcome wholly unforeseen, but to some extent anticipated or feared during the controversy surrounding the patenting of the oil-eating pseudomonad.[2] Publication of the complete sequence of the human genome will provide important insights into the role of genes not only in the causation of disease, but also in various other facets of human life, including human behavior, aging, emotional status, or susceptibility to infectious diseases or environmental insults. With progress in such areas will come the attendant ethical, moral, and legal issues, including the issues on intellectual property rights to human organs made in vitro by triggering differentiation of cultured embryonic stem cells or to hypothetical human-animal hybrids.[3] Since such issues invariably end up in a court of law, there are efforts underway to initiate a dialogue between the members of the scientific community and the judiciary so that all aspects of the science and law, particularly those involving human genetic intervention, are understood and debated in the courts. Thus, the Supreme Court decision on *Diamond* v. *Chakrabarty* appears to have gone beyond what the Supreme Court justices perhaps intended to grant. The subject of "who owns life?" has therefore become a significant, timely, and dominant issue of our times.

NOTES

1. Daniel J. Kevles, "Ananda Chakrabarty Wins a Patent: Biotechnology, Law, and Society, 1972–1980," *Historical Studies in the Physical and Biological Sciences* 25 (1994): 111–35.

2. Ananda M. Chakrabarty, "*Diamond* v. *Chakrabarty*: A Historical Perspec-

tive," in *Principles of Patent Law*, Donald S. Chisum, Craig A. Nard, Herbert F. Schwartz, Pauline Newman, and F. Scott Kieff (New York: Foundation Press, 1998) 783–88.

3. Rick Weiss, "Patent Sought on Making of Part-Human Creatures: Scientist Seeks to Touch Off Ethics Debate," *Washington Post*, 2 April 1998, A12; *Judges Journal* 36 (1997): 1–96.