Bayh-Dole Reform and the Progress of Biomedicine

Allowing universities to patent the results of government-sponsored research sometimes works against the public interest

Arti K. Rai and Rebecca S. Eisenberg

Although the development of pharmaceutical compounds has long been a commercial enterprise, the broader field of biomedical research has enjoyed a very different tradition, one that allows the free sharing of scientific knowledge. But the culture of open science has eroded considerably over the past quarter-century. Proprietary claims have increasingly moved upstream, from the end products themselves to the ground-breaking discoveries that made them possible in the first place. One important reason for this change has been a narrowing of the gap between fundamental research and commercial applications. Once largely a matter of serendipity or trial and error, drug discovery now depends critically on basic knowledge of genes, proteins and associated biochemical pathways. In addition, the practical payoffs of basic research have become easy to anticipate in many cases, making it straightforward to obtain patents for discoveries that in an earlier era would have seemed too far removed from useful application to warrant the effort.

This shift in patenting activity has met little resistance. For example, in 1980 the U.S. Supreme Court held that genetically engineered microorganisms were eligible for patent protection. Shortly thereafter, Congress created a specialized court to hear appeals in patent matters, the Court of Appeals for the Federal Circuit, which has further extended the Supreme Court's expansive approach to patent eligibility. The Federal Circuit has also relaxed the standards normally required for patent protection, such as proof of the practical utility of an invention and of its lack of obviousness—standards that might otherwise have prevented the patenting of incremental advances in biomedical research.

These changes in the economics of research and in the interpretation of the patent laws have been important factors in the proliferation of intellectual property claims for discoveries of a fundamental nature. But perhaps even more significant has been the explicit U.S. policy of allowing grantees to seek patent rights for the results of government-sponsored research. This policy, which began in 1980 with passage of the Bayh-Dole Act, has turned universities into major players in the biotech business.

The Bayh-Dole Act was intended to promote the widespread use of federally funded inventions. The sponsors of the legislation believed that permitting grantees to obtain patent rights and to convey exclusive licenses for their inventions to private corporations would motivate investors to pick up where the government left off. This process, it was hoped, would produce commercial products from discoveries that might otherwise languish in the halls of academe.

This goal is, of course, quite noble. But the law draws no distinction between inventions that lead directly to commercial products and fundamental advances that enable further scientific studies. Universities have taken the opportunity to file patent applications on discoveries like new DNA sequences, protein structures and disease pathways—results that are primarily valuable because they enable more investigation. Columbia University, for example, now holds a portfolio in which 50 percent of its licensed patents represent such research tools. And even when they do not seek patents, universities often try to preserve their expectations for profitable payoffs by imposing restrictions on the dissemination of materials and reagents that might generate commercial value somewhere down the line.

This frenzy of proprietary claiming has coincided with unprecedented levels of both public and private investment in biopharmaceutical research and development—and magnificent progress in health care. So for many people, it may be difficult to see that there is any problem. But in the long run the current system may, paradoxically, hinder rather than accelerate biomedical research. Here we explore how

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Figure 1. Today certain drugs are routinely manufactured using genetically engineered bacteria, which are grown in reactors such as this one. Some attribute the widespread use of recombinant bacteria, and the rapid rise of the biotechnology industry in general, to the cheap, nonexclusive licensing of the underlying patent for shuffling genes into bacteria, which Stanley Cohen (then of Stanford University) and Herbert Boyer (then of the University of California, San Francisco) were granted in 1980. But few people have asked whether the results of this publicly funded research should have been patented in the first place rather than made freely available. The authors, both law professors, explore this question and suggest ways to manage the increasingly broad proprietary claims of government-supported research institutions. (Photograph courtesy of BioReliance Corporation.)

the current system emerged and what could be done to fix some of its problems.

Gold in Them There Halls

In 1979, U.S. universities were granted only 264 patents. But the statistics changed quickly after the passage of the Bayh-Dole Act the following year. In 1997, for instance, U.S. universities received 2,436 patents, a nearly 10-fold increase in 17 years. This rise was significantly greater than the twofold increase in the overall rate of patenting during the same time period and also exceeded growth in university research spending. Biomedical discoveries ac-

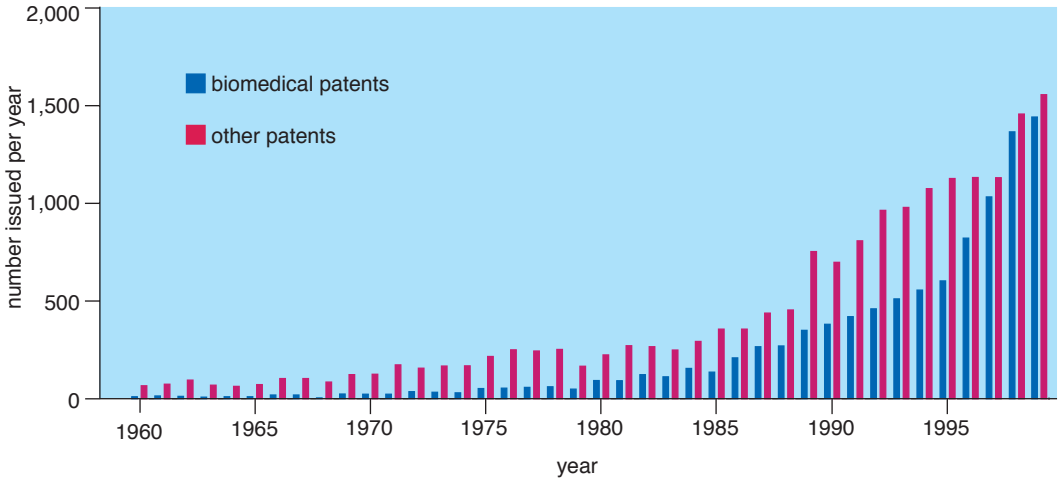

Figure 2. Growth in university patent activity in the United States over the past few decades has been tremendous. Biomedical patents account for an increasingly large fraction, now approaching 50 percent. (Data courtesy of Bhaven N. Sampat, Georgia Institute of Technology.)

count for a large share of these patents, particularly in terms of licensing revenues.

The majority of this patented research was publicly funded. (Despite the increasingly intimate involvement of industry with universities, private companies actually fund only a small percentage of university-based research in the life sciences.) A prominent recent example involves embryonic stem cells. In the 1990s, the National Institutes of Health (NIH) sponsored research at the University of Wisconsin that succeeded in deriving such cells from rhesus monkeys and macaques. The NIH-sponsored research on primates yielded a broad patent for the Wisconsin Alumni Research Foundation, the technology-transfer arm of the University of Wisconsin, which issued an exclusive license to Geron Corporation. This patent covers all lines of embryonic stem cells for primates, including humans (although for complicated reasons, Geron now holds rights to just three types of differentiated human embryonic stem cells).

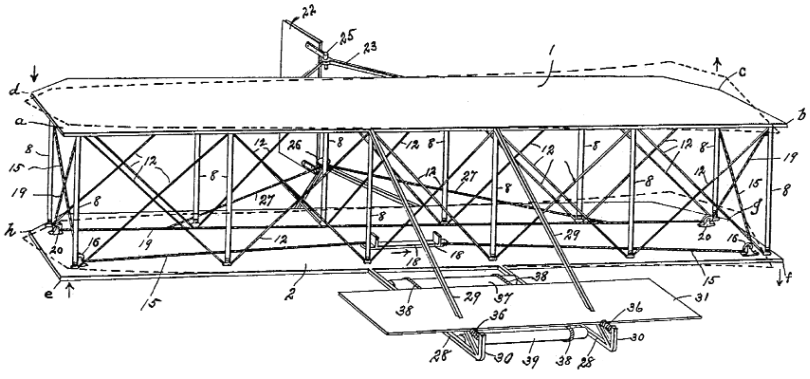

Figure 3. The Wright brothers did not license their wing-warping technique (shown in this drawing from the Wrights' 1906 patent) to the other major American aircraft maker of the time, the Curtiss Aeroplane Company, until compelled to do so by the government at the outbreak of World War I. This history aptly illustrates how proprietary claims can thwart the development of an emerging technology.

Clearly, NIH has a strong interest in ensuring the widespread dissemination of such broadly enabling research tools. But the Bayh-Dole Act significantly restricts what NIH can do. As long as the contractor is based in the United States, funding agencies may restrict patenting only in "exceptional circumstances," when they determine that withholding title to the invention will better promote the goals of the Act. The Bayh-Dole legislation also provides administrative procedures under which a grantee can challenge the determination of exceptional circumstances, with a right of appeal to the U.S. Claims Court. In addition, the agency must notify the Commerce Department, which has primary responsibility for administering this law, each time it claims exceptional circumstances, and it must provide an analysis justifying the action. If the Secretary of Commerce decides that "any individual determination or pattern of determinations is contrary to the policies and objectives of [the Bayh-Dole Act]," he or she must advise the head of the agency and the Administrator of the Office of Federal Procurement Policy and recommend corrective actions. Given these cumbersome procedures, it is perhaps not surprising that NIH declarations of exceptional circumstances have been extremely rare. Indeed, we are aware of only a single case.

The Bayh-Dole Act also permits an agency to compel licensing of the patents that result from research it had previously funded. But an agency can do so only if it determines that the university (or its exclusive licensee) is not taking steps to achieve "practical application of the subject invention" or if such licensing is necessary "to alleviate public health or safety needs or requirements for public use specified by Federal regulations." Exercise of such rights is not subject to an overarching directive that the circumstances be "exceptional." None-

theless, the Bayh-Dole Act seriously restricts the value of this provision by deferring such actions pending elaborate administrative proceedings and exhaustion of court appeals. The administrative obstacles have proved sufficiently high that NIH has never once exercised this option.

Out of Reach

Although the idea of private universities earning large sums of money from publicly sponsored research may be troubling enough for many, the real problem with the Bayh-Dole Act is that it often puts such academic research advances out of the reach. Although one might imagine that patent holders don't enforce their patents for noncommercial uses, some have in fact been quite aggressive in this regard, insisting that university investigators sign license agreements, especially when they seek to transfer materials covered by a patent rather than simply practicing a patented technique inconspicuously in their own labs. Given that patent law offers no significant exemption from liability for experimental use and that the division between noncommercial and commercial research can be blurry, it is indeed foolhardy for academic scientists to rely on the forbearance of patent holders.

Thus some patents can stall scientific progress. This concern is particularly acute for claims to early-stage discoveries that open up entirely new fields. Such patents may be quite broad, permitting their owners to control a wide range of subsequent research. One reply to this argument is that profit-seeking owners of pioneering patents will find it in their own best interest to disseminate their discoveries to as many follow-on improvers as possible. History shows otherwise. The Wright brothers, for example, refused to offer reasonable licensing terms for some of their aeronautical innovations until compelled to do so by the government. One notable recent example in the pharmaceutical industry is the controversy generated when DuPont imposed restrictions on academic investigators wishing to use its "oncomouse" technology, which DuPont controls under an exclusive license from Harvard University, the patentee.

Why would a company not want to license its technology as widely as possible? Isn't that how it makes money? One reason is that issuing such licenses requires considerable time and effort. Given the imperfect information available to the parties involved, the disparate assessments of value to the technology and the danger that one side might misappropriate the research plans of the other once they are disclosed in the course of negotiations, the transaction costs associated with such bargaining are likely to be quite high. And these costs mount quickly when the basic research discoveries necessary for subsequent work are owned not by just one company, but by a number of different entities.

Concern about an "anticommons" or "property rights thicket" is quite pressing in contemporary biomedical research, which often draws from many prior discoveries made by different scientists in universities and private companies. Exchanges of DNA sequences, laboratory animals, reagents and data that were once shared freely are today subject to licenses, material-transfer and database-access agreements. These arrangements have to be reviewed and negotiated before research may proceed.

A standard response to these fears is that market forces will motivate the emergence of patent pools and other institutions for bundling intellectual property rights. But this prediction has not yet been borne out. Indeed, when representatives of biopharmaceutical companies have seen the potential for an anticommons, they have reacted not by forming patent pools, but rather by strengthening the public domain.

The case of single nucleotide polymorphisms, or SNPs, provides an interesting example of this phenomenon. Collections of SNPs are found throughout the genome and are a useful resource for scientists searching for genes involved in specific diseases. These SNPs also promise to be useful in developing diagnostic and therapeutic products. In recent years, various biotechnology companies have identified and sought patents on large numbers of SNPs, provoking concern on the part of both NIH and the pharmaceutical industry about the potential for balkanization of intellectual property rights to this important resource. Paradoxically, the pharmaceutical industry has enjoyed more latitude than NIH to respond to this threat by placing SNPs in the public domain.

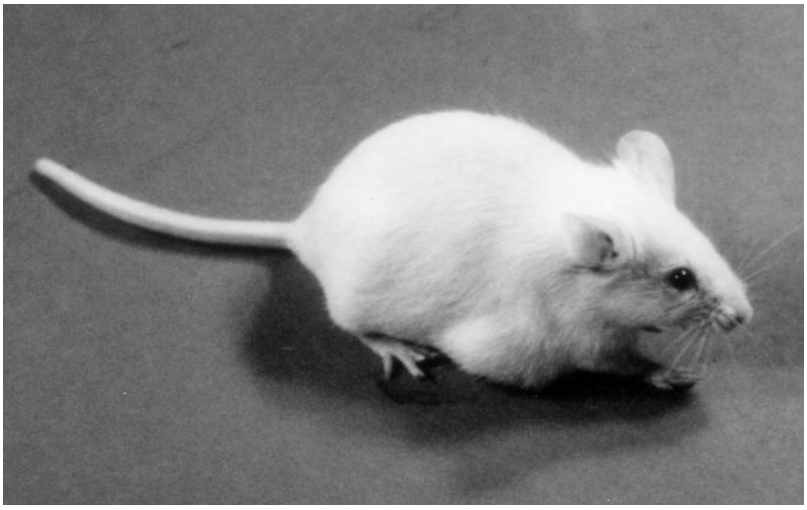

Figure 4. Controversy surrounds the so-called "oncomouse," an animal that has been genetically engineered to be prone to cancer. The technology, patented by investigators at Harvard Medical School, is licensed to DuPont, which demands that all those using such animals—even academic investigators—sign license agreements. (Photograph courtesy of Harvard Medical School.)

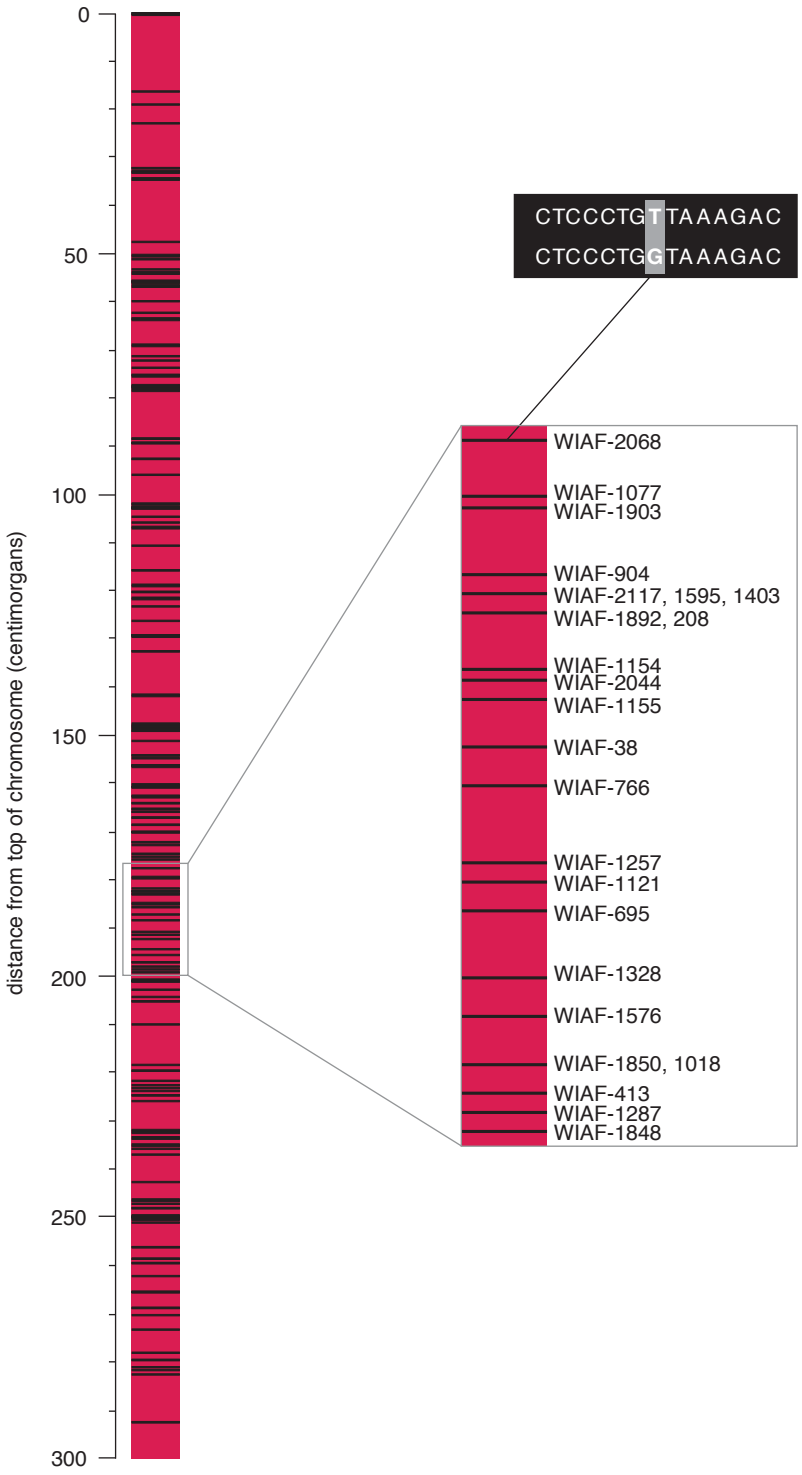

Figure 5. Single-nucleotide polymorphisms, or SNPs, are variations in genetic sequence found at an appreciable frequency (greater than 1 percent) in different individuals of the same species. This mapping shows the known distribution of SNPs on human chromosome 1, with the names of some indicated at the right. The variation in the DNA base sequence that constitutes SNP WIAF-2068 is shown at top, with G, C, A and T representing, respectively, the bases guanine, cytosine, adenine and thymine. Biologists anticipate that an understanding of the genetic diversity now being quantified in this way will have various biomedical uses—for example, in determining an individual's susceptibility to certain heritable diseases. Both the National Institutes of Health and a consortium of private companies have been pushing to keep SNP data in the public domain, for fear that too many proprietary claims on this information will impede its use in medicine. (Data from the Whitehead Institute/MIT Center for Genome Research.)

Pharmaceutical companies have joined together with the nonprofit Wellcome Trust (a U.K.-based nongovernmental partner in the Human Genome Project, which is not bound by the Bayh-Dole Act) in a consortium to sponsor an SNP-identification effort with explicit instructions to put the information in the public domain. The SNP Consortium has candidly embraced a goal of defeating patent claims to SNPs. The willingness of private companies in a patent-sensitive industry to spend money to *enhance* the public domain is indeed curious. We think it is powerful evidence of a perception in industry that claims to intellectual property rights for fundamental discoveries can create significant barriers to subsequent research and product development.

Possible Fixes

One solution might involve changing the patent laws to restrict patents on fundamental research. Congress or the courts might, for example, reinvigorate the "products of nature" limitation on patent eligibility so as to exclude discoveries of DNA sequences, proteins and biochemical mechanisms from patent protection. Lawmakers and judges could also fortify the utility standard to limit the patenting of research tools. Another much-discussed idea is to provide an exemption from infringement liability for research, particularly noncommercial research. Although such legal adjustments are worth considering, it is difficult to calibrate these changes accurately, and the consequences of overdoing it could be grave.

Patents clearly matter to the biopharmaceutical industry, and undue restrictions on them may indeed deter private investment. Although it is possible that these companies—particularly those that make end products—would benefit in the long term from limits on certain patents, many of these businesses continue to insist that they need patents on their research to raise capital. Given that private investment in biomedical research and development today exceeds public funding, the strong belief of investors that patents are essential urges caution in changing the underlying legal rules.

When research is publicly sponsored, however, the argument for strong patent rights loses much of its force. The Bayh-Dole Act does not presume that patents are necessary to motivate grantees to perform research but rather that patents will promote subsequent utilization and development of inventions. The reasoning that lurks behind this presumption is that patents and exclusive licenses are essential to attract the necessary private investment. Whatever the merits of this presumption for patents on final products such as new drugs, it makes little sense for patents on broadly enabling information and techniques that are ready for dissemination to scientists in both

public and private institutions, advances that can be put to use in the laboratory right away, without any further investment.

A classic example is the Cohen-Boyer method for combining DNA from different organisms. Many observers attribute the rapid progress of the biotechnology industry to the fact that this technology was made widely available rather than licensed exclusively to a single company. Although this pre–Bayh-Dole technology was, in fact, patented, it was offered nonexclusively and cheaply to encourage companies to purchase licenses rather than to challenge the patents. These nonexclusive licenses generated some $300 million for the universities that owned the patents, but it is difficult to see how they did anything to enhance product profitability or otherwise motivate subsequent research and development. If anything, the patent royalties imposed a modest tax on product development.

A greater concern is that the Bayh-Dole Act does little to ensure that a university will license such patents nonexclusively. To the contrary, Congress was careful in the terms of the Bayh-Dole Act and subsequent legislation to give universities discretion to grant exclusive licenses, which may be more financially attractive than nonexclusive licensing. Exclusive licenses typically command higher royalties, and companies holding exclusive licenses are more willing to reimburse for patent costs and to provide additional grant funding to the inventor. Indeed, the information available suggests that the majority of university licenses to startups and small businesses are exclusive.

But it is not clear that such exclusive licenses are necessary to achieve the aims of the Bayh-Dole Act. A recent case in which patenting and subsequent exclusive licensing were not necessary for product development involves federally funded research that identified the cell-signalling pathway for NF-κB (nuclear factor kappa B), which regulates genes that function during inflammation, cell proliferation and programmed cell death. This research (which scientists at Harvard, the Massachusetts Institute of Technology and the Whitehead Institute for Biomedical Research carried out in the 1980s) led to a broad patent claiming all drugs that work by inhibiting NF-κb cell signaling. Because the NF-κB pathway has been implicated in diseases ranging from cancer and osteoporosis to atherosclerosis and rheumatoid arthritis, the patent—which was issued just last year—may cover drug treatments for all of these diseases. Indeed, these academic institutions, together with their exclusive licensee, Ariad Pharmaceuticals, are now suing Eli Lilly & Co., claiming that Lilly's osteoporosis drug Evista and its sepsis drug Xigris work in a manner that infringes the NF-κB patent. Ariad has also

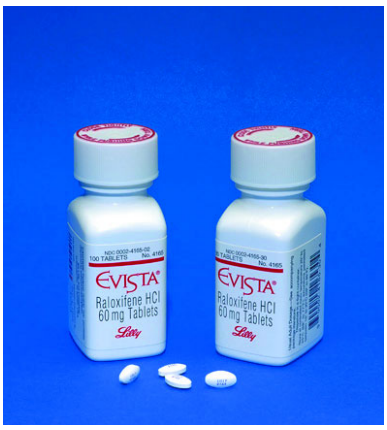

Figure 6. Evista (an osteoporosis-prevention drug, *left)* and Xigris (administered to patients endangered by sepsis, *right)* were developed by Eli Lilly & Co. using basic knowledge of the NF-κB biochemical pathway, which was worked out by scientists at Harvard, the Massachusetts Institute of Technology and the Whitehead Institute for Biomedical Research. Those institutions patented this basic research result and licensed it exclusively to Ariad Pharmaceuticals, which is now suing Lilly for infringement of its patent and also demanding royalties from some 50 other companies with drugs based on the NF-κB pathway. This episode demonstrates that companies are often eager to develop the results of academic biomedical research without first obtaining exclusive rights to it. (Photographs courtesy of Eli Lilly & Co.)

sent letters to some 50 other companies with products that work via the NF-κB pathway, demanding royalties on present or future product sales. Obviously, the companies that are now being asked to pay royalties did not need an exclusive license from Harvard, MIT and Whitehead to motivate them to pursue product development; the prospect of obtaining patents on their own end products was sufficient. In this case, as in many others, pioneering patents issued to academic institutions only thwart innovation.

For many discoveries emerging from government-sponsored research, the benefits of patenting are low relative to its costs. But some discoveries, including some important research tools and enabling technologies generated in the course of publicly sponsored research, undoubtedly require substantial commercial investment to become reliably mass-produced for widespread distribution. For example, technologies and machines for DNA sequencing and analysis, initially developed in academic laboratories, required substantial follow-up investment by private companies to turn them into reliable and commercially available equipment. Patents and exclusive licenses may be crucial to motivate this sort of investment.

The policy challenge, then, is to devise a system that distinguishes cases in which proprietary claims make sense from cases in which they do not. The complexity of biomedical research makes this a formidable task, and the public interest in getting these determinations right demands assigning this responsibility to the most qualified body. Ideally, decisions about the dividing line between the public domain and private property should be made by

William Taufic/Corbis

Figure 7. Development of DNA sequencing machines into reliable commercial products required considerable private investment. Few companies would have pursued such development without patent protection.

institutions that are in a position to appreciate the tensions between widespread access and preservation of commercial incentives without being unduly swayed by motivations that diverge from the overall public interest.

Preserving the Commons

So where should these decisions be made? On first examination, one might think that universities, which reap the rewards of the proprietary restrictions they impose on others but also pay the costs of restrictions that others impose on them, might be interested in maintaining at least some research in the public domain. The problem is that the costs to a university are largely borne by its scientists who cannot get prompt access to the proprietary technologies they seek, whereas the gains from licensing revenues are much more salient to its technology-transfer officers, who are charged with generating revenue. So coming to a consensus might be difficult.

Even when universities recognize that the larger academic community might be better off if they shared their research tools more freely, they face a serious problem: ensuring collective action. So long as other institutions are staking out claims, no university is likely to abstain from asserting its own rights. Appeal to the traditions of open science may not be sufficient, especially given that the scientists who hold those values don't usually make decisions regarding assertions of proprietary rights.

Left to their own devices, universities probably cannot mount the sustained community effort needed to preserve the research commons. But, interestingly, on a number of occasions NIH has been able to use sternly worded appeals to the norms of open science to convince academic institutions to keep basic research in the public domain. For example, in 1996 leaders of the National Human Genome Research Institute (NHGRI), together with the Wellcome Trust and academic researchers at the major human genome mapping centers, resolved that "all human genomic DNA sequence information, generated by centers funded for large-scale human sequencing, should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society." The NHGRI followed up with a policy statement making "rapid release of data into public databases" a condition for grants for large-scale human genome sequencing. The NIH could not, however, go so far as to forbid its grantees from filing patent applications without relying on the cumbersome "exceptional circumstances" clause of the Bayh-Dole Act. Rather than take this step, NIH declared that, as a matter of doctrine and policy, raw human genomic DNA sequence information should not be considered patentable. The statement also warned that NHGRI would monitor whether grantees were patenting "large blocks of primary human genomic DNA sequence" and threatened to invoke the "exceptional circumstances" limitation in future grants. In the specific context of large-scale genome mapping, universities were willing to embrace this policy.

Administrators at NIH undertook a similar strategy for SNPs. Before the SNP Consortium stepped forward to place this information in the public domain, NIH had decided to allocate public funds for SNP identification. Once again, NIH refrained from invoking the "exceptional circumstances" provision of the Bayh-Dole Act. Instead, in its request for applications for SNP-related grants, the agency stressed the importance of making information about SNPs readily available to the research community and asked grant applicants to specify their plans for sharing data, materials and software. The NIH also warned that it reserved the right to monitor their patenting activity.

The efforts of NIH to constrain its grantees in pursuing intellectual property rights have not been limited to genome projects. A more general statement of "Principles and Guidelines for Sharing of Biomedical Research Resources," adopted by NIH in December 1999, also attempts to guide NIH grantees regarding proprietary rights. These principles state that "the use of patents and exclusive licenses is not the only, nor in some cases the most appropriate, means of implementing the [Bayh-Dole] Act. Where

the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote utilization, commercialization, and public availability."

What NIH has sought to achieve through these various statements is broadly consistent with the intent of the Bayh-Dole legislation "to promote the utilization of inventions arising from federally supported research or development." Arguably, however, at least with respect to patentable inventions, NIH has acted outside the scope of its authority, leaving itself vulnerable to legal challenge.

Sound Footing

The time is ripe to fine-tune the Bayh-Dole Act to give funding agencies more latitude in guiding the patenting and licensing activities of their grantees. We propose two modest reforms that would give these agencies, which have the proper combination of knowledge and incentives, somewhat greater discretion to determine when publicly funded discoveries should be put in the public domain.

First, the circumstances in which an agency may prevent its contractor from retaining title to an invention should be liberalized. The current language of the law creates a clear presumption that an agency should exercise this power very infrequently. That should be changed. Once the "exceptional circumstances" language is deleted, the law could be more freely applied to achieve the goal of promoting widespread dissemination and use of research results. The process for review of "exceptional circumstance" determinations should be streamlined as well, with provisions for research to proceed while examination of the decision runs its course.

Second, Congress should modify the requirement that a funding agency's authority to compel licensing of university patents be held in abeyance until all court appeals are exhausted. By the same token, however, an agency should not be given authority to act without some provision for judicial review. Unlike a determination to restrict patenting, a subsequent exercise of the right to compel licensing disturbs settled expectations. If business planning is too readily upset, industry could become wary of investing in university-based technology.

It might be argued that restoring greater authority to agencies would return us to the unhappy position that motivated Congress to pass the Bayh-Dole Act in the first place. This danger appears quite small. In the intervening 23 years, NIH has embraced patenting and technology transfer in furtherance of its mission of improving public health. Moreover, our proposal to give agencies greater authority would not overturn the general presumption in favor of allowing government contractors to patent inventions. It would simply permit agencies to decide that patenting is not warranted in particular cases, while streamlining procedures for making and reviewing these decisions. Giving greater discretion to agencies would also correct a dangerous oversimplification of how best to achieve the important policies underlying the Bayh-Dole Act, by recognizing that patenting and exclusive licensing are not always the best way to go.

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Links to Internet resources for further exploration of "Bayh-Dole Reform and the Progress of Biomedicine" are available on the *American Scientist* Web site:

http://www.americanscientist.org/articles/03articles/rai.html