The Public and the Private in Biopharmaceutical Research

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Advances in fundamental biomedical research play an important and growing role in the development of new therapeutic and diagnostic products. Although the development of pharmaceutical end products has long been a proprietary enterprise,[1] biomedical research comes from a very different tradition of open science, in which longstanding norms call for providing free access to new knowledge in the public domain. This tradition has eroded considerably over the past quarter century as patent claims have reached further upstream from end products to cover fundamental discoveries that provide the knowledge base for future product development.

One important reason for this change has been a narrowing of the conceptual gap between fundamental research and practical applications in biomedicine through advances in molecular biology. Once largely a matter of serendipity or trial-and-error, drug discovery is now critically dependent on fundamental knowledge of genes, proteins, and associated biochemical pathways. The foreseeable practical payoffs of this fundamental research make it easier to obtain patents for discoveries that, in an earlier era, would have seemed too far removed from useful applications to be ripe for patent protection. As these early-stage advances in human understanding have become patentable, new firms have emerged, raising capital to develop and market proprietary research platforms that lie somewhere between traditional academic research and end-product drug development.

The upstream shift in patenting activity has met little resistance from the courts. In 1980 the Supreme Court held that genetically engineered microorganisms were eligible for patent protection, construing the language of the patent statute as permitting patents for "anything under the sun that is made by man."[2] Shortly thereafter, Congress created a specialized court to hear appeals in patent matters, the Court of Appeals for the Federal

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[1] Various empirical studies have underscored the critical role played by patents on end-stage pharmaceutical products. *See, e.g.*, Wesley Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)*, NATIONAL BUREAU OF ECONOMIC RESEARCH, Working Paper No. 7552, 2000 (discussing the importance of patents relative to other mechanisms of appropriation across various industries and concluding that patents are particularly important in the pharmaceutical arena); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, in 3 BROOKINGS PAPERS ON ECONOMICS ACTIVITY 783 (Martin N. Baily et al, eds., 1987).

[2] Diamond v. Chakrabarty

Circuit.[3] The Federal Circuit has further extended the Supreme Court's expansive approach to patent eligibility, particularly for information technology, an area that is becoming increasingly important to biopharmaceutical product development. At the same time, the Federal Circuit has set a low threshold for meeting the utility standard for patent protection, a standard that might otherwise have prevented the patenting of upstream biomedical research that has not yet yielded practical applications.[4] The Federal Circuit's generally supportive attitude towards patents has broadly encouraged imaginative claiming strategies and unprecedented levels of patenting activity.

Another factor of arguably greater significance in promoting intellectual property claims in the early stages of biomedical research has been the explicit policy of the U.S. government to promote patenting of government-sponsored research results by universities, government agencies, and other recipients of federal research funds. This policy, which was codified beginning in 1980 with passage of the Bayh-Dole Act[5] and the Stevenson-Wydler Act,[6] has turned universities into major players in the biopharmaceutical patenting arena. The goal of these legislative initiatives was to promote widespread utilization of federally-sponsored invention. The legislation's sponsors believed that patent rights on such invention were necessary to motivate private firms to pick up where government funding leaves off and develop new discoveries into commercial products. But the legislation draws no distinction between downstream invention that directly leads to a commercial product and fundamental research discoveries that broadly enable further scientific investigation. Universities have taken the opportunity to file patent applications on basic research discoveries, such as new DNA sequences, protein structures, and disease pathways, that are primarily valuable as inputs into further research, accelerating the encroachment of the patent system into what was formerly the domain of open science. Even when they do not seek patents, universities often seek to preserve their expectations for profitable payoffs by imposing restrictions on the dissemination of research materials and reagents that might generate commercial value in subsequent research.

This frenzy of upstream patenting has coincided with unprecedented levels of both public and private investment in biopharmaceutical R&D and impressive scientific and technological accomplishments. In the long run, however, we fear that it may paradoxically

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[3] Cite to law creating Federal Circuit

[4] Compare Brenner v. Manson with In re Brana

[5] Act of Dec. 12, 1980, Pub. L. No. 96-517, Section 6(a), 94 Stat. 3015, 3019-28 (1980) (codified as amended at 35 U.S.C. Sections 200-212 (1994)).

[6] Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311-2320 (codified as amended at 15 U.S.C. §§ 3701-3714).

hinder, rather than accelerate, the biomedical research enterprise. We have three principal concerns.

First, and most obviously, patents on upstream discoveries hinder subsequent research by permitting owners to charge a premium for the use of discoveries that might otherwise be freely (or at least more cheaply) available in the public domain. This inevitably excludes some users who would be willing to pay marginal cost, but not the higher prices that patents permit, a concern that is troubleing for biomedical research given the historical and continuing importance to scientific progress of advances made by researchers in nonprofit institutions. The standard retort to this argument - that without patents to permit pricing in excess of marginal costs, no one would be motivated to incur R&D expenses that were vulnerable to appropriation by free riders - is an empirical claim that is more plausible for discoveries that depend on private investment than for discoveries made with public funds. The more qualified argument for patents on government-sponsored research results - that without patents, these discoveries would languish in government and university archives, neglected by private firms - makes little sense for discoveries that can be broadly disseminated right away without further private investment, thereby enabling research that will generate additional patents on discoveries made further downstream (i.e., closer to a marketable end product).

Second, upstream patents may hinder subsequent research when they give a single entity monopoly control of basic research discoveries that enable subsequent investigation across a broad scientific territory. Because the principle constraint on the scope of patent claims is prior knowledge in the field of the invention, this concern is particularly acute for patents on early-stage discoveries that open up new research fields (such as the discovery of pluripotent embryonic stem cells), as distinguished from narrower technological applications that grow out of and build incrementally upon existing knowledge in an established field. The response to this argument - that patent owners will be motivated to disseminate path-breaking discoveries to as many customers as possible - depends on what we fear are often unrealistic assumptions about the information, foresight and goals of people who are bargaining with current or potential scientific and commercial rivals. Free access to prior fundamental knowledge in the public domain frees researchers from the burden of disclosing confidential research plans to rivals who might use patents on prior discoveries to block or monitor the research of competitors.

Third, a proliferation of patents on interrelated discoveries in the hands of different owners may hinder R&D if subsequent researchers and downstream product developers have to incur significant transaction costs in getting permission from multiple upstream patent owners before they may proceed. This concern is quite pressing in contemporary biomedical research, which draws upon many prior discoveries made by different people

and institutions in universities and private firms.[7] Exchanges of DNA sequences, laboratory animals, reagents, and data that were once subject to a normative expectation of free access are today subject to license agreements, material transfer agreements and database access agreements that need to be reviewed and renegotiated before research may proceed, imposing high transaction costs long before the research has yielded a likely revenue stream that would justify these costs. A standard response to this concern - that market forces will motivate the emergence of patent pools and other institutions for bundling intellectual property rights, thereby reducing transaction costs and permitting the parties to realize gains from exchange[8] - is an empirical claim that has not yet been borne out by the experience of the biomedical research community. The public domain economizes on transaction costs by eliminating the need to find and bargain with patent owners, allowing research to proceed expeditiously and without the risk of bargaining breakdown.

One response to these problems might involve changing the patent laws. One 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, or fortify the utility standard so as to limit the patenting of research tools and platforms, or provide an exemption from infringement liability for researchers. Although such legal adjustments are worth considering and some of them might well be justified, it is difficult to calibrate these changes accurately. Patents clearly matter in the biopharmaceutical industry, and undue restrictions on patent protection may deter valuable private investment. Pharmaceutical firms insist that they need drug patents in order to profit from long, costly and risky investments in research and clinical trials. Biotechnology firms insist that they need patents on their research platforms in order to attract risk capital for further development.[9] Given that private investment in biomedical R&D today exceeds public funding, the strong belief of private sector investors that patents are essential to their profit expectations urges caution in changing the underlying legal rules that support these investments.

On the other hand, when research is publicly sponsored, patents are arguably less important. The Bayh-Dole Act presumes that patents are generally necessary to promote

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[7] Rebecca S. Eisenberg, *Bargaining Over the Transfer of Proprietary Research Tools: Is This Market Failing or Emerging?*, in R. Dreyfuss et al. eds., Expanding the Boundaries of Intellectual Property: Innovation Policy for the Knowledge Society (Oxford 2001).

[8] E.g., Robert P. Merges, *Contracting Into Liability Rules: Intellectual Property Rights and Collective Rights Organizations,* 84 Calif. L. Rev. 1293 (1996).

[9] *See, e.g.*, John Golden, *Biotechnology, Technology Policy, and Patentability*, 50 EMORY L.J. 101, 167-72 (2001) (discussing widespread acceptance of the idea that small, capital-poor biotechnology companies need a patent portfolio to compete in the capital markets).

utilization of inventions arising from federally supported research or development. The argument behind this presumption is that, without patents, product development is unprofitable, and patents on publicly-sponsored research are therefore necessary to attract private investment to develop research results into commercial products. Whatever the merits of this presumption for patents on downstream invention, it makes little sense for upstream research discoveries that might otherwise be broadly disseminated in the public domain for the use of researchers in both the public and private sectors. The farther removed research discoveries are from end product development, the more likely it is that subsequent research will generate additional patents (including patents on commercially viable end products) that will be more important to the profit expectations of private investors than patents on the prior knowledge base. Indeed, patents on the many discoveries that enable product development are more likely to add to its costs than to enhance its profitability. Given that the long course of biopharmaceutical product development typically generates a great many patented inventions on the road to market, the risk that motivated Congress to pass the Bayh-Dole Act - that potential new products would never be developed if the early discoveries from which they spring remain unpatented - seems quaintly out of touch with contemporary R&D and patenting practices.

Although we suspect that for many discoveries emerging from government-sponsored research, the benefits of patenting are low relative to the costs it imposes on further R&D, we recognize that there are important exceptions. Some discoveries - including some important research tools and enabling technologies generated in the course of publicly-sponsored research - undoubtedly require substantial commercial investment in order to translate a university prototype into something that may be reliably mass-produced for widespread distribution. For example, technologies and machines for DNA sequencing and analysis, initially developed in academic laboratories, have often required substantial additional investment by private firms to turn them into reliable, commercial available laboratory equipment. Patents and exclusive license rights may be crucial to motivate this sort of investment.

The policy challenge is to devise a system that does the best job of distinguishing the cases in which patenting makes sense from the cases in which it does not. The complexity of biomedical research makes this a formidable task, and the public interest in getting these determinations right demands assigning this task to an appropriate decision-maker. Ideally, decisions about what to patent and what to place in the public domain should be made by institutions that are in a position to appreciate the tensions between widespread access and preservation of commercial incentives without being unduly swayed by financial interests that are not aligned with the overall public interest.

Under the Bayh-Dole Act, determinations of what to patent are assigned in the first instance to the institution receiving federal research funds - typically a university in the case of NIH-sponsored biomedical research.[10] Universities, in turn, have turned this task over to technology transfer professionals whose job performance is typically measured by the revenue they bring in to the university. If the university declines to pursue patent rights, the sponsoring agency may claim them, and if neither institution wants to patent the invention, the investigator may do so. In other words, if anyone involved in the research - the grantee, the sponsor, or the investigator - thinks the invention is worth patenting, they may prevail over anyone who believes the invention should be left in the public domain. The research sponsor may vary these rules only in "exceptional circumstances," and only by complying with burdensome procedural safeguards.

In 1980, these restrictions on the ability of research sponsors to depart from the pro-patent presumption of the Bayh-Dole Act doubtless seemed sensible enough. At that time, university patenting was the exception rather than the rule, the biotechnology industry was in its infancy, and government research sponsors, particularly the NIH, had a reputation for being hostile to patents to a degree that impeded development of new products and collaborations between academic and commercial investigators. The prevailing belief was that U.S. industry was missing opportunities to build upon a national advantage in university-based research because universities had no incentive to patent their discoveries and had to overcome strong bureaucratic resistance on the part of government sponsors in order to retain patent rights. The story Congress heard was that universities cared only about scientific recognition and were indifferent to patents, that private industry needed exclusive rights under university-owned patents to make product development profitable, and that government funding agencies had to be restrained from indulging their anti-patent reflexes so that universities and private industry could join forces to develop new technologies for the benefit of the U.S. economy.

Two decades later, much has changed. NIH and universities have become active patent claimants and constant collaborators with private industry across the spectrum of

[10] In keeping with its original title -- the University and Small Business Patent Procedures Act -- the Bayh-Dole Act also gives small businesses the right to seek patents on the results of their federally funded research. Congress was quite taken by the "very impressive record in technological innovation" complied by small businesses, S. Rep. No. 96-480, at 1 (1979), but initially rejected proposed legislation (S.1215) that would have extended the same rights to large businesses. Large business interests were not defeated for long, however. In 1983, President Reagan extended the right to retain patent ownership to large businesses in a Memorandum, and Congress quietly endorsed this extension the next year in an inconspicuous housekeeping provision to a 1984 change in the law. Trademark Clarification Act of 1984, § 501(13), 35 U.S.C. § 210(c).

biomedical research.[11] Universities are no longer indifferent to patents, but eager to patent their discoveries in the hope of sharing in the bounty of future blockbuster products. Public research sponsors, such as NIH, have taken to heart their mandate to promote commercial product development as well as continuing scientific progress. Product-developing firms are as likely to lament patents on publicly-sponsored discoveries as rent-diverting siphons as they are to welcome them as rent-preserving protection from competition in potential product markets. Indeed, in the context of the Human Genome Project, the patent-sensitive pharmaceutical industry has repeatedly joined with the NIH in calling for the dedication of new knowledge to the public domain.

In this new environment, Congress' decision to divest funding agencies of any significant discretion in imposing restrictions on patenting makes little sense. Indeed, because of the breadth of their missions and because of their dual roles as both patent owners (who stand to benefit from obtaining and licensing patents) and research sponsors (who ultimately pay the costs that patents impose upon future research), public research sponsors are well-positioned to take into account the impact of upstream patents not only on future product development but also on future scientific research. In contrast, while particular universities should have some incentive to resist patenting – after all, their researchers will have to have to incur the fees and transaction costs associated with licensing research patented by other universities – the immediate gain to be realized from patenting may outweigh the more distant possibility of gain from a university-wide regime of collective self-restraint. Universities face a very significant collective action problem, and traditional norms of open exchange may no longer be sufficiently robust to address this problem. The obstacle to relying solely on universities is particularly large because the primary remaining adherents to open science norms, individual research scientists, do not necessarily make the ultimate decisions about university patenting. By the same token, decisions by funding agencies to forbid patenting in certain circumstances might play a valuable role in buttressing those in the academy who do support open exchange of upstream research.

I. The Bayh-Dole Act and the Increasingly Proprietary Character of University-Based Biomedical Research

Prior to passage of the Bayh-Dole Act of 1980, although some public research sponsors allowed universities to patent publicly-funded research discoveries, grantees

[11]For a recent summary, see National Institutes of Health Response to the Conference Report Request for a Plan to Ensure Taxpayers' Interests are Protected (July 2001), posted on the internet at http://www.nih.gov/news/070101wyden.htm.

rarely went to the trouble.[12] Universities began to show greater interest in patents in the late 1970s as research advances in molecular biology offered promise of near-term commercial applications,[13] but the total number of university patents remained small. In 1979, universities received 264 patents;[14] by 1997, that number had increased to 2,436.[15] This almost 10-fold increase in university patenting was significantly greater than the two-fold increase in overall patenting during the same time period,[16] and substantially exceeded growth in university research spending.[17]

Publicly-funded biomedical research discoveries account for a major share of these university patents, particularly in terms of licensing revenues.[18] (Despite the increasingly intimate involvement of industry with universities, industry actually funds only a small percentage of university-based research in the life sciences.[19]) Most university-owned patents do not cover commercial end products, but rather fundamental research discoveries and research tools. A prominent recent example of a patented basic research discovery made at a university with federal funding is primate embryonic stem cell lines. Although a government moratorium of research on human embryos prevented NIH from sponsoring research to derive specifically human embryonic stem cell lines, NIH paved the way for this research by sponsoring research to derive embryonic stem cells from rhesus monkeys and macaques at the University of Wisconsin. This NIH-sponsored research yielded a broad patent for the Wisconsin Alumni Research Foundation ("WARF"), the technology transfer arm of the University of Wisconsin, covering all primate stem cell lines (which include, of course, human embryonic stem cell lines), and provided disclosure

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[12] *See* Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA.L.REV. 1663, 1683 (1996). For example, the Department of Health, Education and Welfare (now Health and Human Services) allowed academic institutions with established technology licensing offices to patent the results of their research. *Id.*

[13] *See* D.C. Mowery et al., *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980,* 30 RESEARCH POLICY 99, 104 (2001).

[14] *Id.*

[15] Mowery at 104.

[16] In 1979, a total of 48,854 utility patents were granted. By 1997, that number had increased to 111,983. *See* U.S. PATENT STATISTICS, CALENDAR YEARS, 1963-2000.

[17] Mowery at 104.

[18] Mowery at 117 (noting that leading patents at the University of California, Stanford, and Columbia "are concentrated in the biomedical arena.")

[19] David Blumenthal at 369.

support for subsequently filed claims drawn specifically to human embryonic stem cell lines.[20]

Although NIH has a strong interest in ensuring widespread dissemination of such basic research tools to its grantees for use across the broad spectrum of biomedical research, the Bayh-Dole Act constrains its role in overseeing the deployment of intellectual property rights in the results of sponsored research. Funding agencies such as NIH are permitted to restrict patenting under the terms of funding agreements only if the contractor is not U.S.-based or in "exceptional circumstances" when the agency determines that withholding title to the invention from the contractor will better promote the goals of the Act.[21] The statute provides an elaborate administrative procedure for challenging such determinations,[22] including appeals to the United States Claims Court.[23] The agency must notify the Commerce Department, which has primary responsibility for administering the Bayh-Dole Act, each time it makes a determination of exceptional circumstances, and provide an analysis justifying the determination.[24] If the Secretary of Commerce determines that "any individual determination or pattern of determinations is contrary to the policies and objectives of [the Bayh-Dole Act]," the Secretary must advise the head of the agency and the Administrator of the Office of Federal Procurement Policy and recommend corrective actions.[25]

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[20] James A. Thomson, Primate Embryonic Stem Cells, Patent No. 5,843,780, issued December 1, 1998. At the time of its original patent application, University of Wisconsin researcher James Thomson had worked with stem cells in rhesus monkeys and macaques only. Nonetheless, the patent broadly claims all primate embryonic stem cells. Several years later, when Thomson specifically isolated human embryonic stem cells, the University of Wisconsin filed a subsidiary, or divisional, application specifically claiming the human stem cells. This divisional application was granted on March 13, 2001. James A. Thomson, Primate Embryonic Stem cells, Patent No. 6,200,806. Because of the moratorium on federal funding on research on human embryonic stem cells, Thomson's research on human stem cells was funded not by the federal government but by Geron, a biotechnology concern. Geron agreed to provide funding in exchange for exclusive rights to six types of differentiated cells that could be derived from human stem cells.

[21] 35 U.S.C. Section 202 (a) (i), (ii).

[22] The Commerce Department, to which Congress gave rulemaking authority under the Bayh-Dole Act, 35 U.S.C. Section 206 (giving the Secretary of Commerce authority to issue regulations applicable to all federal agencies and to establish standard funding agreement provisions), has promulgated regulations which specify that administrative appeals must "afford the contractor the opportunity to appear with counsel, submit documentary evidence, present witnesses, and confront such persons as the agency may rely upon." 37 C.F.R. Section 401.4(b)(3).

[23] 35 U.S.C. Section 203(2).

[24] 35 U.S.C. § 202(b)(1).

[25] Id.

In addition to these cumbersome provisions for overriding grantee patent rights in the terms of funding agreements, the Bayh-Dole Act also permits agencies to exercise statutory "march-in rights" to compel licensing of a university patent if the agency determines that the university (or its exclusive licensee) is not taking steps to achieve "practical application of the subject invention"[26] or if necessary to alleviate public health or safety needs or requirements for public use specified by Federal regulations.[27] In contrast to the approach taken for ex ante restriction of patent rights in the terms of a grant, exercise of march-in rights is not further constrained by an overarching directive that it be "exceptional." Nonetheless, the Bayh-Dole Act defers agency action from taking effect pending elaborate administrative proceedings and exhaustion of court appeals,[28] and the administrative obstacles are sufficiently cumbersome that the NIH has never exercised these rights.[29]

The expansion of the proprietary sphere in academic science is not limited to patenting of university-based discoveries. As universities have become more aggressive about claiming intellectual property rights, and as the conceptual gap between academic and industrial biomedical research has narrowed, commercial firms that might once have viewed academic researchers as benign, nonprofit benefactors of pre-market science have today come to view them instead as potential commercial rivals. An important consequence of this shift has been an increase in restrictions on the transfer of research tools, even those that are not patented. When universities supply research tools to private firms, they seek cash payments or reach-through royalties on sales of future products in return. When private firms supply academic researchers with research tools, they typically require the scientist and the university to sign a material transfer agreement ("MTA") that may include grant-back provisions calling for an option to license patent rights to subsequent discoveries made through use of the tools.[30] MTAs from both private firms and universities also typically prohibit researchers from sharing these tools with other institutions and call for pre-publication review of research results.[31] Even MTAs *between* academic institutions sometimes contain significant restrictions. Institutional representatives balk at approving these agreements, often leading to protracted negotiations and delays.

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[26] 35 U.S.C. Section 203(1)(a)(b).

[27] 35 U.S.C. §§ 203(1)(b),(c).

[28] 35 U.S.C. Section 203(2).

[29] See Barbara M. McGarey & Annette C. Levey, Patents, Products and Public Health: An Analysis of the CellPro March-In Petition, 14 Berkeley Tech. L.J. 1095 (Fall 1999).

[30] See Report of the NIH Working Group on Research Tools, at 4 (available at www.nih.gov/news/researchtools/index.htm.

[31] *Id*. at 7-8.

NIH, as the principal sponsor of academic biomedical research, has viewed these developments with concern, but has had limited authority to respond. The Bayh-Dole Act constrains its ability to guide the behavior of its grantees, and it has even less influence over how private firms manage the intellectual property that they have created without government funds.

II. *Patents in Biopharmaceutical Research: Finding the Right Balance*

Patents are plainly important to private investors in biopharmaceutical research. In some industries, patents serve primarily as "bargaining chips" to negotiate around patents held by other firms,[32] but in the biopharmaceutical industry, firms hope to use patents to enhance their profits. But the patents that primarily serve this function are patents that permit them to charge higher prices (and earn higher profits) on the products they sell, not patents that permit other institutions to charge firms higher prices for the research tools that they buy.[33]

On the other hand, when public funds support the development of basic research platforms and tools that can be used in many future investigations, patenting may not be the optimal strategy. The case for patenting is particularly weak for technology that may be widely disseminated through publication alone, without the need for exclusive rights as a lure to further commercial investment in order to achieve efficient production and distribution. A classic historical example of such a federally-funded research platform technology - paradoxically often cited in support of university patenting - was the Cohen-Boyer method for combining DNA from different organisms. Many analysts attribute the rapid progress of recombinant DNA technology to the fact that this technology was made widely available rather than licensed exclusively to a single firm. Although the research was in fact patented, the patents (which covered technology that had previously been disclosed at a scientific meeting, and were thus potentially vulnerable to a validity challenge) were licensed nonexclusively at a reasonable rate that encouraged firms to take licenses rather than challenging the patents. These licenses generated considerable revenue for the

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[32] *See* Bronwyn Hall & Rosemarine Ham Ziedonis, *The Patent Paradox Revisited: Determinants of Patenting in the U.S. Semiconductor Industry*, 1980-1994 (National Bureau of Econ. Research Working Paper NO. W7602, 1999) (discussing use of semiconductor patents as bargaining chips to forestall potential infringement litigation).

[33] Of course, some firms sell research tools, and seek patents on these inventions to make this business viable. Even when universities develop research tools with public funds, they may need patent rights to entice private firms to produce and distribute these tools broadly to the scientific community. See discussion *supra* at .

universities that owned the patents, but it is hard to see how the patents themselves did anything to enhance profitability or otherwise motivate subsequent research and product development. (Indeed, the patent royalties imposed a modest tax on product development.) When a publicly-funded technology is licensed widely and nonexclusively, the central (if not only) function of the patent is to generate revenue for the patent owner. Because generating revenue for universities was not the goal of the Bayh-Dole Act,[34] it is worth considering whether research that is effectively disseminated through nonexclusive licensing should be patented at all.

Of potentially greater concern, when a university patents a fundamental research platform pursuant to the Bayh-Dole Act, there is no guarantee that the university will license the platform 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, consistent with its goal of using patents to motivate licensees to invest in further technology development by protecting them from competition. Exclusive licensing is often more financially attractive to universities than nonexclusive licensing, not only because exclusive licenses command higher royalties, but also because firms are more willing to reimburse for patent costs and to provide additional grant funding to the inventor if they have an exclusive license. A recent example is the previously noted patent on primate embryonic stem cell lines held by WARF.[35] Under an agreement that provided a million dollars of research support for subsequent work by the inventor, WARF granted an exclusive license for commercial use of six important cell types that could be derived from these cell lines to a single private firm, Geron. (WARF now appears to regret having made this deal and is in litigation to reform its terms.)

Further obstacles to subsequent R&D may arise when several different firms have patent rights in inventions that must be combined to make use of a research platform, creating an anticommons, or patent "thicket" problem.[36] A developer wishing to use such a platform may have to engage in protracted and costly negotiation with multiple patent holders, each motivated to act strategically.[37]

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[34] Eisenberg, *supra* note __, at __.

[35] As noted earlier, *see supra* __, divisional of the parent application specifically claims human embryonic stem cells.

[36] *See* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998).

[37] *See* Arti K. Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW.U.L.REV. 77, 125-129 (1999) (discussing difficulties in bargaining between upstream and downstream researchers).

The case of single nucleotide polymorphisms, or SNPs (single base points within the genome at which the DNA sequence of individuals differs), provides a good example of this concern. Collections of SNPs occurring throughout the genome are a useful resource for scientists searching for genes involved in specific diseases.[38] SNPs also promise to be useful in developing diagnostic products to predict patient responses to drugs or other treatments.[39] 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 in this important resource.

Paradoxically, in the Bayh-Dole era the pharmaceutical industry has enjoyed more latitude than NIH to respond to this threat effectively by placing SNPs in the public domain. Pharmaceutical companies have joined together with the nonprofit Wellcome Trust, a U.K.-based, non-government partner in the public Human Genome Project that is not bound by the Bayh-Dole Act, in a consortium to sponsor a SNP-identification effort with explicit instructions put the information in the public domain. Unconstrained by the Bayh-Dole Act, the SNP Consortium has candidly avowed a goal of defeating patent claims to SNPs. The willingness of private firms in a patent-sensitive industry to spend money to enhance the public domain is powerful evidence that intellectual property rights in the research results threaten to create significant barriers to subsequent research and product development. [40]

III. *The Role of the NIH in Preserving the Public Domain*

NIH shares the concerns that prompted the formation of the SNP Consortium, but the Bayh-Dole Act limits how it can address the problem. Before the SNP Consortium stepped forward to save the day, NIH decided to allocate public funds for SNP identification. But rather than invoking the cumbersome (and time-consuming) mechanism

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[38] See, e.g., Leslie Roberts, *SNP Mappers Confront Reality and Find it Daunting*, 287 SCIENCE 1898 (2000).

[39] For a discussion of SNP-based "precision" therapies, *see* Allen D. Roses, *Pharmacogenetics and the Practice of Medicine*, 405 NATURE 857 (2000).

[40] Indeed, the SNP consortium is not the only recent example of the private sector stepping forward to defend the public domain in the field of genomics. In the mid-1990s, the pharmaceutical company Merck sponsored an effort to put information about DNA fragments known as expressed sequence tags, or ESTs, into the public domain. More recently, the private sector has been collaborating with the NIH in sequencing the mouse genome and making this sequence publicly available.

of making an appealable declaration of "exceptional circumstances" to justify a departure from the usual presumption of grantee discretion to pursue patents, NIH took a different approach. In its request for applications for SNP-related grants, NIH stressed the importance of making information about SNPs readily available to the research community, asked grant applicants to specify their plans for sharing data, materials and software, specified that the adequacy of the plan for sharing and data release would be considered by NIH staff as one of the criteria for an award, and warned that NIH reserved the right to monitor grantee patenting activity.[41] This approach to forestalling proprietary claims of grantees was arguably inconsistent with the spirit, if not the letter, of the Bayh-Dole Act.

On several other occasions, the NIH, acting in conjunction with academic researchers, has taken action to keep basic research information in the public domain without using the mechanisms of the Bayh-Dole Act. For example, 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 in February 1996 that "all human genomic DNA sequence information, generated by centers funded for large-scale human sequences, should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society."[42] NHGRI followed up with an April 1996 policy statement making "rapid release of data into public databases" a condition for grants for large-scale human genome sequencing.[43]

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 taking this step, NIH included a stern statement in its April 1996 policy 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 might invoke the "exceptional circumstances" limitation in future grants. In the extraordinary context of the Human Genome Project, scientists were willing

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[41] National Institutes of Health RFA HG-98-001, Methods for Discovering and Scoring Single Nucleotide Polymorphisms (Jan. 9, 1998) < http://www.nhgri.nih.gov:80/Grant_info/Funding/RFA/rfa-hg-98-001.html> (visited August 1, 2001).

[42] Eliot Marshall, *Genome Researchers Take the Pledge: Data Sharing*, 272 SCIENCE 477 (1996). This pledge, known as the "Bermuda resolution," echoed conclusions reached in earlier reports from the NIH Ad Hoc Program Advisory Committee on Complex Genomes and the National Research Council (a division of the National Academy of Sciences).

[43] *NHGRI Policy Regarding Intellectual Property of Human Genomic Sequence*, April 9, 1996, available at www.nhgri.nih.gov/Grant_info/Funding/Statements/RFA/intellectual_property.html.

to embrace this limited "no-patenting" norm,[44] and there was no reason to invoke the "exceptional circumstances" clause.The hortatory efforts of NIH to constrain the zeal of its grantees in pursuing intellectual property rights have not been limited to the Human Genome Project. 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 in the deployment of their 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."[45] One factor that counsels in favor of wide dissemination of a particular invention is its status as "a broad, enabling invention that will be useful to many scientists (or multiple companies in developing multiple products), rather than a project or product-specific resource."[46]

The goals that NIH has sought to promote through these various hortatory statements urging widespread dissemination of genomic DNA sequence, SNPs, and research resources are broadly consistent with the stated goal of the Bayh-Dole Act "to promote the utilization of inventions arising from federally supported research or development."[47] Arguably, however, the NIH has acted outside the scope of its statutory authority, leaving itself vulnerable to a potential legal challenge from a recalcitrant grantee.

Consider, for example, the NIH's suggestion that it would find the filing of university patents on large blocks of primary human genomic DNA sequence "problematic." The only legal authority that the NIH has for restricting patenting is the "exceptional circumstances" clause of the Bayh-Dole Act. Because NIH specifically chose not to rely upon the clumsy administrative procedure required by that clause, its suggestion has no legal import whatsoever. The same holds true for NIH's general policy statement

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[44] Even university technology transfer offices, whose institutional culture and self-interest promote a commitment to patenting that is probably stronger than that of the research science community itself, did not challenge the "no-patenting" policy. *See* Eliot Marshall, *Genome Researchers Take the Pledge: Data Sharing*, 272 SCIENCE 477, 478 (1996) (noting that key university patent officials endorsed policy). Some leading officers did, however, admit to being wary of the "bad precedent" that the April 1996 policy might set. *Id.* (quoting Lita Nelsen of MIT).

[45] Department of Health and Human Services, National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice, 64 FR 72090, __ (1999).

[46] Other factors include whether the invention is primarily useful as a tool for discovery rather than as an FDA-approved product or component of such product and whether the resource is readily useable, without the need for private sector involvement in further development.

[47] 35 U.S.C. § 200.

of "Principles and Guidelines for the Sharing of Biomedical Research Resources." Indeed, NIH has no authority under the Bayh-Dole Act to issue broadly applicable substantive regulations concerning the licensing of inventions under all of its grants (as distinguished from specific determinations in the context of particular grants). Congress specifically conferred the broader power to promulgate such regulations on the Commerce Department, not the funding agencies.[48] Thus quite apart from any conflict with the Bayh-Dole Act's broad deference to grantee institutions concerning patenting and licensing, the policy seems to have little legal weight.[49]

That NIH has enjoyed any success in these efforts to constrain the proprietary strategies of grantees so far may be due to the fact that its statements have reflected norms of free exchange that retain some force, at least among a subset of academic researchers.[50] Researchers, and even their associated institutions, might therefore voluntarily acquiesce in abiding by these norms of free exchange, or at least balk at mounting an open challenge.

But there is growing evidence that NIH may require authority beyond the bully pulpit in order to ensure continuing compliance with these norms in the future. Consider, for example, the recent controversy over the broad patent held by WARF on primate embryonic stem cells. Although embryonic stem cells are just the type of broadly applicable enabling technology that should be licensed nonexclusively in the interest of promoting future research and product development, WARF chose to license exclusively some of the most important commercial rights under the patent. To be sure, the WARF case is somewhat unusual in that the exclusive licensee, Geron, provided crucial funding at a point when the federal government refused, on purported ethical grounds, to fund the research necessary to move from chimpanzee and monkey cell lines to human cell lines. But even if the federal government had provided all of the funding, WARF might still have decided to license the invention exclusively, at least with respect to certain fields of use, rather than to follow the Cohen-Boyer model of nonexclusive licensing. Although NIH might in theory exercise its march-in rights to make the invention more broadly available, these rights would be held in abeyance until all court appeals are exhausted, meanwhile delaying use of the invention in research. Given this legal backdrop, it is unsurprising that

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[48] 35 U.S.C. § 208 ("The Secretary of Commerce is authorized to promulgate regulations specifying the terms and conditions upon which any federally owned invention ... may be licensed on a nonexclusive, partially exclusive, or exclusive basis.")

[49] *See* United States v. Mead, 121 S.Ct. 2164, 2170 (2001) (noting that administrative implementation of a particular statute qualifies for "strong" deference under the *Chevron* doctrine only "when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority.")

[50] *See generally* Rai, *Regulating Scientific Research*, at __.

recent negotiations between WARF and NIH over use of embryonic stem cell lines in research left WARF maintaining tight control over commercial applications of the technology.[51]

As patenting by universities gains momentum, the normative baseline in the academic community concerning free exchanges appears to have shifted. If 25 years ago universities thought long and hard before filing a patent application on such a fundamental discovery as gene-splicing, today universities unabashedly proclaim an entitlement to control (and profit from) commercial use of their government-sponsored inventions without apology for resulting restrictions on subsequent R&D. In this environment we expect to see increasing departures from norms that previously constrained proprietary behavior.

IV. *Enhancing the Legal Authority of NIH*

We believe that the time is ripe to alter the Bayh-Dole Act to give funding agencies more latitude in guiding patenting and licensing activities of their grantees. More generally, we would welcome recognition by Congress that patenting is not always or even usually the best way to maximize the social value of inventions and discoveries made with federal funds. We highlight two particular candidates for statutory reform.

First, we would liberalize the standards and simplify the required procedures for an agency to depart from the statutory presumption that the contractor may retain title to an invention in the terms of particular grants. The current "exceptional circumstances" language creates a clear presumption that the agency should exercise its power to restrain patenting very infrequently.[52] This parsimonious approach unduly constrains the authority of agencies such as NIH to use federal funding to enrich the public domain, which might often (not merely in exceptional circumstances) better serve the goal of achieving widespread dissemination and use. Once the "exceptional circumstances" language is deleted, the substantive standard set forth in the current statutory language (permitting departure from the usual rule "when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives of this chapter") may be applied free of the dated 1980 expectation that it will almost never be invoked. Even if an agency determination under the amended language still required an administrative process that was subject to judicial review, there

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[51] Cite to agreement

[52] Thus, even though courts would presumably have to show *Chevron* deference to an agency finding of "exceptional circumstances," such deference would be in tension with the idea that the agency is (by definition) not supposed to find exceptional circumstances in too many cases.

would no need for the agency to useits authority sparingly, and research could proceed while the administrative process runs its course.

With respect to the "march in" provision, we believe that the current substantive standard is less objectionable than the prescribed administrative procedure. In particular, we suggest altering the requirement that march-in authority be held in abeyance pending exhaustion of all court appeals by the government contractor. Indeed, the tolerance for protracted delays inherent in the current process is at odds with the time-sensitive nature of the interests reflected in the substantive standard, such as achieving practical application of the invention "within a reasonable time" and "alleviat[ing] health or safety needs." We would not, however, suggest giving an agency march-in authority before it faces *any* judicial review. Unlike an agency determination that research should not be patented, which is made at the grant stage before any inventions have been made, a subsequent exercise of march-in rights disturbs settled expectations of grantees and licensees that may underlie investments. If these expectations are too readily upset by the exercise of march-in rights, 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 21 years ago in order to eliminate the uncertainty and delays associated with agency discretion over the patent rights available to contractors.[53] Given the widespread embrace of patenting by both universities and NIH in the intervening years, we believe this danger is quite small. Moreover, our proposed amendment would not overturn the general presumption in favor of allowing government contractors to patent inventions. It would simply give agencies more authority to decide that, in particular cases, patenting is not warranted, and streamline procedures for making and reviewing these decisions. More generally, it would 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 necessarily the best way to go.

Another objection to greater agency discretion might turn on whether agencies such as NIH have the institutional competence to make informed and objective determinations regarding when patenting is or is not in the public interest. NIH is likely to be as well informed about the underlying policy issues as universities, and better informed than other government actors such as Congress or the courts. Objectivity poses a greater concern. A skeptic influenced by public choice theory could

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[53] For example, the Senate report on the statute that would become Bayh-Dole observed that "[p]resently, there are at least 24 different patent policies in effect in the Federal agencies. They are frequently contradictory from agency to agency (and even sometimes within the same agency) and have proven to be formidable barriers to organizations interested in participation in Government work." S.REP.NO. 96-480, at 2 (1979).

argue that because NIH, like all political actors, has an interest in increasing its own power by attracting more funding, it will repeatedly find a pressing need for public sector programs, even in research areas where the private sector is already operating. NIH might invoke ostensibly public-spirited arguments for public funding as a means of promoting widespread access to research results, when in fact these arguments would cover self-serving efforts to expand the scope of its own research.

But in our view these public-spirited arguments have considerable force, and we would hesitate to disable research sponsors from advancing them out of suspicion that they may be driven by ulterior motives. When the willingness of private firms to do research depends on their ability to restrict the dissemination of research results, public funding may be essential to ensure that basic research platforms are widely available. That arguments for public funding of research in the public domain might in fact be driven by agency self-interest does not, in and of itself, detract from the soundness of the arguments.

Rather than expanding the authority of funding agencies such as NIH to curtail the proprietary claims of their grantees, one might address the problems presented by the patenting of upstream research discoveries through substantive changes in the patent statute. The chief benefit of this approach - that it would affect patenting not only by publicly funded entities but also by privately funded ones - is also its chief drawback. In the patent-sensitive biopharmaceutical industry, changes in patent law threaten to upset a legal regime that has promoted substantial and valuable investments in R&D. Such changes might be justified if on balance they have the effect of promoting R&D, but it is difficult to fine-tune the patent statute to achieve just the right balance. If Congress were to get the balance wrong, they could undermine research investments in an industry that depends heavily on patenting to return value to investors. By contrast, NIH determinations to restrict patenting by its grantees would not limit NIH's own willingness to invest in research, and would affect the private sector only indirectly. NIH-directed public release of information in a field might, for example, make it harder for private firms to obtain patents in that area and thereby limit the profitability of similar private research investments. To place this concern in proper perspective, it bears noting that the efforts of NIH and the pharmaceutical industry to enrich the public domain in genomics have not prevented the emergence of a robust private genomics industry, and may well have promoted it.

CONCLUSION

Patents on research discoveries impose costs on R&D, and these costs may well exceed any social benefits that they offer in the form of motivating further private investment in product development. It makes little sense to entrust decisions about when to patent the results of

government-sponsored research to the unbridled discretion of institutions that are not motivated to weigh the costs against the benefits. A more sensible approach would give research sponsors such as NIH more authority to restrict patenting of publicly-funded research when such patenting is more likely to retard than promote subsequent research and development. A public research sponsor is particularly likely to invoke such authority to promote free dissemination of discoveries made in the course of grants to pursue the development of fundamental knowledge and research tools with the goal of enabling wide-ranging further investigation. As a likely sponsor of such future investigation, the agency will be motivated to keep its costs down, and this goal will often be better served by restricting patents. A conspicuous recent example is "raw" DNA sequence data generated in the course of the Human Genome Project, a fundamental resource for much future biomedical research. Although in this particular setting NIH has had some success, despite the constraints of the Bayh-Dole Act, in its hortatory efforts to restrict patenting of this fundamental information, hortatory efforts that rely on self-restraint by universities may no longer be sufficient.