Patents and Innovation in Cancer Therapeutics: Lessons from CellPro

AVITAL BAR-SHALOM and
ROBERT COOK-DEEGAN

Risk Analysis Fellow, American Association for the Advancement of Science, Washington, D.C.; Duke University

How scientific knowledge is translated into diagnostic and therapeutic tools is important to patients with dread diseases as well as to regulators and policymakers. Patents play a crucial role in that process. Indeed, concern that the fruits of federally funded research would languish without commercial application led to the passage of the Bayh-Dole Act (PL 96-517), which reinforced incentives to patent the results of inventions arising from federally funded research (Eisenberg 1996). Subsequently, rates of patenting among U.S. academic institutions have increased (Henderson, Jaffe, and Trajtenberg 1988). A recent survey by the Association of University Technology Managers counted 20,968 licenses and options from 175 academic institutions and 6,375 patent applications filed in fiscal year 2000 (Pressman 2002). Analysis suggests that the number of academic patents was already rising when the Bayh-Dole Act was passed in 1980 (Mowery et al. 2001), but it is clear that the act reinforced the patenting norm in research universities and mandated a technology transfer infrastructure at those universities that had not yet established a technology licensing office.

Several concerns were raised when the Bayh-Dole Act was debated. First, patents have a potential danger, as they can be used to block

The Milbank Quarterly, Vol. 80, No. 4, 2002

products from the market and protect monopolies. Indeed, establishing a limited monopoly is the very purpose of patenting. The Bayh-Dole Act thus includes a provision intended to limit monopoly rights when they might undermine public health. Under certain circumstances, government agencies can "march in" to protect the public interest. The second concern refers to the impact of patenting on open science and academic norms. This was not heavily debated before Bayh-Dole passed, in part because the act's central focus was on small businesses and nonprofits rather than academic institutions. Now, however, the possible untoward effects of academic research institutions pursuing their business interests while hindering access to research tools and reducing open publication are receiving attention (R.R. Nelson, personal communication, January 2002).

We present in this article a case study of intellectual property that affected cancer treatment. The case concerns the rise and demise of CellPro, which developed cell separation devices for making stem cell suspensions for bone marrow transplantation. CellPro was a Seattle-area start-up firm founded to develop the technology. The firm was the first to market and secure the approval of the U.S. Food and Drug Administration (FDA) of a cell separation device, but it ultimately went bankrupt and sold its technology assets after losing a patent battle with Johns Hopkins University, Baxter Healthcare Corporation, and Becton-Dickinson & Company. We address how patent law and science claimed this discovery in different ways and for different purposes. The CellPro case was the first time that any federal agency—in this case, the National Institutes of Health (NIH)—was petitioned to "march in" to compel licensing under Bayh-Dole. The relevant patents were owned by Johns Hopkins and exclusively licensed (and sublicensed) to large medical device firms. The case shows the Bayh-Dole statute in action and illustrates the role of patents, particularly the importance of patent licensing practices.

We begin by describing the events according to the accounts of different stakeholders, then turn to observations about the policy decisions made during this process, and conclude with options for policy change. The story starts with the personal involvement of CellPro's former CEO, Rick Murdock, whose mantle cell lymphoma was treated clinically with CellPro's Ceprate instrument. The account continues through two federal district court trials in Delaware, presided over by Judge Roderick McKelvie, followed by the review of those decisions by the Court of Appeals for the Federal Circuit, which hears appeals for all patent cases

in the United States. While the second trial was under way, CellPro petitioned the federal government to "march in" and compel the licensing of the Hopkins patents. We then look at the role of Johns Hopkins and make some observations about licensing and the role of federally funded research under the Bayh-Dole statute.

Patents are important, and for Johns Hopkins University, they were a source of revenue. For the large device firms, particularly Baxter, patents protected them from competition and fostered investment in developing a cell separation device. For CellPro, however, the Hopkins patents spelled doom. Indeed, patents, particularly for pharmaceuticals, are coming under increased scrutiny throughout the world. Our purpose here is not to prove that patents are either good or bad but to show how patents encourage investment in research and development and can also hinder innovation. Their net impact on social welfare is uncertain.

This article examines three features of patents: (1) the breadth of patent claims; (2) the way that patents are licensed and sublicensed, which is influenced by owners and licensees; and (3) the secrecy that limits accountability to the public, even when inventions result in part from federal funding and are conducted at academic institutions whose core values are open discourse and the creation and dissemination of knowledge. For two decades, under the Bayh-Dole statute, universities have drifted into practices that can pit their business interests against their academic values.

The CellPro story raises difficult questions about the use of federally funded research and university-based intellectual property. It also shows how patent law may or may not play out differently in medical fields than it has in other high-tech economic sectors. Enhancing or obstructing computer technology or automobile manufacture is different from quashing a firm producing a life-saving cancer drug or device. Cancer therapeutics are subject to an additional layer of moral (and political) analysis. Although the principles of traditional patent law still apply, they collide with norms of fairness more often, and sometimes with greater effect, than they have done in other high-tech fields.

Our story starts from Claim 1 of U.S. patent 4,965,204, issued and assigned to Johns Hopkins University on October 23, 1990: "A monoclonal antibody which specifically binds to an antigen on non-malignant, immature human marrow cells, wherein said antigen is stage specific and not lineage dependent, and said antigen is also specifically bound by the antibody produced by the hybridoma deposited under ATCC Accession

No. HB-8483."[1] The syntax and circumlocution are typical of patent claims, which are constructed as factual assertions linked by verbs that may sound like standard English but often have a specific legal meaning. (For example, a DNA sequence "comprising" ACTG refers to any sequence that *includes* that sequence within it, whereas "consisting of" ACTG means exactly and only ACTG. That is, "comprising" has a much broader scope than "consisting of" does.) Awkward sentences like these can be worth billions of dollars. Claims define the boundaries of the intellectual property that its inventor controls. Patents cost tens of thousands of dollars to obtain (and many times that amount for worldwide rights) and can cost millions to defend in litigation. For example, the legal fight over patents on recombinant insulin cost around $30 million (Marshall 1997). In our story, Claim 1 killed CellPro and thereby eliminated Baxter's competitor, increased the price (and presumably Baxter's profits), and suppressed an alternative technological approach to cell separation devices. CellPro's technology now belongs to its nemesis, Baxter.

Curt Civin's Invention

The first inventor listed on the Hopkins patent was Curt Civin, a pediatric oncologist in training at Hopkins who was studying molecular immunology. In 1981, he raised a series of monoclonal antibodies against a cell line, KG-1a, developed by Koeffler and Golde at the University of California at Los Angles from a patient with acute myelogenous leukemia (Koeffler and Golde 1978). One of those antibodies, My-10, became the foundation for four patents. It recognized an antigen, ultimately designated CD34, on the outer surface of stem cells (undifferentiated cells that give rise to many blood cell lineages: red cells, lymphocytes, macrophages, and granulocytes). The CD34 antigen was stage specific, meaning that it was present on stem cells but not on differentiated cells of the many lineages that develop from the CD34-bearing cells (they lose their marker as they differentiate). This specificity for stem cells was why Civin's monoclonal antibody was useful as a molecular handle to differentiate, and ultimately purify, stem cells from other cells in the bone marrow.

A method to enrich stem cells is immensely useful. The reason is that stem cells replenish the cell lineages lost when bone marrow has been

[1] U.S. patent 4,965,204, issued October 23, 1990.

destroyed by high doses of chemotherapy to treat leukemia, lymphoma, breast cancer, or another malignancy. Civin's discovery of an antibody to label stem cells was an advance widely recognized as a major achievement.

In 1984, Johns Hopkins University filed a patent application based on Civin's My-10 antibody. The patent office subsequently "divided" it into four separate applications, which in effect were clusters of claims that constituted separate inventions. All four patents were ultimately granted, and two of them became important to the CellPro story. The more important one is U.S. patent 4,965,204 (October 23, 1990), claiming the My-10 antibody and other antibodies that recognize CD34. The other relevant patent, U.S. Patent 4,714,680 (December 22, 1987), claims, among other things, a suspension of cells enriched in CD34-bearing (stem) cells. A suspension of stem cells is introduced into patients for bone marrow transplantation.

Civin did his initial work with internal Hopkins funds and then obtained grants from the National Cancer Institute (NCI) and the Council for Tobacco Research and the Heart of Variety Fund. As a Hopkins faculty member, Civin assigned his patent rights to Johns Hopkins University. Johns Hopkins licensed the patents exclusively to Becton-Dickinson & Company. Becton-Dickinson then sublicensed them exclusively to Baxter (and Baxter to two other firms on a nonexclusive basis). The use of the NCI's federal dollars meant that the invention was subject to the Bayh-Dole Act.[2]

The Hopkins patents illustrate the difference between what a patent claims and what a scientific symposium or publication claims. If Civin had claimed at a conference of molecular immunologists that he had discovered all monoclonal antibodies that bind to CD34, his reputation would have been permanently damaged for claiming findings beyond his own data. But that is what his lawyers asserted when they prosecuted the patents, complying with the norm under patent law. The purpose of scientific publications is to offer evidence and rigorously interpret the results. The purpose of the patent system is the reverse: it is to mark boundaries on intellectual property, encompassing as many plausible future discoveries and applications as possible without invalidating the

[2]Patent and Trademark Law Amendments Act of 1980, P.L. 96-517, amended again in 1984 as P.L. 98-620; becoming U.S. Code as 35 USC 200-212 and regulations as 37 CFR 401.

patent. The "scope" of a claim is determined by how likely it is that a future invention will infringe on it, that is, what expanse of future discoveries it covers.

Patent examiners accept or reject a claim according to how the invention described in the patent can be used by those "skilled in the art." If fulfilling the claim requires "undue experimentation," then it should be rejected. The inventor does not necessarily have to demonstrate all the elements implied in the claim, however, and indeed rarely does so. Rather, the purpose of a patent is to exclude others from making, using, selling, or creating minor variations of the invention. Whereas scientific publications call for specificity, the patent system requires some specificity, albeit balanced against the need for claims broad enough to block imitators from taking a free ride on an inventor's work. One main difference is the presumptions of the claim. A scientist should not claim credit for a discovery until it is fully documented. But in patent law, an inventor must describe the invention in enough detail that someone else can make and use it, but a patent generally claims more than has been fully demonstrated. The gap between the two is not the same for all kinds of inventions, and indeed the difference between the scope of patent claims and that of scientific claims generally narrows over time as the state of the art advances. The broadest claims are generally granted to "pioneer" patents, that is, to the first in a new technology. The patent office does this to encourage investment in breakthrough technologies. This broad scope also has implications for inventions that depend on cumulative innovation.

Those seeking to invalidate a patent must demonstrate that the invention as described in the patent is *not* novel, useful, or inventive—and thus does not meet the patent's criteria—or they can argue that an invention is inadequately described or that the inventor deliberately hid pertinent information from the patent office. If claims are too broad, they can be declared invalid or unenforceable, and the entire patent will collapse. The presumption favors the inventor, and the burden of proof lies with the person challenging the patent.

At the time, the scope of the Hopkins patents was in the range of other monoclonal antibody patents. Patent scope was explicitly addressed by the federal district court and reviewed by the Court of Appeals for the Federal Circuit. The scope of claims does not appear to have been an issue in the CellPro case, but we will later return to whether it could have been, or should have been.

Rick Murdock's Salvation

CellPro was founded in 1989, based on research at the Fred Hutchinson Cancer Center in Seattle ("the Hutch"). CellPro's scientific founder was Ronald Berenson, who took his idea to develop an instrument to separate stem cells from other cells to his former Stanford colleague Richard A. Miller. They decided to found a company. One of the nation's premier venture capital firms, Kleiner Perkins Caufield & Byers, was one of the initial investors.

The company rested on two technologies: (1) an antibody that identified stem cells and (2) a method for using those antibodies to purify specific cells from pools of mixed cells. In 1993, Berenson received three patents for the "immunoselection of cells" using biotin,[3] to which the protein avidin binds with extraordinary specificity and strength (hence the name, for *avid binding*). Biotin is a small molecule that can be covalently linked to many large molecules such as antibodies. Once biotinylated, avidin can "grab" an antibody (or other protein). If it is bound to a cell, the antibody can be used to identify antigen-bearing cells, thus separating them from other cells. If the avidin is bound to beads on a column or in a slurry, for example, then the bound cells can be enriched by washing away all the cells that do not bind the biotinylated antibody. The cells then can be freed for use in, say, transplantation. Or the same general technique can be used to deplete cells bearing a specific marker. Here the antibody binds the cells bearing, for instance, a tumor cell–specific marker. These cells are discarded so that tumor cells will not be reimplanted in a patient. The Berenson patents specifically note both uses of the biotin-avidin method: to enrich bone marrow stem cells and to deplete tumor cells.

Another antibody, called 12-8, was developed by Robert Andrews, Jack Singer, and Irwin Bernstein at the Hutch, but it was not patented. Its discovery was published in 1986 (Andrews, Singer, and Bernstein 1986), in a paper that cites Civin's 1984 paper describing the My-10 antibody. The 12-8 antibody was raised against the same KG-1a cell line as Civin's My-10, using the standard Kohler-Milstein method for making monoclonal antibodies. The 12-8 antibody also bound to CD34, but

[3]U.S. patent numbers 5,262,334 (November 16, 1993), 5,225,353 (July 6, 1993), and 5,215,927 (June 1, 1993). Assigned to the Fred Hutchinson Cancer Research Center and licensed to CellPro.

12-8 was an IgM antibody, whereas My-10 was an IgG and recognized a different "epitope," or specific binding site, on the CD34 molecule. In addition, 12-8 was easily biotinylated, whereas My-10 was not, making 12-8 amenable to Berenson's avidin-biotin cell separation method. The 12-8 antibody could have been patented, as it was a different embodiment and had a functional utility different from that of My-10 (it could be readily biotinylated). If 12-8 were patented, however, its use might fall within the scope of the Hopkins patent (the courts determined that it did, since Claim 1 included all antibodies that bound CD34). So even if 12-8 had been given a separate patent, its use would still have required a license to use the Civin antibody patent. In patent parlance, even if the Hutch had patented its 12-8 antibody, the Civin My-10 patent would have been "dominant."

Thomas D. Kiley, a lawyer, was one of CellPro's board members. In 1976, when Kiley was working in Los Angeles, Herbert Boyer, his friend and a scientist at the University of California at San Francisco—a pioneer of recombinant DNA research—asked him to draw up some papers to hire the first employees for a new firm, Genentech, in the San Francisco Bay Area (Abate 2001). Kiley later became Genentech's lawyer and was directly involved in the litigation of several seminal biotech patents. By 1989 he was well known in biotech venture capital circles. Kiley thought that the Hopkins patents would not hold up in court, because under U.S. law, a patent can be obtained only if the invention has not been publicly disclosed more than one year before the patent application is filed. Civin had published an abstract that mentioned the My-10 antibody more than a year before he filed his patent application. Kiley offered his opinion to the CellPro board (Murdock and Fisher 2000) and also asked his colleague, Coe A. Bloomberg, at the law firm of Lyon & Lyon for his opinion. Bloomberg agreed that the Hopkins patent was invalid, which he told CellPro's board. His opinion was later put into writing, first in February 1990, commenting on the '680 patent (on cell suspensions) and in April 1991, on the '204 patent (the My-10 antibody patent) (Bloomberg 1990, 1991). Bloomberg's letters, however, did not explicitly address the crucial Claim 1 of the '204 patent and did not assess the options for working around the patent or choosing to risk infringement (a so-called infringement analysis or assessment).

In December 1991, CellPro hired Rick Murdock from Baxter as its president. Murdock had joined Baxter when it acquired his previous start-up firm, HemaScience. Murdock was the first human on whom

HemaScience's blood separation device was tested. Although he was not with CellPro when the initial discussions of the Hopkins patents took place, his book describes the situation: "I've never known exactly when CellPro's original management became aware of the existence of these [Civin] patents. What is certain is that management believed completely that these patents presented no serious legal problems." Those artful sentences, as we shall see, dodge a number of important points. In Murdock's eyes, the decision hinged on Kiley's views. "Kiley didn't equivocate at all. Not in the slightest. He was a respected patent attorney, a Genentech man, and there was absolutely no reason to doubt him" (Murdock and Fisher 2000, 44–5).

CellPro moved swiftly to develop two cell separation devices, one for laboratory experiments and the other for clinical use. These Ceprate instruments could be used to deplete tumor cells, enrich stem cells, or both. Becton-Dickinson wanted $1 million for a license for the therapeutic use of the Hopkins patents, but CellPro refused. Its refusal caused some problems with raising capital, as many investors "walked away because of the patent issue." Clearly, some investors thought there might be patent risks, but enough of them invested to take CellPro from conception into production. The patent issue was raised again during the second round of financing in 1990, but Coe Bloomberg's opinion "had allayed most fears" (Murdock and Fisher 2000, 45). These decisions were made before Murdock joined CellPro in December 1991.

Just before Murdock was hired, CellPro decided to license the Hopkins patents again, now from Baxter (which had obtained an exclusive sublicense from Becton-Dickinson), on a nonexclusive basis, "even though our attorneys had assured us that legally we didn't need them, [but] because we didn't want to fight Goliath" (Murdock and Fisher 2000, 48). In January 1992, Baxter sent a letter offering a license with an up-front fee of $750,000 and a royalty rate of 16 percent on the antibody portion of CellPro's disposable kit (the set of reagents to be used in conjunction with the instrument, including antibodies for selecting or depleting specific cell types). CellPro responded with an offer of a $500,000 up-front payment that could be applied to royalties "not to exceed 30% of the value of the kit" (Murdock and Fisher 2000, 51). Two other firms, SyStemix and Applied Immune Sciences, paid $750,000 and agreed to pay Baxter royalties of 8 percent. Murdock argued that CellPro should be given more lenient terms because it had demonstrated the technology and was much further along in developing it. The

counterargument was that CellPro was emerging as Baxter's lead competitor, as Baxter was trying to develop its own instrument based on the My-10 antibody and magnetic bead technology instead of the biotin-avidin system. But CellPro was well ahead of Baxter in progress toward the market. CellPro's discussions with Baxter shifted to foreign marketing (which CellPro was willing to cede) but were deadlocked over how to handle the U.S. market. CellPro could not give it up, and Baxter wanted a big piece of it. The negotiations never culminated in a license.

Meanwhile, CellPro continued its technical development and then the clinical testing of its Ceprate instruments. The clinical trials began in June 1991, and Berenson filed a patent application for the avidin-biotin method in October 1991. CellPro's technical work was going well, but frustration over the licensing negotiations led management and the board to conclude that Baxter intended to use the Hopkins patents to block CellPro. Accordingly, their discussion switched to deciding whether to sue Baxter now or to wait to be sued for infringement. In April 1992, CellPro filed suit in Seattle, alleging antitrust violations and asserting that the Civin patents were invalid and unenforceable. That suit was later dismissed.

In May 1992, CellPro demonstrated its first successful bone marrow reconstitution following chemotherapy for breast cancer. In June, Murdock became CellPro's CEO (as well as remaining its president). CellPro's successful third round of financing took place later in 1992, creating further momentum toward the market. In September 1993, CellPro received approval to market its instrument in Europe.

During 1994 and 1995, CellPro's financial status fluctuated. The company needed cash to continue its clinical testing while awaiting the FDA's approval for the large U.S. market and to cover its legal costs. The private firm Corange agreed to buy $90 million of equity in CellPro, but the deal fell apart in 1995 with the turnover of Corange's senior management.

In January 1994, Baxter began clinical trials using its competing instrument, the Isolex. In March 1994, Johns Hopkins University, Becton-Dickinson, and Baxter filed a patent infringement suit against CellPro in Delaware's federal district court. Thus began the long march toward two jury trials and an appeal.

A month-long jury trial began in July 1995 in Wilmington, Delaware. The jury found the Hopkins patents invalid and unenforceable on all

103 counts presented to it.[4] The jury found that all the patents were obvious in light of prior art and that each claim was not enabled. CellPro was vindicated. While the company was basking in its court victory, it received another shock.

Murdock had noticed a few lumps under his skin, but he felt fine. He began to worry, however, and in December 1995, he was diagnosed with lymphoma. The precise type of lymphoma was not clear at first, but ultimately the diagnosis was mantle cell lymphoma, an especially poorly behaved malignancy. Murdock and his physicians, one of whom had testified in the patent trial, decided to see whether CellPro's clinical version of the Ceprate instrument could be used for both tumor depletion and stem cell enrichment (its use for breast and other cancers had employed only stem cell enrichment, not tumor cell depletion). Murdock was scheduled to undergo high-dose chemotherapy after a sample of his marrow had been extracted and passed through the Ceprate instrument—in two runs, one using the 12-8 antibody to enrich his stem cells and the other using different antibodies to deplete the mantle cell tumor cells. His stem cells would then be reimplanted in his body, in the hope that the tumor cells were gone and that only healthy stem cells remained to replenish his blood and immune cells.

The CellPro staff, led by Nicole Provost, undertook the "Rick Project" driven by desperation to save their CEO's life. Having been the first patient for the HemaScience instrument, Murdock was once again a first patient, this time for higher stakes. CellPro decided not to use the magnetic bead technology for cell separation in one of the separation steps (enrichment of stem cells, depletion of tumor cells), because Baxter was using it in its Isolex system. It would have been logical to use one method, avidin-biotin binding or magnetic bead separation, for the stem cell enrichment step and the second method for tumor cell depletion. Instead, the CellPro team, which included Murdock, decided to use CellPro's proprietary biotin-avidin system for both steps, making them technically more difficult. After a frenetic eight weeks, Nicole Provost's team succeeded, and Murdock survived to write his book, *Patient Number One*, about CellPro.

Amid this personal turmoil, the patent infringement case came back to life. In April 1996, the U.S. Supreme Court handed down a new

[4]Civil Action no. 94-105-RRM. U.S. District Court for the District of Delaware 894 F. Supp. 819; 1995 U.S. Dist. LEXIS 11407, August 4, 1995.

ruling in the *Markman* case. It held that "the construction of a patent, including terms of art within its claim, is exclusively within the province of the court,"[5] meaning that the judge alone was to decide the meaning of the *law*, including the way in which patent claims were stipulated, and the juries in patent cases were to sift through the *facts*. The judge in CellPro's jury trial, Roderick McKelvie, ruled that "no evidence exists in the record to support the jury's finding of noninfringement with respect to claim 1 of the '204 patent when that claim is properly construed."[6] In June 1996, Judge McKelvie decided that there should be a retrial and that as a matter of law, CellPro had infringed the '680 and '204 Hopkins patents. The retrial would determine whether the remaining two patents had been infringed and would also address the validity of all the Hopkins patents (if the patents did not meet the patent criteria, the patents would be invalid, and infringement moot).[7]

Judge McKelvie's Fury

A profile of the judge in the *National Law Journal* opens, "If he can't quite walk on water, U.S. District Court Judge Roderick R. McKelvie comes mighty close" (Slind-Flor 1997, A1). Judge McKelvie came to prominence in part because of his decision about the second CellPro trial. The article about the judge quotes him as saying, "Arrogance is probably one of the worst traits I see in lawyers." Judge McKelvie heard Attorney Thomas Kiley's testimony as a witness in the CellPro trials, and Murdock described Kiley as "quite a character" and noted that "even Kiley admits that at times he can seem arrogant" (Murdock and Fisher 2000, 56). Thus it was not Murdock, or even CellPro, that was in Judge McKelvie's cross-hairs but, rather, their lawyers and, behind them, CellPro's initial investors. In the section of his 1997 ruling that sealed CellPro's fate, Judge McKelvie laid out the core of his argument—that Kiley and Bloomberg rendered their opinion on the Hopkins patents without due diligence and used the oral and written statements about

[5] *Markman et al. v. Westview Instruments, Inc., et al*. (95-26), 517 U.S. 370 (1996); see http://supct.law.cornell.edu/supct/html/95-26.ZS.html.
[6] Civil Action no. 94-105-RRM, U.S. District Court for the District of Delaware; 931 F. Supp. 303; 1996 U.S. Dist. LEXIS 9850, June 28, 1996.
[7] Civil Action no. 94-105-RRM. U.S. District Court for the District of Delaware; 931 F. Supp. 303; U.S. Dist LEXIS 9850, at 78.

Civin's patents to entice investors while also expecting to stave off a "willful infringement" ruling. McKelvie quoted CellPro's IPO prospectus, noting that "based on the advice of Lyon & Lyon, special patent counsel to the company, CellPro believes the . . . [Civin] patents are invalid and unenforceable."[8]

McKelvie's ruling is a clear explanation of the relevant patent law and a careful chronology of events. Its conclusions speak for themselves:

> Five years of effort to bring this matter to a resolution have left the plaintiffs [Hopkins et al.] with too many examples of conduct by and on behalf of CellPro that demonstrate a contempt for Dr. Civin and his patents; for the people at Johns Hopkins, at Baxter, and at Becton Dickinson; for the people who have worked for them, for the law; and for our system of civil justice. . . .
>
> CellPro almost proved plaintiffs' case for them, with its weak and disingenuous defense of alleged good-faith reliance on the advice of counsel. Kiley's testimony was insincere and lacked credibility. The Lyon & Lyon opinions were so obviously deficient, one might expect a juror to conclude the only value they had to CellPro in the world outside the courtroom would have been to file them in a drawer until they could be used in a cynical effort to try to confuse or mislead what CellPro, its Board, and counsel must have expected would be an unsophisticated jury. . . .
>
> The opinions were not prepared at a time when the CellPro Board was considering whether to proceed with the apparently infringing work. Rather the opinions were prepared after those business decisions had been made. The opinions appear to have been prepared for two other reasons: to assist CellPro in raising funds and to immunize the company from a claim [of willful infringement] for enhanced damages. . . .
>
> The [Lyon & Lyon] opinions are a weak pass at the quality of work one might expect from independent counsel. The opinions are shallow. For example, they fail to speak to the substantial burden of proof CellPro would face when it took on the task of trying to show the Civin patents were invalid. . . . Not one of the three prior art references cited in the February 27, 1990 opinion as anticipating the '680 patent on cell suspensions even refers to a cell suspension. While this deficiency might not have been obvious to the investors or others on the Board, it should have been obvious to Kiley. . . . Kiley's testimony as to why CellPro had not asked for an infringement analysis was not credible.

[8]Civil Action no. 94-105-RRM, U.S. District Court for the District of Delaware, 978 F. Supp. 184; 1997 U.S. Dist. LEXIS 14314, at 12.

> One element of the strategy CellPro has adopted in this battle has been to hold itself out as a warrior in a twentieth-century holy crusade. It claims it is out to advance science, to save lives, to fight cancer, and improve the human condition. If it infringed Dr. Civin's patents, so it says, it was only to do good. . . . As is often the case in a world of images and perceptions there is some truth to this. No doubt the doctors, the scientists, and the administrative staff associated with CellPro share a desire to use their knowledge and skills to make a contribution to our community. In other ways, however, this image is a façade constructed by the venture capitalists who started this business. Behind the science, the medicine, and the potential for treating cancer patients are investors who have demonstrated that their primary motivation is not humanitarianism, nor even responsible capitalism. . . . CellPro's motivation, as expressed by the words, conduct, and testimony of its founders, is greed.

The jury opted for the highest figure presented to it for damages, and Judge McKelvie then trebled them, to $7.6 million, based on finding *willful* infringement, and then added attorneys' fees of $8 million. He noted that early in its business plan, CellPro had set aside $7 million for the litigation and contingency of a damage award and had $60 million in liquid assets as of December 1996, so it could afford to pay the $15.6 million settlement. Thereafter, CellPro would owe Baxter a royalty of more than $1,000 on each Ceprate device and antibody kit sold in the United States.

CellPro could likely have paid the costs of losing the lawsuit, but it could not survive the terms for its future business. In effect, the licensing terms and royalty rates gave Baxter the commanding position and undermined CellPro's viability as an autonomous competitor. Having lost the case and with Judge McKelvie overseeing the ensuing settlement, CellPro was in an extremely weak bargaining position. Its only hopes were, first, an appeal to the Court of Appeals for the Federal Circuit and, second, a provision of the Bayh-Dole statute that had never been used.

In August 1998, Judge Alan Lourie of the Court of Appeals for the Federal Circuit (CAFC) wrote the opinion for a three-judge panel that heard the appeal.[9] The CAFC reversed Judge McKelvie on two relatively minor points: Judge McKelvie had imposed a ban on foreign sales and had decided not to consider a particular publication as "prior art." But

[9]U.S. Court of Appeals for the Federal Circuit, 97-1495, 98-1017, *The Johns Hopkins University, Baxter Healthcare Corporation and Becton Dickinson and Company v. CellPro, Inc.*, August 11, 1998.

the CAFC sustained Judge McKelvie on all the essentials. The CAFC reviewed the first claim of the '204 patent and concurred on the patent's scope, that the claim properly extended to all antibodies that bound to the CD34 molecule, not just a specific epitope (the part of that molecule recognized by My-10). Most notably, it concurred that

> Kiley should have been on notice concerning the [Lyon & Lyon] opinion's obvious shortcoming and accordingly of the impropriety of CellPro's course of action. . . . Such shortcomings should have been especially troublesome to a knowledgeable practitioner like Kiley, especially considering that the opinions did not express an opinion concerning infringement of the broadest claims.[10]

The CAFC removed McKelvie's ban on export and remanded the case to the district court for a decision about whether the one reference excluded from consideration would render one or more of the patents invalid (it did not). But the terms of doing business in the U.S. market, the make-or-break issue for CellPro's continued viability, remained as dictated by Judge McKelvie's ruling.

The Dilemma for the National Institutes of Health

CellPro's other hope lay with a provision of the Bayh-Dole statute enabling the federal government to mandate compulsory licensing. One day after the second trial began in March 1997, CellPro petitioned Donna Shalala, as the secretary of the U.S. Department of Health and Human Services (HHS), to "march in" and reclaim rights to the Hopkins patents, asserting that the way Johns Hopkins had exercised those rights was antithetical to the public's health (Cutler and Bayh 1997). Secretary Shalala delegated the review of the march-in petition to the National Institutes of Health (NIH), the agency whose funding had contributed to the Hopkins patents.

The request that HHS "march in" encompassed several arguments. Foremost was that CellPro had obtained the FDA's approval for its Ceprate SC device (the model designed for clinical use), to enrich CD34 stem cells for use in autologous bone marrow transplantation (Siegel

[10]Ibid.

1996). Although Baxter's product was being used in clinical trials, it was much further behind in development. CellPro had decisively beaten Baxter to market with an FDA-approved product. The petition noted that the purpose of the Bayh-Dole Act (and Birch Bayh, one of CellPro's petitioners, was one of the bill's chief sponsors in his former role as a U.S. senator) was "to promote the commercialization and public availability of inventions."

Under the Bayh-Dole Act, march-in provisions can be triggered

1. Because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use.
2. To alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees.
3. To meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees.
4. Because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204.[11]

CellPro's petition requesting HHS to march in was unprecedented; march-in rights had never been invoked by any federal agency before. CellPro argued that it needed a license for the invention in order to meet the health needs of its patients, as its instrument was on the market and Baxter's was not and might never be. By then, the Ceprate device was being used at 300 institutions, for more than 5,000 patients. CellPro's letter requesting the march-in noted that Baxter was discussing selling the division that was developing its Isolex cell separation device (it ultimately did so, and the resulting instrument was manufactured and marketed by Nexell but then reverted to Baxter in 2001). The march-in petition also argued that Johns Hopkins had ignored the preference for small businesses[12] when it granted a license to Becton-Dickinson, and

[11]Section 204 of the Bayh-Dole Act (35 USC 204) establishes a presumption for U.S. manufacture ("manufactured substantially in the United States") unless a U.S. licensee is impractical. The grantee or contractor must petition for a waiver to allow nondomestic manufacture from the funding agency in individual cases.

[12]Section 202 stipulates a preference "except where it proves infeasible after a reasonable

Becton-Dickinson, when it granted a sublicense to Baxter. At the center of the dispute was the breadth of the Hopkins patent claims. CellPro's march-in petition claimed, "CellPro does not use the My-10 antibody discovered by Dr. Civin. It is only because the patent claims were written broadly and claimed to cover antibodies—antibodies discovered under federal grant programs at other institutions—that there is even an issue." It also noted that the NIH might need to develop guidelines for deciding when to march in and suggested that the NIH might want to investigate the kind of royalty "layering" that was evident in the Hopkins patent agreements (Hopkins got payments and royalties from Becton-Dickinson, Becton-Dickinson from Baxter, and Baxter from its sublicensees). CellPro offered to accept the original licensing terms that Baxter had initially offered but then had withdrawn and petitioned HHS to mandate a compulsory license from Hopkins to CellPro.

In August 1997, the NIH declined to march in (Varmus 1997). This was the end of a long and tortuous process, accompanied by a vigorous public relations initiative mounted by CellPro, to which Hopkins and Baxter responded in kind. The NIH concentrated on two issues: whether Baxter had taken steps to make its product available to the public on reasonable terms and whether there was a health need that Hopkins and Baxter were failing to meet. On the first point, NIH decided that Baxter had taken steps to develop its product and noted that Baxter had European approval and had filed for the FDA's approval in February 1997, just weeks before CellPro submitted its march-in petition (Nexell Therapeutics's Isolex was ultimately approved in July 1999).[13]

The question of an unmet health need was harder to resolve and became "the central inquiry and priority of the NIH in evaluating CellPro's petition" (Varmus 1997). The NIH mentioned that a vigorous debate was under way about the value of stem cell selection in bone marrow transplantation, and of bone marrow transplantation in general. It also pointed out that the FDA's approval was based on reduced toxicity, rather than on the demonstrated improvement of stem-cell engraftment, disease-free survival, or overall survival. But the fundamental basis for the

inquiry, in the licensing of subject inventions shall be given to small business firms" (35 USC 202(c)(7)(D).

[13] Arno and Davis argue that NIH's focus on "working the patent" misinterpreted or ignored the statutory requirement that an invention be available "on reasonable terms" (Arno and Davis 2001). What those terms should be, and whether they amount to more than due diligence regarding efforts to commercialize an invention, is a matter of dispute (Arno and Davis 2002; Bayh and Dole 2002).

NIH's judgment was that "the administrative record demonstrates that Hopkins and Baxter have taken appropriate steps to reasonably satisfy this need" by permitting the continued sale of CellPro's Ceprate until the FDA approved Baxter's Isolex. The NIH relied on the federal district court's determination that CellPro had sufficient financial reserves to survive until the CAFC decided its appeal (by now the second trial had been decided).

The NIH was concerned about using its authority to influence the marketplace:

> We are wary, however, of forced attempts to influence the marketplace for the benefit of a single company, particularly when such actions may have far-reaching repercussions on many companies' and investors' future willingness to invest in federally funded medical technologies. . . . On balance, we believe it is inappropriate for the NIH to intercede in this matter to ensure CellPro's commercial future. Viability and success in the private sector is appropriately governed by the marketplace, and significantly influenced by management practices and decisions. CellPro had the opportunity to license the invention from Baxter but decided against doing so, and instead risked patent infringement litigation. (Varmus 1997)

Although the NIH declined to march in, it did pledge to monitor "issues related to patient access to the CellPro or Baxter devices during the period priority to FDA approval and availability for sale of a comparable alternative device" (Varmus 1997).

CellPro's Demise and Nexell's Retreat

All doors had slammed shut on CellPro. The restrictions on the sale of Ceprate sent its stock into a nosedive (from levels already well below its former peak), and CellPro filed for reorganization (bankruptcy) in September 1998, just a month after the CAFC decision was announced. That same week, CellPro sold its intellectual property in a deal that ultimately became part of Nexell Therapeutics (Baxter Healthcare 1997; Beason 1998; Marsh 1998; Nexell 2001a). Baxter bought 800 of CellPro's instruments to make them available for ongoing trials. CellPro canceled its planned clinical trials and soon passed out of existence, leaving Nexell to become the sole purveyor of cell separation instruments. Rights to what had been two competing approaches (*CellPro v. Baxter*)

were now owned by a single firm, Nexell, which raised its prices on Isolex instruments and on Ceprate kits, which it was now distributing (Murdock and Fisher 2000).

The expected growth in demand for cell separation instruments fell when the results from the breast cancer trials of high-dose chemotherapy and bone marrow transplantation showed little benefit from the added cost and significant toxicity of the treatment. Breast cancer was by far the largest potential market, and so when high-dose chemotherapy with bone marrow transplant was called into question, this market for cell separation instruments markedly shrank. In June 2001, Nexell and Baxter announced that sales of the Isolex instrument would revert to Baxter (Nexell 2001b). Nexell continued as a research and development firm until it began to wind down operations in May 2002, and in October 2002 the board decided to dissolve the company (Nexell 2002). The impact, if any, of any royalty stacking associated with the Civin patents is difficult for those outside the company to judge.

Hopkins's Mission

The faculty manual for Johns Hopkins University has incorporated the intent of the Bayh-Dole statute into its instructions: "The School of Medicine strives to support its faculty, staff, and certain students in securing commercial development of intellectual property resulting from their research so that the benefits of that research may reach society at the earliest opportunity. This effort is consistent with the University's mission of developing new knowledge and facilitating the practical application of such knowledge for the benefit of the public" (Johns Hopkins University 2001, 1). The main intent of the Bayh-Dole Act is to ensure the practical use of inventions made in federally funded research by creating a financial incentive through patent rights. Academic research centers have been quick to patent their creations. Transferring technology through patent licensing is a complicated business and has drawn academic research centers into business relations—just as it was intended to do. In the most recent survey by the Association of University Technology Managers (AUTM), 6,375 patent applications were filed by academic institutions in 2000, and 3,764 patents were issued to them (Pressman 2002). The more than 20,000 active licenses have produced $1.26 billion of licensing revenue, compared with the

$29.5 billion of sponsored research at the surveyed institutions, including $18.1 billion in federal funds. Roughly half the licenses were exclusive, and half were nonexclusive. In earlier surveys, life sciences patents accounted for more than 70 percent of the licensing income and patent applications (the question about specific fields was dropped after the 1997 survey) (AUTM 2000), corroborating the findings of Mowery and colleagues, who also found that health and life sciences dominated the licensing at three major universities (Mowery et al. 2001).

The pharmaceutical and biotechnology businesses have some unusual characteristics relevant to the CellPro story. First, they are, and have long been, uniquely dependent on the patent system. Although many high-tech businesses require patents, none do so to the extent of biotechnology and pharmaceuticals (National Academy of Engineering 1992). Second, pharma and biotech are also uniquely dependent on academic research, as corroborated by the work of the late Edwin Mansfield in his surveys of high-tech executives, analyses of patent citation literature, and distribution of patent ownership (Cockburn and Henderson 1996; Gambardella 1995; Henderson, Jaffe, and Trajtenberg 1998; Mansfield 1991, 1995; Narin, Hamilton, and Olivastro 1997; Narin and Olivastro 1992; Narin and Rozek1988). In short, federal funding agencies, academic research institutions, and industrial firms have created a thriving mutualism.

The Nexell-Baxter story is a good example. Academic research at Johns Hopkins led to a useful discovery, the Civin antibody and its use in enriching stem cells, which was licensed to firms capable of developing and marketing therapeutic instruments. In this case, the complexity of this mutualism was apparent in another way, in that the main market for cell separation devices was the academic health sector, which performed most of the bone marrow transplants and complex cancer treatments. In sum, a discovery was made in an academic health center, cycled through the private sector to develop instruments that were bought mainly by academic health centers for their clinical research and treatment services.

The CellPro story is a variation on the government-academe-industry theme. The National Cancer Institute (NCI), a federal agency, funded research at the Hutch, an academic research center affiliated with the University of Washington. The discoveries there were patented and licensed to a start-up firm, CellPro, the third vertex in the biotechnology triangle.

The CellPro story also exposes some less appealing aspects of the government-academic-industrial collaboration. Curt Civin found a monoclonal antibody to stem cells, thereby showing it could be done. He

did not discover the 12-8 antibody, although he pointed to the path that the Hutch researchers used to find their own antibody. Civin (and Baxter) certainly did not develop the Ceprate instrument, which entailed the avidin-biotin technology and dozens of other important elements (separation columns, pumps, elution methods) and immense amounts of "tacit knowledge" needed to make it work.

Civin made his first antibody in 1981 and received a patent for it in 1990, but the Isolex instrument that used it for cell separation was not approved by the FDA until 1999. This 18-year incubation period is typical of biomedical therapeutics, including drugs, usually taking two decades from seminal discovery to FDA-approved agent (Cockburn and Henderson 2000). Those years entail an immense amount of engineering and development. One of the main justifications for strong patent protection is that although development and clinical testing are costly, once the product is developed, it may be relatively inexpensive to manufacture and sell. Protection from free riders is needed, therefore, to attract firms to invest in the development and clinical testing of products and services.

The CellPro story shows that this "free-rider" rationale for patent protection may be incomplete. In this case, the patent did not stop free riders, because the Hutch and CellPro were not *just* free riders. CellPro was investing heavily in developing its instrument and in conducting clinical trials to demonstrate its medical utility. The Hutch team followed Civin's lead when it developed the 12-8 antibody. If the Hopkins patent had a somewhat narrower scope—for example, if Hopkins had to demonstrate and describe more than one CD34 epitope before it could claim them all—the 12-8 antibody might not have been seen to infringe (or Hopkins would have had to develop an antibody to the different epitope recognized by 12-8 before claiming it). The scope of the Hopkins patents, particularly the antibody patent, was broad. Should it have been broad enough to claim all antibodies to the CD34 antigen discovered in the future? Civin never discovered a second antibody, and yet a different team in a different place found one that bound to a different molecular site. Should the first discovery have been able to block the use of the second? This is standard in patent law, but it was not necessarily true for this case, nor will it be for analogous situations linked to gene-based patents. It was not contested in the CellPro litigation, but it could have been. The story was about a "winner take all" victory in the patent stakes. Hopkins certainly had a powerful argument that the Hutch group benefited from Civin's work. But should that assistance for one component of

the technology have been sufficient to destroy the entire company and monopolize the market for cell separation instruments as a whole? This case thus raises questions about patent scope. But even more than that, it raises questions about licensing practices.

When the NIH decided not to march in, it leaned heavily on the argument that Baxter had licensed the Hopkins patents to two other firms. The NIH contended that it was basically CellPro's error in walking away from the licensing terms offered to it. Neither of Baxter's other licensees ever got a product to market, and even Nexell (40 percent owned by Baxter and presumably given favorable terms) apparently had difficulty making the instrument profitable. The situation in this case was complicated by the growing competition between the prospective licensor and licensee. By the time CellPro renewed its effort to license the Civin patents, it was ahead of Baxter, so Baxter had a clear incentive to use the patent to slow down CellPro, in a way that it did not with its other sublicensees. Was CellPro wrong to reject the terms it was offered?

In retrospect, it was. Merges has pointed out many options for firms to enable cumulative innovation despite patent thickets (Merges 1996). Suzanne Scotchmer and her coauthors looked at whether cooperative research and development agreements between firms might be able to resolve such problems that arise when licensing patents have been issued (Green and Scotchmer 1995; O'Donoghue, Scotchmer, and Thisse 1998; Scotchmer 1991, 1999). The CellPro case illustrates how the uncertainties of patent scope and technological development at the time that licensing decisions are actually made can cause serious problems in the real world for real companies, regardless of the theoretical options. The fact that many biotechnology products have gone all the way through patent litigation shows that disputes are common (see Eisenberg 1997 and 1999 for a list of cases, including tissue plasminogen activator, insulin, growth hormone, and erythropoietin). The abundance of conflict suggests that uncertainties about licensing make the theoretical benefits of early licensing hard to translate into actual practice. Scotchmer is surely right that "patent policy is a very blunt instrument trying to solve a very delicate problem" (Scotchmer 1991, 40). It is, nonetheless, an instrument that can destroy companies, and CellPro may not be the last to be ruined by patent infringement that could, in theory, be avoided by earlier licensing.

The details of the licensing agreements are difficult to assess. While Johns Hopkins posted on its Web site dozens of documents pertinent to the CellPro case, what it did not make public is much more

significant: the licensing agreement between Johns Hopkins and Becton-Dickinson and its various sublicenses. Hopkins is not alone in keeping its business deals secret. Bayh-Dole provided few tools for policymakers to determine whether making the licensing agreement public really made a difference, because little information is reported back. The act's only provisions regarding public access to information are to authorize agencies to *withhold* data to protect the confidentiality of proprietary information.[14] Contractors and grantees are free to be more open, but few are, and without incentives to the contrary, have little interest in being so. Stanford University openly prosecuted the Cohen-Boyer patents (on recombinant DNA), and its licensing terms were highly public, but that laudable norm of openness has long since disappeared. Since the early 1980s, the trend has been toward secrecy in university licensing. This is not necessarily driven by deliberate policy but is the natural result of strong incentives to protect proprietary data in the absence of any countervailing incentives for transparency.

Hopkins did post a document entitled "Litigation Surrounding Stem Cell Selection—Myth versus Reality." Two of those "myths" bear an uncanny resemblance to what actually happened: the shutdown of CellPro clinical trials and Baxter's monopoly of cell separation instruments. In light of history, a third "myth" also seems arguable—that Baxter's royalty demands were too high. Perhaps most disturbing was the vigorous defense of the university's "rights" and the assertion that CellPro's challenge to them had technology policy tottering on the brink of destruction. The Hopkins press release was entitled "Risk to Technology Transfer Averted" and claimed that a march-in "could have ended two decades of spectacular success" in technology transfer (Johns Hopkins University 1997). It asked rhetorically, "How fragile are the new relationships between business and academia?" Even though press releases should not be held to a scholarly standard of accuracy, this one strayed particularly far afield. The Bayh-Dole statute does give universities rights, but these are contingent and could be changed by Congress, and arguably should be if and when their exercise reduces the net social benefit. Hopkins's position appears most consistent with the simple theory that the public benefit would have been optimized by Hopkins's maximizing its financial return and then aligning its interests with its licensees and sublicensees. Hopkins would have been far more credible if it had made arguments, marshaled

[14] 35 USC 205.

facts, and made public the nature of its agreements rather than merely asserting that any threat to its exclusive licensing rights was tantamount to a direct threat to academic-industrial relations in biotechnology. Johns Hopkins University was not alone; many other universities wrote letters supporting its position. This fidelity to a simplistic notion of technology transfer and the rhetoric conveying it are worrisome. Major research universities with significant patent portfolios should examine how they license their intellectual property as a public trust and ensure that their business interests do not take precedence over their academic values (R.R. Nelson, personal communication, January 2002).

Johns Hopkins University and Baxter and Becton-Dickinson certainly benefited from the Civin patents, but it does not follow that the world did as well (although it is also not clear that it did not). Even if the Civin patents were necessary to induce investment from Baxter to develop the Isolex instrument, they also killed CellPro and negated all the investments made in it. This is not a case of a federally funded invention that would have languished in Hopkins's laboratories without the Civin patent incentive. Investors were willing to finance the research and development necessary to get an instrument through the FDA's approval at CellPro without a patent on the 12-8 antibody. The case is clear: with no Civin patents, the instrument would still have been on the market. That said, this case does not fundamentally challenge the Bayh-Dole framework of patent rights. After all, CellPro licensed the avidin-biotin separation patents from the Hutch under Bayh-Dole and touted the value of its proprietary technology to investors. The Civin patents were not necessary to get the product to market, but we cannot generalize this to say that *no* patents on federally funded inventions were needed to induce private investment. Assessing net social benefit is not easy for either side in this case. The conclusion is not that Bayh-Dole is wrong or right, but it does show that at least one component "invention" in cell separation devices—the antibodies used to label cells—did not need to be patented in order to be used in clinical practice. It thus provides a counterexample of the pervasive ideology that patents are inherently innovative. It shows that assessing the social benefits of Bayh-Dole will be complicated. The benefits of Bayh-Dole can be captured, at least in part, by the AUTM survey and other evidence. CellPro is a cautionary tale that there is also a dark side of patenting that needs to be assessed and that is not revealed in the current data. And without the tools for gathering more information about patent-licensing practices, they never will be.

A letter written by the attorney hired by Hopkins and Baxter to litigate the case raises other questions about academic values. Donald Ware sent a threatening letter to Murdock's publisher on the eve of his book's publication. The letter claims that the story is about "the technology invented at Johns Hopkins" (Ware 2000), a point with which Murdock understandably disagrees. Such bullying letters are common among business foes, but if they start to govern academic institutions, then academic values will begin competing with university business interests.

The main question that our story raises about the role of universities is whether they have responsibilities beyond pure commercialization for inventions arising from federally funded research. The Bayh-Dole Act clearly recognized that at times the public health might not be best served in the way a patent is licensed. Otherwise, it would not have included the "public health" march-in criterion. But the CellPro case makes clear that march-in rights are unlikely *ever* to be exercised (see the following discussion for additional reasons). Students at universities holding patents relevant to AIDS treatments have begun to raise questions about the licenses their universities have signed,[15] and the CellPro case could have raised similar questions about whether Hopkins's business interests coincided with the public interest and, if not, whether the university had any responsibility to influence the conduct of its sublicensee, Baxter. Students and faculty at academic research institutions, and donors who contribute to them, may view some university behavior in pursuit of technology licensing as conflicting with academic norms. If so, patent licensing terms may become yet another item for university presidents to worry about, and technology licensing offices may need to consult with, or at least consider more carefully, the academic norms of their institutions, in addition to the revenue they generate and the business interests of their licensees.

[15] Student and public interest groups have begun to pressure their administrations to take account of the public health impacts of university licensing practices and to call attention to the need for fair access to technologies developed with government funding (http://www.cptech.org/ip/health/aids/gov-role.html). Universities involved include Yale, the University of Michigan, and the University of Minnesota. The Yale AIDS Network is perhaps the most prominent. It was formed in the spring of 2001 "as an outgrowth of student and faculty pressure upon Yale to respond to the need for cheaper HIV/AIDS treatment in South Africa by relaxing the University's patent on the antiretroviral drug d4t there."). See http://www.cptech.org/ip/health/fund/yalePR05192001.html.

The secrecy currently surrounding licensing transactions at academic research centers seems likely to come under fire, as well it should. In our view, when the research underlying intellectual property involves public funds, the terms of the licensing should be made public. This will cause discomfort for technology-licensing offices, and in some cases, making the terms public may undermine the desired commercialization. We believe, however, that the presumption should be in favor of openness and that in any event, the Bayh-Dole statute should be amended to ensure accountability and feedback on how inventions arising in federally funded research are licensed. If not all the data are made public, they should at least be available to federal agencies for analysis and be subject to congressional oversight. There are, moreover, precedents for openness in academic patenting and licensing. The open licensing of the Cohen-Boyer patents did not prevent Stanford and the University of California from sharing between $200 million and $300 million derived from the use of this seminal patent (National Research Council 1997). The Cohen-Boyer patent predated the Bayh-Dole Act, but how Stanford and the University of California licensed it was very much in the original spirit of Bayh-Dole, ensuring that research using tools developed from federally funded research could be applied freely in academia while also producing revenues from commercial products and services. But nothing would have stopped the universities from choosing to exclusively license the technology, and if they had, and particularly if they had forced other academic institutions to abide by an exclusive license to a single firm (which would have been legal), it could have seriously slowed science and the development of biotechnology.

Some Lessons and Observations

Summary of the Consequences

A monopoly position is often what patents produce in therapeutics, so the CellPro case is neither unprecedented nor surprising. Exclusive licensing is intended to produce a limited monopoly. Every major research-intensive drug company vigorously defends its patent rights, and none hesitates to kill any competition that threatens its markets, even when those business decisions raise prices and limit public access. It is the nature of the business.

The fact that the CellPro case has ample precedent in other areas of therapeutics does not, however, imply that national policy has struck the right balance between patent rights, on one hand, and public access and price, on the other. That the system works does not prove that it is near an optimum. The patent system is filled with arbitrary rules, such as the patent term, and arcane but important practices, such as the broad scope given to "pioneer" patents. The wealth of public rhetoric justifying the patent system as essential—while very likely true—is ironic given the dearth of empirical analysis that policymakers need to assess its costs and benefits. Without solid information, the attacks on and defenses of current patenting and licensing practices will remain strong on rhetoric and weak on evidence.

The patent system is a rough proxy for measuring the public's willingness to pay for innovation. Our own view is that the patent system is fundamentally sound but that the details of the current practice are frustratingly opaque and vigorously guarded by vested interests, with little independent scholarship to guide policy. This article is in part an effort to show how big and complicated the questions are and how important it is to address them.

In the end, the rise and demise of CellPro is a *Rashomon* story (Kurosawa 1950), with "where you stand depending on where you sit." One view is that it is shameful that a large multinational company used a discovery made in part with federal funds to crush a small start-up company developing a life-saving instrument, on the basis of patents for just one of many component elements. The end result has been higher prices and fewer incentives for quality innovation (because the competing technology is licensed now to the sole manufacturer). How can that be in the public interest?

It can be in the public interest if such events in the system as a whole are balanced by the value of other products and services produced with investments that would not be possible without patents or a Bayh-Dole framework. From this perspective, the CellPro case illustrates the power, and indeed the value, of the patent system. In Judge McKelvie's view, the law prevented the investors from circumventing a patent to take a free ride. The investors used a standard method to raise an antibody against the same cell line that Civin did, but they failed to acknowledge the value of his invention by getting a license. Baxter's success in destroying CellPro is an incentive for companies to license valuable patents and develop the resulting inventions, as well as an object lesson for those who

ignore the patent law. The marginal gain in Baxter's profits justifies future investments in research and development. It ensures that companies of all sizes will continue to invest in developing products because they know there will be financial rewards for doing so. The system depends on letting patents do their work and being able to translate a win in the patent game into a win in the marketplace.

Lessons for Start-Ups Similar to CellPro

Perhaps the most important lesson for start-ups is not really new: infringe patents at your peril. We cannot know whether Judge McKelvie correctly concluded that CellPro's board decided deliberately to infringe a patent, because they believed it was not valid, they could work around it, they could later get a license when their business position was stronger, or they could afford to lose a lawsuit and still have a viable business. This story demonstrates that patents are extremely powerful, even if they apply to only one component of a complex technology. If that is the message, a corollary message is just as clear: patents are not an unalloyed good—they carry a real risk if questions about patents covering one component of a technology can kill an entire business. The message is not to develop drugs, devices, or other products and services for which there is any question of infringement, especially if the patent licensee has deep pockets, regardless of whether or not you can beat them to market or produce a superior product.

Lessons for the Patent Office

This story's main question for the U.S. Patent and Trademark Office is the proper scope of patent claims. Scholars of patent law point out how important scope can be, especially of technologies that depend on cumulative innovation (Green and Scotchmer 1995; Merges and Nelson 1990; O'Donoghue, Scotchmer, and Thisse 1998; Scotchmer 1991, 1999). It is well known and widely accepted that "pioneer" patents are given broad scope, in effect making them more valuable by ensuring that making subsequent inventions will license the dominant patent. But when the invention is just one component needed to make a final product or process, when the invention is mainly a research tool, or when for other reasons there are apt to be many subsequent dependent inventions, then there is an opportunity for real mischief. Heller and Eisenberg raised

the prospect of an "anticommons" when it becomes difficult to accumulate sufficient intellectual property to develop products and services (Heller and Eisenberg 1998). Walsh and colleagues examined whether the patenting of research tools is becoming a problem (Walsh, Arora, and Cohen 2000). They found no firm evidence that it has become a problem but expressed concern that it could be in the future, based in part on reported pervasive de facto infringement. Current practice embodies a potentially fragile set of "gentlemen's agreements" not to enforce patents when doing so would cause public relations problems or a backlash from researchers whose work could be valuable to patent holders.

The CellPro case is not an obvious instance of the anticommons problem, however—or if it is, it is a very simple one. It involved a relatively small set of patents and only two universities and two principal firms, compared with future inventions that may draw on dozens or even hundreds of life science patents owned by a larger group of more disparate players. If CellPro could be ruined because of one patent, what will be the outcome in these more complex cases? Permitting broad claims may be an accepted norm in patents, but in biology that norm may warrant renewed attention and monitoring. The impact of a patent's broad patent on biological technologies could be greater than it has been in other areas—and experiences with aircraft engines, automobile manufacture, and radio broadcast demonstrate that patent logjams can sometimes impede rather than promote innovation (Cowan 1996; Merges and Nelson 1990).

Lessons for the NIH

Barbara McGarey, the NIH official most involved in the march-in proceedings, wrote an article about CellPro (McGarey and Levey 1999). Several of her observations are worth recounting. First, she notes the NIH's understandable reluctance to enter a business dispute, to intrude in a "market," implicitly invoking the invisible hand of Adam Smith. The "market" in pharmaceuticals and biotechnology, however, is not remotely like what Adam Smith was referring to. Rather, this market is strongly influenced by government action, and as intervenors in this "market," the NIH would have to stand in line behind many other federal agencies: the FDA, the Patent Office, the Securities and Exchange Commission, the courts, and the Centers for Medicaid and Medicare Services (which, along with the Department of Veterans Affairs and the

military health system, make the U.S. federal government the world's largest purchaser of drugs and devices). There is no way that the government could avoid interfering. CellPro's survival was in the NIH's hands, whether it wanted it there or not. The NIH cannot escape responsibility for the consequences. It is intervening when it offers grants that result in valuable technology, and it is responsible for overseeing the impact of those actions, including how the resulting inventions are used. The argument that NIH should not intervene in the market defeats the purpose of patenting, which is a government-enforced exclusionary right: patents are inherently anticompetitive and premised on government intrusion into the market. It remains an open question, however, whether NIH has the appropriate tools to carry out such oversight. The Bayh-Dole march-in provisions appear to be poorly suited to their task, and even if they could be used, it is not clear that the NIH currently has the business acumen needed to intervene effectively—that is, to make informed business predictions (Richards 1999).

McGarey argues persuasively that the NIH had little reason to intervene given the terms of the court settlement. Baxter agreed to ensure the continued availability of CellPro's instrument until Baxter's Isolex received the FDA's approval. Although CellPro argued that killing it would block access to a valuable technology, the company died, and cell separation instruments remained on the market. McGarey also persuasively contended that a march-in by the NIH would amount to second-guessing the court-mandated licensing terms. The Bayh-Dole statute does not state explicitly that high prices or monopoly status should be avoided (although some recent commentary on Bayh-Dole does suggest that its drafters intended that drug prices be one of the triggers for a march-in) (Arno and Davis 2001). In the future, the NIH may confront few cases whose health consequences are much more clear-cut, in which one company has a product on the market and the other does not, and the product is part of a life-saving cancer therapy (and has a CEO whose survival depended on its success). McGarey makes the case that CellPro wanted intervention for an indication not approved by the FDA (use in both cell depletion as well as its approved indication for stem cell enrichment), but her argument is weak, particularly in regard to cancer therapy, in which half the uses of approved drugs are for unapproved indications. The NIH's argument regarding the uncertainty of the instrument's utility also is weak, since Ceprate's ability to reduce the toxicity of bone marrow transplant symptoms was a major

consideration and sufficient for the FDA's approval. But Baxter's assurance that it would continue to make the CellPro instrument available until its own instrument had been approved by the FDA made the NIH's decision seem reasonable. Indeed, it is hard to see how it could have decided otherwise.

The most interesting part of McGarey's article is her analysis of the flaws in Bayh-Dole's march-in mechanism. March-ins will almost surely always involve a nasty dispute: why else would there be a petition to intervene? Court action will often be pending during march-in proceedings, just as it was in this case. The agency contemplating a march-in will therefore often be called in while the judiciary is already actively engaged with the same parties or after the courts have made their decisions, in which case executive action would matter only if it reversed court decisions (otherwise it would be moot). The procedures stipulated in Bayh-Dole also have a built-in asymmetry that discourages march-ins. If an agency decides not to march in, the case is over. If it does decide to march in, the party whose patent is subject to compulsory licensing can contest the decision, which compels the agency to defend its action against a party with a strong financial stake.

McGarey also implies the limitations of a science agency trying to make business judgments. The NIH is poorly positioned to make market judgments, and her article makes explicit its anxiety about intervening, in the NIH's formal response to the march-in petition, in its press statements, and in the NIH director Harold Varmus's statements to the press. The NIH conducts and funds science, but it has little information about licensing terms other than those for inventions from the NIH's laboratories. In this case, the NIH did not have the data that would have enabled it to judge the likelihood that the competing Baxter instrument would obtain market approval. Those (proprietary) data were at the FDA, which therefore would have been better able to make the call. This problem might be solved if executive branch agencies agreed to share their analytical capacity or proprietary data (clearly permitted under Bayh-Dole, whose confidentiality provisions refer to sharing data only "outside government"), but doing that would require further reflection. It did not happen in this case.

This limited capacity for business analysis applies also to the National Science Foundation, the Department of Energy, the Environmental Protection Agency, and other "science" agencies with the most at stake under

Bayh-Dole. The Department of Defense is arguably better able to analyze the markets in which it purchases weapons and has done so in radio broadcast, nuclear technologies, aircraft engine manufacture, and other areas.

McGarey also makes the telling point that under 28 USC 1498, the federal government already has the authority to use a patented invention without a license. McGarey believes that the only real value of the march-in authority is as a threat to force grantee and contractor institutions (or their licensees) to alter course. But this is not a very credible threat and seems even less so after reading her article. One unanswered question in the CellPro case is why the threat of a march-in was not used in this case. McGarey does not discuss whether NIH ever threatened Hopkins with a march-in to force a settlement. If the NIH was reluctant to intrude into the market, its failure to coerce the parties to reach an agreement—an authority it does have—meant that the courts, not the market, had to decide CellPro's fate. A more "market- based" solution would have been to allow CellPro and Baxter to compete in selling rival products, on the terms that Baxter had offered to other companies (with some penalty for infringement to date) under an agreement reached by the companies—under the threat of a court-imposed settlement (against CellPro) and a march-in (against Baxter). Such a threat might have forced the parties to a settlement that permitted CellPro's survival but also a license (and fees) for Baxter. Why the NIH did not use a march-in threat is not explicit in McGarey's article or the NIH documents. Was it because of timing relative to the court cases? Was it tried and failed? Was it the threat of march-in that induced Baxter to allow CellPro to remain on the market until Baxter's cell separation instrument were FDA-approved and to purchase 800 CellPro machines so that clinical trials could continue? Or was the threat never raised because the NIH decided that the facts of the case did not merit it?

Options for Congress in Considering Revision of the Bayh-Dole Statute

The Bayh-Dole statute could be amended in at least four ways that are under discussion: (1) to change or eliminate the march-in provision, (2) to create a research exemption from patent infringement, (3) to permit petition for reexamination of patents, and (4) to increase the transparency of how patent rights arising from federally funded research and

development are licensed and used. McGarey's analysis points to at least one serious flaw in the Bayh-Dole statute: the cumbersome and asymmetric march-in mechanism that seems to render it useless, except as its use by the Department of Defense and as a threat to hold over the heads of patent owners and licensees. Her analysis would logically lead to the conclusion that the march-in process should be altered so that it can actually work, given the business conflicts in which it is likely to be invoked. McGarey does not specify in detail how to fix the march-in provision. Agencies could provide guidance on interpreting the criteria for march-in, although the courts might or might not enforce such "soft" regulation. Congress could specify in more detail the criteria for invoking a march-in to guide agency action. Or if the United States adopted a process for opposing patents, march-ins might become less important because a patent's validity could be challenged soon after it was issued. Rai and Eisenberg suggested another way to reform the Bayh-Dole Act: giving the funding agencies more power to decide when patents are not the best way to translate federally funded research into practical applications (Rai and Eisenberg 2001). This would have the advantage of intervening early in the process (thus reducing both cost and uncertainty) but would require legislation. That remedy would not apply to a case like CellPro, however. March-ins could also be removed from the Bayh-Dole Act, in essence acknowledging that they are unlikely ever to be exercised in their current form. This, however, would eliminate the threat, however weak, that agencies could use to alter the behavior of their grantees, contractors, and licensees of Bayh-Dole patents.

Congress could also exempt research performed by federal grantees and contractors from infringement of patents derived from federally funded research. This would reduce the problem of patent rights' encumbering research tools, because federal grantees and contractors could use research tools derived from earlier federally funded research. But a research exemption would also dampen private incentives to develop inventions for research markets, including instruments, reagents, and other products and services for which academic research institutions constitute a sizable fraction of the market. CellPro is a case in point. If the exemption were extended to all federal grantees and contractors doing "research," it would surely cover academic health centers. Most bone marrow transplantation was (and is) conducted at major research universities, because it uses the infrastructure at major research centers. Would either CellPro or Baxter have had a market under such a research exemption?

The answer is likely to be a qualified yes, but a broad research exemption would weaken incentives to develop some technologies.

Congress could also consider a step that would apply not just to patents under Bayh-Dole but to all patents. In Europe, private parties can formally oppose a patent that they believe has been erroneously issued. They can challenge a patent in "opposition" for nine months after it is published. Although the United States has a patent reexamination process, those challenging a patent are not directly involved in the process, which takes place between the U.S. Patent and Trademark Office and the patent holder. The European and Japanese systems of patent opposition allow competitors directly to oppose a patent before litigation begins.[16] For patents with broad scope, this may be one way to reduce uncertainty about patent validity earlier and at less cost. Robert Merges argues for moving closer to the European opposition system instead of the current U.S. reexamination process (Merges 1999). An empirical study comparing experiences with U.S. reexamination and European opposition outcomes, which includes biotechnology-relevant patents, is under way (Graham et al. 2002; Hall 2001). Its results will be a welcome addition to the debate about this policy option.

The final problem is transparency. When we tried to gather information about university licensing practices while we were working on this article, we discovered that university licensing offices generally do not share licensing agreements. Aside from some informal exchange of approaches at meetings of university technology managers and licensing executives, there is no public database of "benchmark" rates, and potential licensees report widely disparate practices regarding royalty rates, due diligence clauses, nondisclosure agreements, and other terms. We do not necessarily believe that unfettered openness is necessary, desirable, or even possible, but we do believe that this is one place where the current "policy" has become nondisclosure—that is, pervasive secrecy—and there are strong arguments for at least a partial disclosure of licensing practices in aggregate (and sometimes of individual agreements). At the least, this is an area for legitimate government oversight, by both the executive branch and Congress, so that agencies and congressional overseers have more data to work with, even if the records are not entirely

[16]It is worth noting that patent holders appear to initiate almost one-third of "opposition" proceedings, generally to add or expand claims after a patent has been issued. An opposition system can thus benefit patent holders as well as competitors or other parties.

public. We further believe that the consequences of secrecy should be openly discussed with university technology licensing offices, firms that license from them, academic leaders (including university presidents), and the public, whose dollars fund the science giving rise to most of the intellectual property being licensed.

A 1994 report noted many deficiencies in the NIH's capacity for monitoring patents resulting from NIH funding (DHHS 1994a). According to another report on patents at the Scripps Research Institute, 51 of its 125 patents from the period in question were developed with NIH funds and included the required disclosure of government rights in its patents. After its review, Scripps amended its patents to give Bayh-Dole rights to the government on 43 of the remaining 74 patents, and the NIH believed that an additional 11 had been developed with federal funds (DHHS 1994b). In 1995, the NIH began using its new Edison database to monitor invention disclosures and patents. Since then, the General Accounting Office (GAO) and the DHHS inspector general have found that the NIH and other funding agencies still are not notified of many patents developed with federal dollars, which by law are supposed to be reported. The GAO found that many inventions were not reported to agencies, and the DHHS inspector general found specifically that 143 of 633 inventions judged to have resulted from NIH grants had not been reported, and grantee institutions agreed with that judgment about 79 of those (and disagreed about the other 64) (U.S. Congress 1999). If agencies do not know about patents, they certainly cannot monitor their licensing. And if agencies are in the dark, then policymakers will know even less. While we are confident that the Bayh-Dole Act is, on balance, an improvement over previous policy, we are far less confident that any problems in patenting and licensing will be discovered and analyzed, given the inadequacy of the current data and the absence of empirical study. In our view, the absence of provisions to enable useful feedback is a serious weakness of the 1980 Bayh-Dole Act and its amendments.

Patents are an important element in the innovation system, particularly in medicine. How patents are managed can foster or hinder innovation and can expand or restrict access to the fruits of federally funded biomedical research. The Bayh-Dole statute increased the number of academic patents and licenses, its intended effect. It also has second-order effects, however, which have received less attention, because information about licensing is not publicly available and few scholars have studied it. Congress is contemplating changes in the Bayh-Dole statute to create

explicit research exemptions and to increase the transparency of licensing, and Congress may also need to address the awkward mechanism for exercising the government's march-in rights if it ever expects those rights to be used.

References

Abate, T. 2001. The Birth of Biotech—How the Germ of an Idea Became the Genius of Genentech. *San Francisco Chronicle* (April 1). Available at http://www.sfgate.com (accessed April 2, 2001).

Andrews, R.G., J.W. Singer, and I.D. Bernstein. 1986. Monoclonal Antibody 12-8 Recognizes a 115-kd Molecule Present on Both Unipotent and Multipotent Hematopoietic Colony-Forming Cells and Their Precursors. *Blood* 67:842–5.

Arno, P.S., and M.H. Davis. 2001. Why Don't We Enforce Existing Drug Price Controls? The Unrecognized and Unenforced Reasonable Pricing Requirements Imposed upon Patents Deriving in Whole or in Part from Federally-Funded Research. *Tulane Law Review* 75:631–94.

Arno, P.S., and M.H. Davis. 2002. Paying Twice for the Same Drugs. *Washington Post* (March 27):A21.

Association of University Technology Managers (AUTM). 2000. *AUTM Licensing Survey, Fiscal Year 1999 Survey Summary*. Boston. Available at http://www.autm.net/surveys/99/survey99A.pdf (accessed August 28, 2002).

Baxter Healthcare. 1997. VIMRx and Baxter Sign Letter of Intent to Form New Cell Therapies Business. Press release (June 12). Available at http://www.baxter.com/utilities/news/releases/1997/06-12VIMRX.html (accessed February 8, 2002).

Bayh, B., and B. Dole. 2002. Our Law Helps Patients Get New Drugs Sooner. *Washington Post* (April 11):A28.

Beason, T. 1998. Suit-Ravaged CellPro Declares Bankruptcy. *Seattle Times* (September 29):C1.

Bloomberg, C. 1990. Re: Civin U.S. Patent No. 4,714,680. Letter to Christopher Porter, CellPro (February 27).

Bloomberg, C. 1991. Re: Civin U.S. Patent No. 4,965,204. Letter to Christopher Porter, CellPro (April 15).

Cockburn, I., and R. Henderson. 1996. Public-Private Interaction in Pharmaceutical Research. *Proceedings of the National Academy of Sciences* 93:12725–30.

Cockburn, I., and R. Henderson. 2000. Publicly Funded Science and the Productivity of the Pharmaceutical Industry. Paper

prepared for the National Bureau of Economic Research Conference on Science and Public Policy, April. March 2000 draft available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=226428 (accessed July 7, 2002).

Cowan, R.S. 1996. *A Social History of American Technology*. New York: Oxford University Press.

Cutler, L.N., and B. Bayh. 1997. Letter to former DHHS Secretary Donna Shalala requesting that the department issue a license to CellPro on the Hopkins patents (March 3).

Eisenberg, R.S. 1996. Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research. *Virginia Law Review* 82:1663–1727.

Eisenberg, R.S. 1997. Structure and Function in Gene Patenting. *Nature Genetics* 15:125–30.

Eisenberg, R.S. 1999. Intellectual Property Issues in Genomics. *Trends in Biotechnology* 14:302–7.

Gambardella, A. 1995. *Science and Innovation: The U.S. Pharmaceutical Industry during the 1980s*. Cambridge: Cambridge University Press.

Graham, S.J.H., B.H. Hall, D. Harhoff, and D.C. Mowery. 2002. Post-Issue Patent "Quality Control": A Comparative Study of US Patent Re-examinations and European Patent Oppositions. Unpublished manuscript. Available at http://www7.nationalacademies.org/step/Hall_et_al_paper.pdf (accessed October 8, 2002).

Green, J.R., and S. Scotchmer. 1995. On the Division of Profit in Sequential Innovation. *Rand Journal of Economics* 26:20–33.

Hall, B.H. 2001. The Global Nature of Intellectual Property: Discussion. Toronto Intellectual Property Conference, May. Available at http://emlab.berkeley.edu/users/bhhall/bhhdisc_toronto501.pdf (accessed August 1, 2002).

Heller, M.A., and R.S. Eisenberg. 1998. Can Patents Deter Innovation: The Anticommons in Biomedical Research. *Science* 280:698–701.

Henderson, R., A.B. Jaffe, and M. Trajtenberg. 1998. Universities as a Source of Commercial Technology: A Detailed Study of University Patenting 1965–1988. *Review of Economics and Statistics* 80:119–27.

Johns Hopkins University. 1997. Threat to Technology Transfer Averted. Press release (August 25). Available at http://www.hopkinsmedicine.org/press/1997/AUGUST/970805.HTM (accessed August 6, 2002).

Johns Hopkins University. 2001. Johns Hopkins Medicine. Intellectual Property Guidelines. Policy adopted October 13, 1983, and modified June 8, 1992, October 27, 1992, and April 2, 2001 by the Board of Trustees. Available at http://www.hopkinsmedicine.org/lbd/IPG/som_intpol.html (accessed August 26, 2002).

Koeffler, H.P., and D.W. Golde. 1978. Acute Myelogenous Leukemia: A Human Cell Line Responsive to Colony-Stimulating Activity. *Science* 200:1153–4.

Kurosawa, A. (director). 1950. *Rashomon*. New Line Entertainment. A Japanese film in which key events occur in the same order, but four different witnesses describe disparate accounts of a rape and murder, Moral responsibility and blame shift with each telling of the story. Based on an ancient Japanese folktale.

Mansfield, E. 1991. Academic Research and Industrial Innovation. *Research Policy* 20:1–12.

Mansfield, E. 1995. Academic Research Underlying Industrial Innovations: Sources, Characteristics, and Financing. *Review of Economics and Statistics* 77:55–65.

Marsh, B. 1998. VIMRx Pharmaceuticals' Irvine Unit to Buy out Rival That Violated Patents. *Los Angeles Times* (September 29): D12.

Marshall, E. 1997. Courts Take a Narrow View of UC's Claim. *Science* 277:1029.

McGarey, B.M., and A.C. Levey. 1999. Patents, Products, and Public Health: An Analysis of the CellPro March-in Petition. *Berkeley Technology Law Journal* 14:1095–116. Available at http://www.law.berkeley.edu/journals/btlj/articles/14_3/McGarey/html/reader.html (accessed August 31, 2002).

Merges, R.P. 1996. Contracting into Liability Rules: Intellectual Property Rights and Collective Rights Organizations. *California Law Review* 84:1293–390. Available at http://www.law.berkeley.edu/institutes/bclt/pubs/merges/contract.htm (accessed June 27, 2001).

Merges, R.P. 1999. As Many as Six Impossible Patents before Breakfast: Property Rights for Business Concepts and Patent System Reform. *Boalt High Technology Law Journal* 14:577–615. Available at http://www.law.berkeley.edu/journals/btlj/articles/14_2/Merges/html/text.html (accessed August 5, 2002).

Merges, R.P., and R.R. Nelson. 1990. On the Complex Economics of Patent Scope. *Columbia Law Review* 90:839–916.

Mowery, D.C., R.R. Nelson, B.N. Sampat, and A.A. Ziedonis. 2001. The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980. *Research Policy* 30:99–119.

Murdock, R., and D. Fisher. 2000. *Patient Number One*. New York: Crown.

Narin, F., K. Hamilton, and D. Olivastro. 1997. The Increasing Linkage between U.S. Technology and Public Science. *Research Policy* 26:317–30.

Narin, F., and D. Olivastro. 1992. Status Report–Linkage between Technology and Science. *Research Policy* 21:237–49.

Narin, F., and R.P. Rozek. 1988. Bibliometric Analysis of U.S. Pharmaceutical Industry Research Performance. *Research Policy* 17:139–54.

National Academy of Engineering. 1992. *Time Horizons and Technology Investments*. Washington, D.C.: National Academy Press.

National Research Council. 1997. *Intellectual Property Rights and Research Tools in Molecular Biology*. Washington, D.C.: National Academy Press.

Nexell Therapeutics, Inc. 2001a. The Contents of This Bag Will Change Medicine: 2000 Nexell Therapeutics Annual Report. Available at http://www.nexell.com/IR/pdf/2000Annual.pdf (accessed February 8, 2002).

Nexell Therapeutics, Inc. 2001b. Nexell Therapeutics to Focus Exclusively on Development of Advanced Cell Therapies. Press release (June 12). Available at http://www.nexellinc.com/IR/2001 Press/2001JUN12.htm (accessed February 8, 2002).

Nexell Therapeutics, Inc. 2002. Nexell Therapeutics Announces Plan of Liquidation and Dissolution. Press release (Oct. 17). Available at http://biz.yahoo.com/bw/021017/170070_1.html (accessed October 18, 2002).

O'Donoghue, T., S. Scotchmer, and J-F. Thisse. 1998. Patent Breadth, Patent Life, and the Pace of Technological Progress. *Journal of Economics and Management Strategy* 7:1–32.

Pressman, L., ed. 2002. *AUTM Licensing Survey: FY2000*. Northbrook, Ill.: Association of University Technology Managers, Inc. Summary available online at http://www.autm.net/surveys/2000/summary-noe.pdf (accessed August 28, 2002).

Rai, A.K., and R.S. Eisenberg. 2001. The Public and the Private in Biopharmaceutical Research. Paper prepared for a conference on the public domain, Duke University, November 10. Available at: http://www.law.duke.edu/pd/papers/raieisen.pdf (accessed August 6, 2002).

Richards, B. 1999. Cancer Fighters: How a Corporate Feud Doomed Human Trials of Promising Therapy. *Wall Street Journal* (August 6):A1 ff.

Scotchmer, S. 1991. Standing on the Shoulders of Giants: Cumulative Research and the Patent Law. *Journal of Economic Perspectives* 5:29–41.

Scotchmer, S. 1999. Cumulative Innovation in Theory and Practice. GSPP Working Paper 140 (February) (under revision for *Journal of Economic Literature*). Available at http://socrates.berkeley.edu/~scotch/cum-r&d.pdf (accessed July 11, 2002).

Siegel, J.P. 1996. Premarket approval letter #BP94-0001 to Monica Krieger of CellPro (December 6). Available at http://www.fda.gov/cber/PMAltr/P940001L.htm (accessed March 28, 2001).

Slind-Flor, V. 1997. Del. Judge on IP's Frontline. *National Law Journal* (September 15):A1ff. Available at http://www.jlx.com/patents/0915ipjudge.html (accessed March 28, 2001).

U.S. Congress, General Accounting Office. 1999. Technology Transfer: Reporting Requirements for Federally Sponsored Inventions Need Revision. GAO/RCED-99-242 (August).

U.S. Department of Health and Human Services (DHHS), Office of the Inspector General. 1994a. NIH Oversight of Extramural Research Inventions. OEI-03-91-00930 (May).

U.S. Department of Health and Human Services (DHHS), Office of the Inspector General. 1994b. Underreporting Federal Involvement in New Technologies Developed at the Scripps Research Institute. A-15-93-00029 (June).

Varmus, H. 1997. Determination in the Case of Petition of CellPro, Inc. (August 1). Available at http://www.nih.gov/news/pr/aug97/nihb-01.htm (accessed May 31, 2001).

Walsh, J.P., A. Arora, and W.P. Cohen. 2000 (October). The Patenting of Research Tools and Biomedical Innovation. Paper prepared for the Science, Technology and Economic Policy Board, National Academy of Sciences. Preliminary discussion draft available at http://www7.nationalacademies.org/step/Walsh_et_al_paper.pdf (accessed August 28, 2002).

Ware, D.R. 2000. Letter to Crown Publishers on Behalf of Johns Hopkins University, Becton Dickinson and Company, and Baxter Healthcare Company. In *Patient Number One*. New York: Crown.

Acknowledgments: Dr. Cook-Deegan was supported in part by a Robert Wood Johnson Foundation Investigator Award in Health Policy Research, through the Kennedy Institute of Ethics, Georgetown University, where he benefited from the advice of LeRoy Walters and Stephen McCormack. The authors thank the National Cancer Policy Board and its staff, for whom an earlier draft of this paper was prepared. We also thank the reviewers, and in particular Arti Rai and Rebecca Eisenberg, who not only commented but engaged in an ongoing dialogue to improve the analysis.

Address correspondence to: Robert Cook-Deegan, Director, Center for Genome Ethics, Law & Policy, Duke University,127C North Building, Box 90141, Durham, NC 27708 (e-mail: bob.cd@duke.edu).