Access to Intellectual Property in Biotechnology: Constraints on the Research Enterprise

Ronald Sederoff with **Laura Meagher**
Professor and Director
Forest Biotechnology Group
North Carolina State University
Raleigh, North Carolina

Associate Dean/Associate Director of Research
Cook College/New Jersey Agricultural Experiment Station
Rutgers, the State University of New Jersey
New Brunswick, New Jersey

Intellectual property rights (IPR) in biotechnology are having a dramatic negative effect on the progress of nonprofit research. Although patent policy and law intend to facilitate research progress, the current practice has led to many barriers in access and use of genetic materials and DNA technology. Such barriers restrict the free exchange of information and threaten the health of our nation's scientific enterprise. Policies related to patents and licensing are increasing the cost of research at a time when funds for research are being reduced.

We wish to discuss some current issues related to research in biotechnology carried out in academic institutions, particularly land-grant universities, and the rapidly changing roles of scientists in relation to intellectual property and industry. The rapid changes in the arena of intellectual property are more acute in the area of biotechnology, which is still in the early stages of development and where many issues are not yet well defined. Further consideration is needed of the costs and benefits of current patent policy and law. Problematic examples are discussed. Some provision (amendment or extension of law) should be made to foster the conduct of basic research in universities and other nonprofit research institutions, and to some extent provide an exemption from the law that governs commercial research and development.

Biotechnology and the Land-Grant Universities

Life is not simple for an academic institution engaged in biotechnology research today. As land-grant universities attempt to redefine their mission relative to society, conflicts arise over the interrelated roles of research and protection of

intellectual property. Even as intellectual property rights are pursued more vigorously by universities, the heart of the research enterprise is being constrained by the protection of intellectual property owned by others. Industry can invest much more in obtaining and defending intellectual property than universities can. As the law stands, and as current policies are enforced, it is unlikely that the balance will tilt in favor of the universities.

In the last two decades, universities have redefined their approach to technology transfer. The universities have simultaneously viewed it as a channel for added revenue and as a vehicle for ensuring that the discoveries of the laboratory are transformed into goods and services beneficial to society. Aggressive businesslike pursuit of protection for intellectual property generated at a university (which can then be licensed to a company for development) has led to the erosion of an apparent special status for universities as the home of exclusively "philosophical" activities. With this change, university efforts actually receive no "research exemption" and university faculty have no special right to explore patented inventions or to utilize protected findings or technologies.

Constraints on the research enterprise have significant implications for the well-being of society. When researchers are restricted in attempts to extend our knowledge of the world around us, society pays a cost of lost innovation, which is crucial for economic development and the wellbeing of our citizens. It is of particular concern when the research is carried out with federal funds and the cost of the research is either greatly increased, or it becomes impossible to carry out the research at all.

The traditional relationship of scientists and their funding agencies has changed. Since the Bayh-Dole Act of 1980, funding agencies have allowed intellectual property to be owned by the institution where the research was conducted. Generally, universities will retain ownership of patents even if the majority of the funding for a specific project comes from outside sources. Industry-funded research at universities usually requires some specific industry rights to licensing that ensures some potential or expressed degree of access to intellectual property resulting from the research. If a company obtains exclusive rights to license, they can have a great deal of control over subsequent technology based upon the patents. In many cases, related projects conducted by the same scientist are derived from public funding, often confounding the issue of who owns what.

Issues of Ownership

Under appropriate conditions, the sequence of nucleotides that represents a gene may be patented. The patenting of genes must still satisfy criteria of novelty, utility and reduction to practice. Anonymous gene sequences with no knowledge of function are not sufficient for patent protection. It is not yet resolved to what extent similar sequences are covered by specific gene patents. If a gene for a specific enzyme was patented, should that patent cover all genes

encoding that function or only that specific sequence? Much of the variation between related genes for the same function could be significant and valuable. What if the gene was obtained from a related member of the same species that had a different sequence? What if the gene was from a distantly related species? Some principles of what constitutes "equivalence" for a particular gene remain to be resolved. The issue of equivalence is important because once a sequence of a gene of known function is made available through publication or through a public database. It is possible for a molecular biologist to obtain an equivalent gene from another individual of the same species or of a different species. The different species could be as distantly related as a plant and an animal.

Issues of ownership of genes have become more critical as more large-scale sequencing projects are carried out to identify genes from organisms for commercial application. Specific genes with potential application can then be patented which means that use of these genes could be removed from the public domain, and research into their potential applications could be curtailed.

It is common practice to use patents and licensing to protect some genes where commercial development is possible. Current procedures for obtaining use of licensed genes can be extremely cumbersome and expensive. In fact, negotiating agreements that allow universities to conduct research with genes owned by industry can delay research for years. Such delays are unreasonable when research objectives are noncommercial and are supported by federal funds. Similar situations arise for other DNA sequences used as promoters or vectors for transformation. In the past, constructs have been available with restrictions on distribution and potential commercial application, but without cost. This situation appears to be changing, and charges are being added to such agreements. A new promoter, highly expressed in plant cells, has recently been made available through a licensing agreement to individual university laboratories for $1500.

As individual genes have been patented, the question of patentability may be raised about genomic maps. The process of constructing gene maps is derived from genetic studies conducted before 1920, and is fundamentally unchanged, except for the new kinds of molecular markers and the computer software that greatly facilitates map construction. We know of no examples of the patenting of an entire genomic map. However, specific genetic markers on genomic maps have patent potential for specific purposes such as diagnosis. These genetic markers would also have utility for disease detection in humans, and in breeding of plants and animals. Once a specific marker is located that would predict resistance to a disease, for example, it would be relatively easy for a mapper to identify other markers that would be equivalent in their ability to predict resistance, but would bear no relationship to the original marker in sequence, only in genome location and linked to an allele of specific interest. It remains to be resolved to what extent markers can be protected by patent, and whether such protection might extend to adjacent regions of the genome.

A related issue to genomic mapping is the sequencing of entire genomes of specific organisms. The first entire sequence of a free living organism, the bacterium, *Haemophilus influenzae* Rd., has recently been completed. Such information could have industrial applications. However, the extent and utility of patentable information from genomic sequencing remains to be defined.

Genomic Mapping using PCR

New polymerase chain reaction (PCR)-based genomic marker technology (discussed below) has revolutionized genetic analysis for many species of plants and animals. This use of PCR was unanticipated. It represented a new application of PCR on a very much larger scale for individual laboratories than had been anticipated. Licensing of PCR has dramatically increased the cost of genomic mapping. The costs of licensing for this type of genetic analysis raise the cost of each reaction from several cents to about 30 cents a reaction. A typical mapping experiment can require tens of thousands of reactions, and a large experiment may involve a million reactions. Experiments that would have cost hundreds of dollars for materials instead now costs many thousands due to the licensing strategy for PCR. These greatly increased costs result from the patented process of PCR, and from the unusual status of the enzyme, Taq polymerase, used for the PCR reactions.

Taq polymerase has an unusual status as a reagent for molecular biology because its purchase from an approved source confers a license to practice PCR. As a result of this licensing strategy, the costs have placed an unanticipated burden upon laboratories exploring the large scale use of PCR for genomic mapping and genomic sequencing.

Taq polymerase is a heat-stable DNA polymerase purified from the thermophilic bacterium *Thermus aquaticus.* A process patent on PCR and the use of a natural enzyme for this process, Taq polymerase, (US Patent Nos. 4,889,818 and 5,079,352) have been licensed to the research community by the holders of the patents (Hoffman-La Roche Co.) through the purchase of the enzyme from specific suppliers (licensed by Hoffman-La Roche), and through the purchase of equipment and accessories from The Perkin-Elmer Corporation. The worldwide research community is considered to be an important market for the licensing of the PCR process and for the sale of the enzyme. As a result of the patenting, licensing and pricing strategy, the cost of the enzyme is far more expensive than most other widely used, easily purified enzymes of nucleic acid metabolism, such as restriction enzymes.

Of the hundreds of enzymes used as reagents in molecular biology, few are restricted through their use in a patented process. Taq polymerase cannot be purified legally by individual investigators for use with PCR. Scientists who wish to practice PCR are required to purchase the enzyme and are prohibited from purifying the enzyme for their own use. The purification of the enzyme is relatively easy and would provide the enzyme at a fraction of the current commercial price.

RAPD Markers

Randomly Amplified Polymorphic DNA (RAPD) markers, developed by DuPont Co. scientists and almost simultaneously at the California Institute of Biological Research in San Diego, provided a novel DNA marker technology for genomic mapping in plants and animals. The method was advantageous because it could be applied with no prior information and could be done using small amounts of DNA. The method was particularly useful for species with no history of genetic analysis or DNA sequencing. The cost of Taq polymerase has been the major barrier to the application of this technology to a number of new problems, for example, a large site adaptation study planned for loblolly pine that would require 1.5 million PCR reactions, making the research too expensive to undertake.

Recently, a new patent has been issued to DuPont that covers the use of RAPD markers. DuPont has licensed exclusive rights to the use of this marker technique for certain species to an Australian company, ForBio Ltd., which will license RAPD markers to individual laboratories at a specific charge for each RAPD reaction. RAPD reactions also use PCR and require licensed use of Taq polymerase. However, ForBio and DuPont have decided not to charge fees for research carried out in universities or government laboratories that "has no commercial purpose." This distinction deserves consideration; it could set a precedent for protecting freedom of inquiry.

Alternative Marker Technologies

The high cost of licensing both PCR and RAPD technology has stimulated interest in alternative methods. Several such methods are available, each with different advantages and disadvantages. These include microsatellites, amplified fragment length polymorphism (AFLP) or use of cDNA-amplified polymorphisms (CAPs) and others. All require PCR, except for the earlier methods of restriction fragment polymorphism (RFLP). RFLP methods are not well suited to large-scale experiments.

Unintended Negative Effects

For most if not all enzymes used in routine research in molecular biology, the cost of obtaining the enzyme from commercial sources is advantageous relative to the cost of producing enzyme in a research laboratory. The relative cost of production and the price of the product results in reasonable profit to the producers and savings in time to the purchasers. There is no incentive for infringement. The current circumstances surrounding the use and production of Taq polymerase are different. At a cost of a few thousand dollars, laboratories working on a small scale could, in short time, easily produce for their own research use what would cost millions of dollars through the current PCR/Taq polymerase licensing strategy. The ability to produce their own enzyme would allow some laboratories to conduct research that is essentially not affordable under current licensing requirements. Thus, the current environment could

foster deliberate patent infringement to the detriment of both the patent system and the university research enterprise.

Advances in mapping technology based on PCR raise several issues that epitomize problems affecting the current national research effort and the future of publicly funded university-based research. There is no doubt that the invention of specific amplification of DNA through PCR has been one of the most significant new techniques in biotechnology. Current strategies of intellectual property protection and commercialization may impede or block research efforts, exacting a social cost. Proprietary constraints on the practice of PCR have three aspects: the practice of the invention, the specific enzyme used to practice the invention, and the equipment needed to practice. The patent holders have chosen to license the practice of PCR through the sale of enzyme and sale of equipment that can be used to practice PCR. In part because the large-scale application to mapping was unanticipated, the licensing strategy has had unintended negative effects on U.S. research, and related research worldwide.

Biotechnology arose from several decades of research based upon the free exchange of information and materials. Most research during these crucial formative years was "basic" and was supported by public funds or foundations. Little consideration was given to intellectual property, and new information was released and made available through publication or conferences. If many of the fundamental advances made during this time had been patented, it is unlikely that the field of biotechnology would have developed by this time. It is instructive to consider how the past 45 years of progress would have been constrained if each major discovery or new process was patented and licensed. Essentially no restrictions or licensing costs were placed on any processes or molecules involved in biosynthesis, in vitro synthetic processes, methods of purification, or products of these processes. These fundamentally important advances remain unconstrained today. The free exchange of information depended upon public funding, and a certain "culture" promoting free exchange in the conduct of research.

If a major shift occurs from public funding to industrial funding, and if current intellectual property protection strategies continue to be pursued, the nature of the university research enterprise related to biotechnology could change in dramatic ways. Industrial research is more likely to remain short-term in perspective and will focus upon practical applications and products for development rather than discoveries of general interest. Industry-driven research is more likely to be directed to produce patents rather than publications. Academic objectives of scholarly work are different from that of patents in purpose and standards of proof. One of the challenges to universities is the need to maintain the high standards of scholarship while pursuing patentable technology.

What is the Cost of Research Not Done ?

The value of university research lies in the addition to the knowledge base of our society. New information and resultant technology drive economic development, maintains a competitive advantage for the nation as a whole and leads to a better informed and more productive citizenry. If wisely applied, such information should provide a basis for the conservation of natural resources and the ability to extend a higher living standard to our citizens and others throughout the world. Thus, there is an assumption that the benefits of research have high value. Yet, the inability to quantify such benefits and to predict when, how, and specifically to whom the benefits accrue means that benefits may pale in comparison to the extremely visible and quantifiably high costs of doing research. However, if another nation has invested in research and as a result has a major technical and competitive advantage, the costs of research not done become large and obvious. Currently, intellectual property protection strategies have inadequately accounted for the value of basic research.

The success, not only of our research enterprise per se, but also of our improvement of quality of life, has stemmed in large part from the traditional, unfettered pursuit of basic knowledge that has been the hallmark of our universities. With the decline in public spending and the increasing focus of the private sector upon short-term results, we are in danger of failing to build the foundation for discoveries in the long term. The problem is exacerbated by the constraints placed upon academic researchers by current interpretations of intellectual property protection. When we restrict the ability of the not-for-profit research community to take findings and push them to new discoveries and when we create costs of doing research that are prohibitive, we hinder the innovation that has served this country well — innovation that we need more than ever before.

Need for a Research Exemption for Not-for-Profit Research

In recent years, university professors have been surprised to find themselves restricted by copyright and patent laws that had not been defined or enforced in past decades. In practice, university researchers have often assumed that they could operate under a research exemption, not subject to the same constraints as industry, because they were supported by public funds and worked for not-for-profit or state-supported institutions. Recent rulings, however, have made it clear that these assumptions were not correct. Universities are subject to many of the same restrictions as any industrial organization. In contrast to the currently held belief of most university faculty, there is no general research exemption for university-based research.

Many scientists have the false perception that there is a general exemption for university or government-based research if it is purely philosophical in purpose. It is argued that universities have lost the claim to a philosophical exemption

because they file patents, exercise patent rights, and receive fees for licensing and royalties. A different basis for exemption based on the sovereign rights of the states and their agency to enjoy immunity from patent infringement, has been ended by an amendment of the Copyright Act of 1990 that put the states on the same footing as other defendants. The federal government, however, has not lost these rights of sovereignty and could expand the scope of an exemption. Federal employees and recipients of federal grants could be considered agents of the government for such purposes, thus effectively receiving an exemption for government-sponsored research.

In conclusion, there is a need to modify patent policy or law in order to encourage basic research. The current status of the law and its interpretation is unnecessarily restrictive and impedes innovation and discovery. Even though universities will continue to play a role in discovering information that will be useful to industry, publicly funded basic research should still be distinguished from corporate research for profit. It is important that our current intellectual resources, the envy of the world, be fostered and maintained for future commercial development and for the well-being of our citizens.