

University-Based Science and Biotechnology Products

Defining the Boundaries of Intellectual Property

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THE CREATION OF A SUCCESSFUL new medication or other biotechnology product usually represents the culmination of a long process of development, with origins in a number of pivotal basic science discoveries. With the rapidly escalating number and complexity of research techniques, the development of novel drugs, biologics, devices, diagnostic tests, and other medical technologies requires an unprecedented level of cooperation and investment of resources from public and private institutions. The possibility for lucrative profits has also expanded sharply, with the top blockbuster drugs and biologics reaching millions of patients and reaping multibillion-dollar returns.

Several recent court cases highlight how the medical product development process can be significantly affected by questions regarding ownership of basic science and biotechnology research discoveries. In one case,¹ the owner of patented equipment sued university scientists using it for experimental work; in another case,² a university's rights to the products of research by its faculty were dismissed, allowing a pharmaceutical company that marketed a drug based on those findings to keep all the financial returns. Excessive proliferation of intellectual property hurdles can hinder cooperation or make collaborative efforts

The pharmaceutical and biotechnology industries have long relied on patenting as the primary means of allocating ownership and control over new discoveries. Yet, patent protection is a double-edged sword that has major implications for the future of innovation in biomedical science in the United States. Excessive "upstream" patenting of genes and molecular targets could hinder further research by creating a need for expensive and inefficient cross-licensing. However, limiting such basic science patenting could allow private entities to use the results of years of costly publicly funded research to produce and market lucrative products without compensating university- or public sector-based innovators. Academic and other nonprofit research centers would, therefore, be deprived of revenue for pursuing novel therapeutics or other seminal research work that may not be patentable. Recent court cases illustrate the inherent conflicts in allocating ownership and control of basic biomedical discoveries. Several options exist to avoid the complex problems of overlapping basic science patents while still rewarding pivotal discoveries and encouraging further innovation. These include establishing basic science patent pools and mandating arbitration arrangements that would assign credit and royalties for biotechnology innovations that depend on prior research that was performed, financed, or both in the public sector.

JAMA. 2005;293:850-854

www.jama.com

insurmountably expensive. However, without legal recognition of the key contributions and rights of early stage researchers, the public credit and financial rewards based on their discoveries will inure almost exclusively to those who control the final step in production.

This tension has its roots in the basic structure of US intellectual property systems and technology transfer policies. Since 1790, the US government³ has awarded patents to encourage innovation by granting inventors the right to

prevent others from making, using, or selling their inventions for a limited period of time. In modern times, complicated research techniques and collaborations from multiple sources are the norm, a situation for which the

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patent system has difficulty accounting. Basic investigations conducted at universities and academic medical centers, usually publicly funded, often produce key insights about the mechanisms underlying physiological function and disease states. Private corporations can then commercialize these insights by designing and marketing new therapeutics or other medical technologies based on them. In this chain of development, allowing patenting of each incremental innovation could risk generating a dense thicket of overlapping intellectual rights and thus hinder research efforts. However, restricting patenting rights to the end product alone ignores earlier scientific and financial contributions. Where intellectual property law draws the line has billion-dollar ramifications for universities and academic medical centers attempting to support their research budgets, for patients who depend on the creation of innovative medical products, and for society, which ultimately benefits from and pays for these discoveries.

Biomedical Patenting and Technology Transfer

Through the 1970s, the federal government held the intellectual property rights to any inventions that were developed with federal funds, including those by biomedical scientists. During this period, it usually allowed inventions to be used freely, without a requirement for licensing any rights. But some questioned whether this approach sufficiently encouraged further development of that intellectual property. The National Aeronautics and Space Administration, for example, reported a commercialization rate of less than 1% for inventions under its free use policy, but found an 18% to 20% rate for inventions in which its contractors controlled intellectual property rights.⁴

In an attempt to speed technology transfer from publicly funded institutions to the marketplace, Congress passed the Bayh-Dole Act in 1980, which allowed nongovernmental organizations to control patents on inven-

tions developed with federal funds.⁵ One of the architects of the law argued that transferring intellectual property ownership would be necessary for the efficient translation of basic research because “what is available to everyone is of interest to no one.”⁴

The Bayh-Dole Act coincided with a new era of medical research that emphasized the molecular and genetic basis of disease, starting with advances in isolating and cloning genes. The United States Patent and Trademark Office (USPTO), the government agency charged with determining the patentability of inventions, was soon inundated with applications to patent newly identified proteins, methods to regulate cellular processes, and human genome sequences. Initially, the USPTO held a relatively permissive view of what constituted a patentable discovery in the biomedical research arena, and several researchers pushed the limits of what could be patented. Applications were granted for small genetic fragments such as expressed sequence tags, probes that are used to identify DNA segments that do not have utility by themselves, and for single nucleotide polymorphisms, single base-pair genetic differences that can be identified even in the absence of any knowledge of their role in disease. By 1999, more than 3000 patents for human genome sequences linked to genetically based diseases had been granted.⁶

Under the Bayh-Dole Act, universities and other centers funded by government grants engaged actively in the patenting and licensing process. Before 1980, academic institutions received fewer than 250 patents per year; by 2002, they were awarded more than 3000 patents per year with licensing revenues surpassing \$1.2 billion.⁷ While most university technology transfer operations struggle with legal fees and operating costs,⁸ some have moved management of their researchers' intellectual property rights into the private sector quite successfully. Gene-splicing techniques patented by the University of California and Stanford University became an industry standard and have

raised more than \$150 million in royalties since the late 1970s.⁹ Columbia University licensed its patent on a novel way to treat glaucoma to Pharmacia, which eventually developed the blockbuster drug latanoprost, earning the university \$20 million in gross royalties in 2000 alone.¹⁰

Limiting Upstream Patents in Biomedical Research

As biomedical patenting increased and university-industry ties became closer, some questioned the social good of patenting basic science discoveries.¹¹ Concern increased that patenting discoveries such as specific genes, receptors, or transcription factors might create a mass of intersecting monopoly rights and therefore hinder future research and public benefit. Heller and Eisenberg warned of an “anticommons” where “multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use.”¹² For translational researchers, acquiring the manifold patent rights needed to do their work could become at best time-consuming and expensive, and at worst impossible if a patent holder refused to grant access. For example, in the case of hemochromatosis, one study found that laboratories stopped developing or offering genetic testing for the disease after the issuance of patents that covered the test.¹³ In another example, owners of a patented genetic test for breast cancer have sought to block others from using the test.¹⁴

The *Madey v Duke University* case¹ threatens to exacerbate this patent thicket. The litigation arose after physics professor John M. J. Madey left Duke University, but researchers there continued to operate laser equipment that he had patented. Traditionally, investigators conducting experiments in the pursuit of scholarly or other non-commercial purposes can use an item they own even though it is patented. Madey sued Duke University for violation of his intellectual property rights, but the university argued that its non-profit academic status allowed it to use

patented items for experimental or educational purposes. The Court of Appeals for the Federal Circuit—the highest patent court under the Supreme Court—held that the experimentation infringed on Madey's patents and could not be performed without his permission. The court found that the fact that research is conducted in a university setting does not make it devoid of commercial implications. It argued that Duke University, “like other major research institutions of higher learning, is not shy about pursuing an aggressive patent licensing program from which it derives a not insubstantial revenue stream.”¹¹ The worrisome implication is that any research conducted in these academic settings, no matter how fundamental or removed from the marketplace, may violate the rights of those who hold patents on the research tools used.

In the past several years, scientists, policymakers, and judges have responded to the fear of a developing anticommons. Some sought to put specific genetic technologies in the public domain to prevent them from being patented.¹⁵ The USPTO finalized new guidelines in 2001 requiring demonstration of a credible, specific, and substantial usefulness for all new inventions,¹⁶ to make it more difficult to patent biomedical discoveries such as expressed sequence tags and DNA molecules encoding proteins with unknown biological activity.

In 1997 the courts also restricted the broad reach of certain biochemical patents, ruling on a suit brought by the University of California against pharmaceutical manufacturer Eli Lilly and Company, for infringement on its patents on recombinant plasmids used to produce insulin.¹⁷ Based on its sequencing of rat cDNA, the university claimed rights to the cDNA encoding all mammalian insulin-producing plasmids. However, the court held that since the university's patent covered only rat cDNA sequences in its written description, it did not encompass Lilly's human cDNA plasmid.¹⁷ The university's patent was thus limited to the rat

insulin, for which the commercial market is far more limited.

Problems With Restricting Upstream Patenting

Limiting intellectual property protection can also have damaging consequences. When academic centers perform publicly financed basic research and the discoveries are not protected by a patent, private corporations can develop enormously profitable clinical products based directly on that work without having to provide any compensation in return.

The *University of Rochester v GD Searle* case² exemplifies this situation. With support from the National Institutes of Health, Rochester researchers studied the mechanism of action of nonsteroidal anti-inflammatory drugs on the cyclooxygenase 2 (COX-2) and cyclooxygenase 1 isoenzymes, and helped clarify how each mediates different cellular processes.¹⁸ Their findings helped define how selective inhibition of COX-2 (primarily responsible for inflammation), over cyclooxygenase 1 (which mediates protection of gastric mucosa), could have benefits over less-selective conventional nonsteroidal anti-inflammatory drugs by reducing gastrointestinal damage.^{19,20}

In the 1980s and early 1990s, the Rochester researchers also developed an assay for determining whether a new drug would selectively inhibit the COX-2 receptor. The USPTO granted the university a patent covering both a “method for selectively inhibiting” the COX-2 receptor and way to measure the capacity of new compounds to do so.²¹ Pharmacia was among a number of pharmaceutical companies that sought to develop a drug based on this discovery and used the screening methods identified in the Rochester patent to screen more than 600 compounds over a period of 8 months to find a workable, selective COX-2 inhibitor.² When negotiations over licensing arrangements did not result in an agreement, Pharmacia ignored the university's patent. Ultimately, Pharmacia (later Pfizer, which purchased Pharmacia)

marketed celecoxib, for which annual worldwide sales by 2003 approached \$3 billion.²²

The university sued for violation of its rights, but the Western District Court of New York ruled that its patent was not enforceable. Since the Rochester team did not take the “last, critical step” of synthesizing a specific compound, the court found, “the inventors could no more be said to have possessed the complete invention claimed by the [Rochester] patent than the alchemists possessed a method of turning base metals into gold.”² The Court of Appeals for the Federal Circuit upheld the decision.²³ Pharmacia and other companies owed the university nothing.

In the marketplace for therapeutics and other clinical products that draw heavily on public-sector research, manufacturers that control the intellectual property of the final product are free to set high market prices and restrict efforts to license the product's use. Both Congress and the National Institutes of Health have tried to require companies that develop drugs based on publicly funded research to make their products available at a “reasonable price,” but neither has been able to implement this regulation, due to industry's opposition to potential restrictions on its profits.²⁴ To the extent that key aspects of medical technologies rely on studies that were publicly funded, some critics have begun to ask whether the citizens of the United States are in effect paying twice for such research.²⁵

The outcome of the debate is likely to have a major effect on the development of medical products and basic science research at universities and medical centers. While federal funding of research in academic centers has increased in recent years,²⁶ further growth is expected to slow sharply and public funding in general has accounted for a diminishing percentage of total biomedical research expenses.²⁵ Limiting basic science patenting would shift corporations' investment in academic research toward “downstream” ventures that can be quickly developed into

profitable products, including the development of known commercial quantities, such as “me-too” drugs that copy successful products already on the market. There would be less incentive to fund more basic research, because its results would automatically enter the public domain.

In addition, biomedical researchers might be less willing to publish early results, preferring to keep them closely guarded until they can be carried forward to become a patentable product. A survey of academic life scientists in 1997 found that commercialization of research was associated with delays in publication.²⁷ Academic centers may also try to enter the drug development market by themselves. Stanford University and the University of California both at San Francisco and at San Diego have recently formed a consortium to explore commercializing their discoveries themselves.²⁸ But universities often do not have the same expertise in these areas as established biotechnology or pharmaceutical companies, and they may not have the resources to devote to the efforts, which could hinder the pace and efficiency of further development.

Limiting patent protection to the final product can deprive basic science research of the financial support it requires. On the other hand, complex cross-licensing requirements for research tools and discoveries could slow the development of new products, and the resulting costs would be passed on to the public in the form of even higher prices. Intellectual property law stands at a crossroads between these competing considerations. A few options for reform can be considered.

Transforming Patent Policy

One possible solution would be to encourage the development of basic research patent pools. These are agreements to combine several patents under one umbrella so that all may use and profit from the technology for a single licensing fee.²⁹ Patent holders usually create a separate business entity to coordinate the pool and develop agree-

ments on sharing of the proceeds. Patent holders benefit because in the case of complex research techniques, individually patented tools or discoveries might be of no value on their own, and researchers benefit because they would not have to negotiate with many different entities for complementary intellectual property rights.³⁰

Several other industries, such as electronics and telecommunications, work in an environment in which different firms hold patents for small components or processes within larger networks. Levin has reported that firms in these so-called “cumulative industries” have developed systems of “cross-licensing their entire patent portfolios and determining the net flow of royalties by ‘scoring’ the most important patents in each portfolio.”³¹ Perhaps as a result, while patenting has increased in the last 20 years in parallel with biomedical science, managers in these other research-intensive industries report that they consider patents less important to protecting returns on innovation.³² At the same time, the costs of resulting products in electronics and telecommunications have decreased, in marked contrast to the pharmaceutical industry.

Medical research may have once been defined by discrete discoveries in individual laboratories, but it currently more closely resembles a cumulative industry. Like building a computer, identifying targets and engineering compounds increasingly requires the interplay of many layers of transistors (genes) and circuits (enzyme pathways). By importing business models such as patent pools, biomedical companies along with government and academic research centers could develop more efficient ways of exchanging intellectual property and setting reimbursement without hindering progress or driving costs to unaffordable levels. The USPTO has suggested applying patent pools to biotechnology as a means of integrating the large numbers of patents in the field.³³

Unfortunately, in this aggressive marketplace, it could be difficult to prevent some participants from making un-

reasonable licensing demands. But numerous federal and state laws require fair pricing in arenas from copyrighted materials to corporate self-dealing, and courts have constructed “fair” royalty rates in cases of stolen trade secrets.³⁴ The same principles could be used to guide the marketplace of patent licensing in basic biomedical research.

A different strategy would be to design an administrative law arbitration mechanism to which aggrieved parties could turn if they cannot arrive at an agreement on their own. This scenario has long been used in worker’s compensation cases³⁵ and has been suggested for settling medical malpractice disputes.³⁶ The Federal Trade Commission recently proposed one way that such a panel could function as an alternative to lengthy, costly litigation to provide “meaningful post-grant review” of disagreements over the legitimacy of a patent.³⁷ Alternatively, we propose that a body of experts could retrospectively examine the development of a product and assign equitable credit. This process might help officially recognize a seminal discovery that is not yet patentable. Such a system already exists in the film industry for assigning positions such as “written by” and “story by” for scripts that result from years of collaborations and revisions by dozens of people.^{38,39} Arbitrators could construct reasonable reimbursement rates, based on market prices, for researchers who develop the “plotlines” for future products but do not write the specific lines of dialogue—for example, celecoxib could have been conceived as written by Pharmacia, based on a story by the University of Rochester.

Nevertheless, such an arbitration process would require a difficult and inherently subjective analysis to assign values to different contributions. We suggest a simpler remedy might be to require companies that make use of publicly funded research to allocate to the National Institutes of Health a percentage of its revenues from the product. This approach would acknowledge that such research is a public good, like trans-

portation infrastructure or education, and require those companies that profit from it to help finance the publicly funded science that made it possible. This approach could significantly boost the funds available to academic medical centers and universities. However, to the extent that any of these arrangements are constructed to resemble previous attempts to impose a "reasonable pricing" requirement on products created with federal funding, they could likewise succumb to political pressure from special interest groups like the pharmaceutical industry.

Conclusion

For the past 25 years, academic medical centers, encouraged by federal legislation, enormous markets, and constrained public-sector budgets, have attempted to claim a share of the profits that result when their research is

transformed into lucrative medical products. Discouraging the patenting of basic science discoveries and limiting the breadth of biomedical patents may provide a windfall for those who manufacture and sell the end results of this work, but it may do so at the expense of academic centers and others who conduct the basic biomedical research on which these products are based. With the clinical and economic consequences of this work increasing each year, it is becoming ever more important to define the intellectual lineage of a new product, particularly if it proves to be an economic "blockbuster." This can help ensure that appropriate parties, from a policy and equity standpoint, are recognized for their work without harming the efficiency of biomedical research or threatening the capacity to discover and disseminate future generations of medical products.

A more nuanced attribution of "ownership" in basic science and biotechnology research will be difficult, but must be attempted. At minimum, a mechanism must be sought for ensuring fair compensation for such basic research discoveries to the biomedical research enterprise as a whole. The public sector community currently faces a sharp curtailment in the rate of growth of support from the National Institutes of Health and other federal sources. A major goal of science policy in the coming years will be to create a more versatile body of intellectual property law for biomedical research that also rewards the seminal work, often conducted in non-profit institutions and funded by taxpayer support, on which newly patented therapeutics, diagnostic tests, and medical devices depend so heavily.

Financial Disclosures: None reported.

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